Osteoporosis

2

THE YEAR IN OSTEOPOROSIS

K. ÅKESSON
J. D. ADACHI and
A. D. WOOLF

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THE YEAR IN OSTEOPOROSIS

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Preface

KRISTINA ÅKESSON, RICK ADACHI, ANTHONY WOOLF

There continue to be enormous advances in the knowledge and understanding of the scientific and clinical aspects of osteoporosis over the last years, with increasing numbers of publications appearing in a wide spectrum of journals both in the clinical (internal medicine, primary care, rheumatology, orthopaedics, endocrinology, gynaecology, gerontology) and the many areas of basic science (genetics, biophysics, materials, cell biology). The purpose of this book is to help those interested in osteoporosis remain up to date by experts in the field providing a critical appraisal of the most important recent publications that they have identified and by communicating the key messages.

The literature from the past 18 months is reviewed, covering all aspects of osteoporosis that are relevant to the practitioner or researcher working within this area. Advances in our understanding of the epidemiology of osteoporosis are first considered, reviewing the impact and who is most at risk. The pathogenesis and the important role of genetics are considered as well as specific situations of glucocorticoid-induced and other secondary causes of osteoporosis. The use of ultrasound and bone markers for case-finding and monitoring response to treatment are reviewed. Other factors that influence bone quality are also considered. Prevention involves maximising bone strength through physical activity and nutrition, preventing falls and reducing the impact of falls. There is also new evidence for pharmacological treatment of osteoporosis and fracture prevention. How to apply this evidence to the population at highest risk – the very elderly – is considered. Finally, the development of new therapies based on a better understanding of the scientific background to osteoporosis is reviewed.

This volume therefore provides a comprehensive update of recent advances in many aspects of osteoporosis that will help ensure best practice in its prevention and management on a background of a better understanding of the scientific basis.

Part I

Epidemiology and pathophysiology

1

Impact of the condition

L JOSEPH MELTON III

Introduction

Adverse outcomes of osteoporosis relate mainly to osteoporotic fractures. Hip and spine fractures are associated with increased mortality, and fractures of all types may lead to disability and a reduced quality of life [1]. Moreover, expenditures for the care of these fractures are high. This chapter reviews recent reports on the burden of osteoporosis with respect to mortality, morbidity and cost.

Mortality from osteoporosis

Mortality is increased in patients with low bone density even before fractures occur [2], but death is most closely linked to fractures. The influence on survival varies with the type of fracture. Hip fractures are the most serious: the hazard of death is increased by more than 10-fold in the first weeks following fracture, then diminishes [3]. Mortality is also increased following vertebral fractures, and serious underlying medical conditions, which also increase the risk of osteoporosis, are presumed to be responsible [4]. By contrast, no excess mortality follows distal forearm fractures, although other limb fractures have been linked to greater death rates [5]. These observations have been extended by recent reports that better describe the risk of death associated with incident hip fractures and define the proportion of deaths that can be attributed directly or indirectly to vertebral fractures.

Effect of hip fracture on mortality in elderly women: the EPIDOS Prospective Study

Empana J-P, Dargent-Molina P, Bréart G, for the EPIDOS Group. *J Am Geriatr Soc* 2004; **52**: 685–90

BACKGROUND. Although mortality in the first year following hip fracture may be several times higher than corresponding death rates in the population at large, hip fractures tend to occur in persons with more clinical problems and functional deficits than others of similar age and sex. Consequently, the excess mortality attributable to

hip fracture is likely to be overestimated. To address this issue, 7512 ambulatory volunteers were recruited from women aged 75 years or older in Amiens, Lyon, Montpellier, Paris and Toulouse, France. After completing baseline functional and clinical examinations, these women were followed every 4 months for 4 years. A multivariate proportional hazards model assessed the association of hip fracture, as a time-dependent variable, with mortality after adjusting for age and baseline health status.

INTERPRETATION. During a mean follow-up of 3.9 ± 0.9 years, 338 women had a first hip fracture and 60 of these died. Their age-adjusted post-fracture mortality rate was 112.4 per 1000 woman-years versus 27.3 per 1000 for the 6115 women who did not have a fracture of any type ($P<0.001$). Compared with the unfractured women, the relative risk (RR) of death following hip fracture was 3.3-fold greater than expected, but the RR was reduced to 2.6 after taking their older age into account and further reduced to 2.1 by adjusting for the greater prevalence of other independent mortality predictors in the women with hip fractures (Table 1.1). This increased risk of death appeared more pronounced in the first 6 months following fracture (RR 3.0; 95% confidence interval [CI] 1.9–4.7) than afterwards (RR 1.9; 95% CI 1.6–2.2; $P=0.09$). In both time periods, cardiovascular disease was the most common cause of death listed on death certificates; death was attributed to the hip fracture in only three instances.

Comment

It has long been obvious that hip fractures are associated with excess mortality, but the exact timing has been controversial, as has the proportion of deaths that might properly be blamed on the fracture itself. These data are consistent with the notion that two types of patients may be involved. First, a frail, sick group of very elderly women whose hip fracture is just another comorbid event; secondly, a group of

Table 1.1 Overall relative risks (RR) of mortality after hip fracture

	Model 1*	Model 2†	Model 3‡
Variable	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Hip fracture	3.3 (2.5–4.3)	2.6 (1.9–3.4)	2.1 (1.6–2.8)
Age (per 5 year increase)		1.4 (1.3–1.5)	1.4 (1.3–1.5)
Grip strength (per 10 kPa increase)			0.9 (0.9–1.0)
Assistance required for IADLs (per activity needing assistance)			1.2 (1.1–1.2)
Walking outdoors daily			0.8 (0.7–0.9)
Ever leave neighbourhood			0.7 (0.6–0.9)
Angina pectoris			1.3 (1.1–1.6)
Antihypertensive medications			1.2 (1.0–1.5)
Diabetes mellitus			1.4 (1.0–1.8)
Hospitalization in previous 12 months			1.5 (1.2–1.7)

*Hip fracture only; †hip fracture plus age; ‡hip fracture plus age plus baseline health status variables.
IADL, instrumental activities of daily living (e.g. meal preparation, shopping, etc).
Source: Empana *et al.* (2004).

healthier women whose hip fracture may then precipitate rapid functional decline. This is an important distinction because the former group accounted for 38% of the deaths following hip fracture even in this study, which was based on relatively healthy ambulatory volunteers; these deaths are not likely to be preventable by an osteoporosis intervention that prevents the fracture itself.

An estimate of the worldwide prevalence, mortality and disability associated with hip fracture

Johnell O, Kanis JA. *Osteoporos Int* 2004; **15**: 897–902

BACKGROUND. Despite increasing recognition that osteoporosis is an important public health problem, there are few estimates of its global burden. The most devastating consequence is hip fracture; the current number of hip fractures worldwide has been estimated, as has the number expected in the future based on the growing elderly population [6]. However, the impact of hip fractures with respect to disability and premature mortality has not been quantified. To assess the burden, the incidence of hip fracture in women and men aged 50 years or older in different socioeconomic regions was identified, and corresponding regional population numbers and mortality in 1990 were taken from the World Development Report [7]. To compute years of life lost, excess mortality from hip fracture was based on data for Sweden. The prevalence of hip fractures in 1990 was calculated from the estimated number of hip fractures in each region combined with mortality rates for those with and without hip fracture. Disability weights were assigned to hip fracture survivors to estimate disability-adjusted life years.

INTERPRETATION. In 1990, there were an estimated 1.31 million new hip fractures worldwide, 52% of which were in the established market economies of North America, Western Europe, Australia and Japan. The prevalence of hip fracture with disability in 1990 was 4.48 million (73% women), leading to 1.21 million years of life disabled due to hip fractures. An estimated 740 000 deaths were associated with hip fracture (Table 1.2), a quarter of which may have been due to the fracture *per se*. There were 2.92 million disability-adjusted life-years lost (Table 1.3), or 1.75 million disability-adjusted life years lost after adjusting also for age. This represents 0.1% of the overall burden of disease worldwide but 1.4% of the overall burden among women in the established market economies.

Comment

This analysis reveals that the years of life lost as a result of hip fracture are substantial, as is the burden of disability among survivors worldwide. The data further confirm that the burden of osteoporosis, as judged by hip fracture, is now greatest in the established market economies. However, this is likely to change dramatically in the future since the population of older individuals is growing most rapidly in Latin America and, particularly, in Asia. Thus, it has been estimated that by 2050 almost half of all hip fractures will occur in Asia [6]. As a consequence, the future burden of osteoporosis will also be greater in those regions.

Table 1.2 Estimated number of deaths in 1990 associated with hip fracture in different regions of the world in men and women

Region	Women	Men	Total	%
Established market economies	267 574	95 738	363 312	49.2
Former socialist Europe	83 359	23 445	106 804	14.5
China	40 931	46 122	87 053	11.8
Middle Eastern Crescent	30 359	23 433	53 792	7.3
India	22 484	28 467	50 951	6.9
Latin America/Caribbean	24 017	13 367	37 384	5.1
Other Asia/islands	20 525	13 631	34 156	4.6
Sub-Saharan Africa	2533	2095	4628	0.6
World	491 818	246 298	738 116	100.0

Source: Johnell and Kanis (2004).

Table 1.3 Disability-adjusted life years lost due to hip fracture in different regions of the world in men and women (not weighted for age)

Region	Women	Men	Total	%
Established market economies	1 076 000	334 000	1 410 000	48.3
Former socialist Europe	339 000	93 000	432 000	14.8
China	179 000	188 000	368 000	12.6
Middle Eastern Crescent	116 000	83 000	199 000	6.8
India	101 000	114 000	215 000	7.4
Latin America/Caribbean	98 000	52 000	150 000	5.1
Other Asia/islands	77 000	51 000	128 000	4.4
Sub-Saharan Africa	11 000	9 000	20 000	0.7
World	1 998 000	924 000	2 921 000	100.0

Source: Johnell and Kanis (2004).

Excess mortality after hospitalisation for vertebral fracture

Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. *Osteoporos Int* 2004; **15**: 108–12

BACKGROUND. As mentioned above, it is well known that there is excess mortality following osteoporotic fractures of the hip and spine (radiographic as well as clinical vertebral fractures). However, the timing of mortality following a vertebral fracture is not as well described and neither is the proportion of deaths that should be attributed (directly or indirectly) to the vertebral fracture, since deaths could be due to underlying comorbidity. To examine mortality in these patients, all admissions to Swedish hospitals for vertebral fracture (International Classification of Diseases, Ninth Revision, rubric 805) in women and men 50 years of age or older in a 10-year period

were identified from the National Swedish Register. Subsequent deaths were ascertained from a national death registry. The death rate following vertebral fracture was estimated with a Poisson model.

INTERPRETATION. In 28.8 million person-years of observation in the Swedish population in 1987–1996, 16 051 men and women aged 50 years or more were hospitalized with a vertebral fracture, of whom 5662 died during follow-up to 1998. Compared with mortality rates in the general population, at all ages and in both sexes, the risk of death was markedly increased immediately after the vertebral fracture. After a short period of declining risk, the risk of death increased with age at a rate that was higher than in the general population and comparable to that seen 1 year after a hip fracture (Fig. 1.1). The short-term excess mortality was assumed to be due to deaths related to underlying comorbidity, and the remainder were presumed to be due to the vertebral fracture. Both the deaths associated with a vertebral fracture and those due to a vertebral fracture were quite uncommon relative to overall death rates in the population (Table 1.4). Under these assumptions, a minority of deaths following hospitalization for vertebral fracture are attributable to the fracture itself.

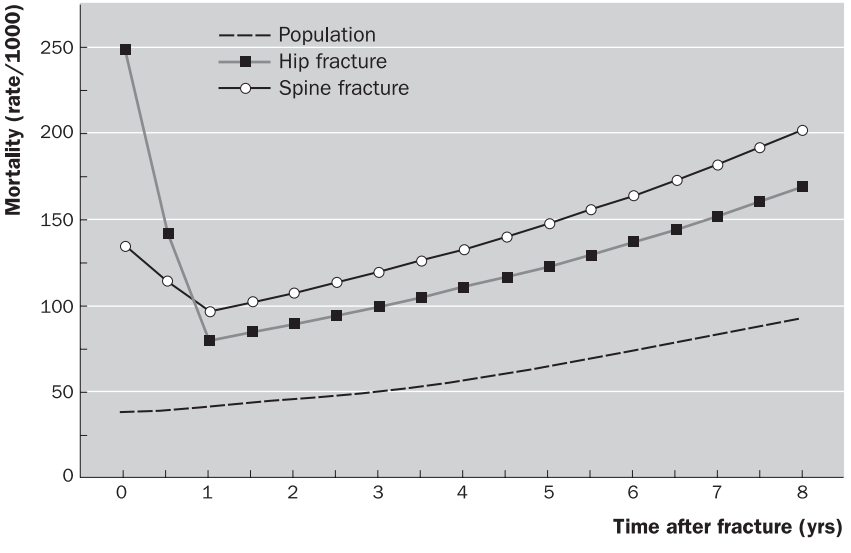

Fig. 1.1 Pattern of mortality in the general population and following hospitalization for vertebral or hip fracture in women (illustrated at the age of 78 years). Note the steep decrease in mortality following the fracture; after a nadir value, mortality increases at a rate greater than that in the general population. Source: Kanis *et al*. (2004).

Table 1.4 Deaths (per 1000 per year) in men and women in the general Swedish population and following hospitalization for vertebral fracture

	Deaths/1000 in men			Deaths/1000 in women		
Age (years)	**All deaths**	**Associated with vertebral fracture**	**Due to vertebral fracture**	**All deaths**	**Associated with vertebral fracture**	**Due to vertebral fracture**
60	7.93	0.01	0.00	4.56	0.01	0.00
65	14.32	0.01	0.00	7.82	0.03	0.00
70	25.86	0.03	0.01	13.42	0.08	0.01
75	42.94	0.07	0.03	24.49	0.23	0.02
80	71.33	0.13	0.06	44.72	0.51	0.04
85	118.48	0.23	0.13	81.63	0.93	0.09
90	196.79	0.34	0.28	149.02	1.60	0.19

Source: Kanis *et al*. (2004).

Comment

For this most severe subset of vertebral fractures (i.e. those in patients admitted to hospital), a quarter of all deaths were attributable to the vertebral fracture. The rest may have been due to the underlying comorbidity common in such patients, which may account not only for the death but also for the vertebral fracture itself [4]. However, most patients with vertebral fractures are not hospitalized; indeed, many are never formally diagnosed. Thus, the overall mortality burden from vertebral fractures, estimated here at 0.1% of all deaths in Sweden, is relatively small. However, as reviewed in the next section, the morbidity attributable to vertebral fractures may be substantial.

Morbidity from osteoporosis

More important than mortality is the morbidity that may result from osteoporotic fractures [1]. Again, hip fractures contribute most to this burden, but the more severe vertebral fractures can lead to chronic pain and kyphosis and their adverse influence on most activities of daily living is almost as great as that of hip fractures [8]. Even forearm fractures can be disabling with respect to some specific activities of daily living (e.g. preparing meals), although the global impact is far less. Recently, additional evidence has emerged that osteoporotic fractures, and perhaps osteoporosis itself, may also have serious adverse consequences for quality of life.

Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study

Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. *Osteoporos Int* 2004; **15**: 87–94

BACKGROUND. Hip fractures result in costly hospitalizations and lengthy rehabilitation procedures, despite which functional recovery and quality of life may be impaired. In the absence of an appropriate comparison group, any deterioration in physical, mental or social functioning is likely to be attributed to the hip fracture. In reality, however, part of this decline may result from underlying comorbid conditions and ageing. Thus, the impact of hip fractures on functional outcome and quality of life can only be addressed by longitudinal controlled studies. To document these effects over the succeeding year, 159 elderly Belgian women with a first hip fracture were matched for age and residence with an equal number of women without hip fracture. Functional status was measured with the Rapid Disability Rating Scale version 2 (RDRS-2) questionnaire (18 items in three domains [activities of daily living, degree of dependence and cognitive impairment], with scores ranging from 0 [best] to 54 [worst]) before hospital discharge and again 12 months later. To examine longitudinal changes in health-related quality of life, fracture subjects and controls also completed the Medical Outcomes Study Short Form 36 (SF-36) questionnaire. Paired *t* tests were used to compare means and linear regression was used to quantify the influence of various factors on functional status and quality of life.

INTERPRETATION. For the 134 women still alive at 1 year, the mean RDRS-2 score before hospital discharge was 16.2 and 3.5 in patients and controls, respectively ($P<0.001$). During the year following hospital discharge, the mean RDRS-2 score improved to 13.0 in women with hip fracture and worsened to 4.3 in the control group ($P<0.001$ in both groups). After adjustment for potential confounders, including age and comorbidity, the estimated functional decline attributable to a hip fracture was 24% in the first year. Poor functional status upon discharge was the strongest predictor of poor functional status at 1 year. Similar trends in various aspects of quality of life were observed using SF-36 scores (Fig. 1.2). However, only 51% of the study population was able to complete the SF-36 questionnaire after 1 year, and the subjects included here were considerably younger, less cognitively impaired and had better functional status (all $P<0.001$).

Comment

The results of this study indicate that women who sustain a hip fracture continue to suffer from substantial functional impairment and lost quality of life at 1 year, despite significant recovery during this 12-month period. Function upon hospital discharge is the strongest predictor of functional status a year later. Assessing quality of life with self-administered questionnaires is subject to considerable bias in this population, because of non-response. This suggests that impairments in quality of life following hip fracture, as serious as they appear to be, may yet be underestimated.

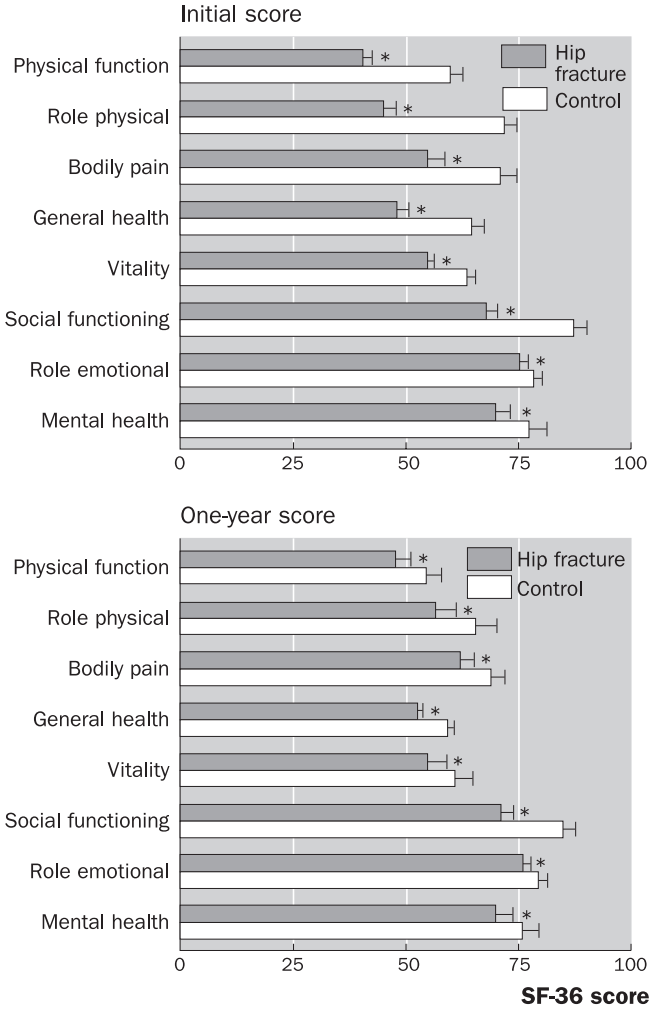

Fig. 1.2 Impact of hip fracture on different domains of quality of life: SF-36 scores at hospital discharge (initial score) and 1 year after hospital discharge. *P <0.05 between fracture patients and controls. Source: Boonen *et al*. (2004).

Changes in quality of life among elderly patients with hip fracture in Taiwan

Shyu Y-IL, Chen M-C, Liang J, Lu JR, Wu C-C, Su J-Y. *Osteoporos Int* 2004; **15**: 95–102

BACKGROUND. Most data concerning quality of life in hip fracture patients are derived from Western developed countries and little is known about the problem in Asia. However, quality of life can be viewed as part of the social fabric of a people and, therefore, may vary significantly across cultures. To examine longitudinal changes in health-related quality of life during the year following hospital discharge, 110 subjects with hip fracture (mean age 79.3 ± 7.4 years; 67 female) attending a major medical centre in Taiwan were enrolled in a prospective study. Face-to-face interviews were conducted using the SF-36 questionnaire 1, 3, 5 and 12 months after hospital discharge. Generalized estimation equations were used to assess differences in each quality of life dimension (physical functioning, role disability due to physical health, bodily pain, vitality, general health, social functioning, role disability due to emotional health, and general mental health) at each time-point (available data were used on subjects who died during follow-up).

INTERPRETATION. Compared with community-dwelling elderly subjects, hip fracture patients had reduced scores in most dimensions of SF-36, the scores for physical function and role limitation being the lowest because of physical problems during the first month after hospital discharge. Most dimensions of SF-36, except general health, improved significantly from the first to the third month (Fig. 1.3). After the third month,

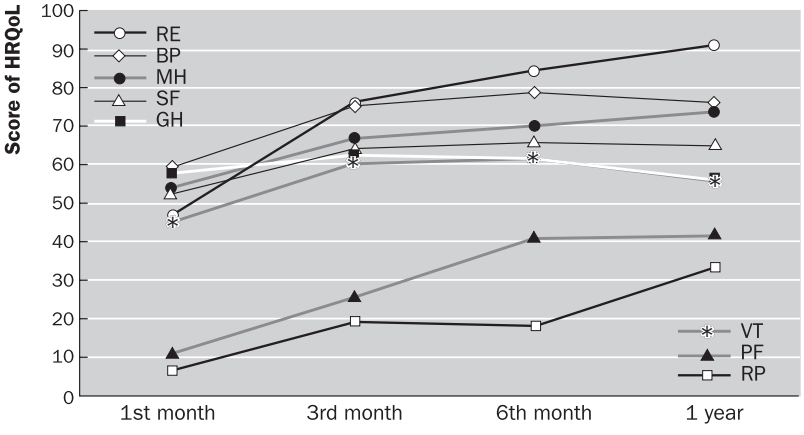

Fig. 1.3 Longitudinal changes in health-related quality of life during 1 year after hospital discharge. BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PF, physical functioning; RP, role physical. Source: Shyu *et al*. (2004).

physical functions kept improving significantly until 6 months after hospital discharge. Role limitation due to physical problems reached a plateau between the third and sixth months, and then again improved significantly between the sixth month and the first year after hospital discharge. The other dimensions of SF-36 remained stable from the third month after discharge onward. These results indicate that various aspects of quality of life recover differently following hip fracture.

Comment

Taiwan differs substantially from Western countries in its social organization. In particular, most dependent elderly persons in Taiwan are cared for by family members since Chinese culture emphasizes devotion to parents, social orientation and interdependence, characteristics that are less prominent in the West. With continued increases in the elderly population, hip fractures will represent a growing healthcare problem in Asia [6]. Since the majority of hip fracture patients never recover completely in terms of their activities of daily living or social functioning, their families will suffer the extra burden of caregiving. Culture-specific interventions will be needed to ameliorate this problem.

Back pain, disability, and radiographic vertebral fracture in European women: a prospective study

O'Neill TW, Cockerill W, Matthis C, *et al*. *Osteoporos Int* 2004; **15**: 760–5

BACKGROUND. Clinic-based studies suggest that functional impairment following a clinically apparent vertebral fracture persists, though pain decreases. However, the majority of vertebral fractures do not come to clinical attention, and there are few population-based data on changes in back pain and disability following the identification of a radiographic vertebral fracture. Data from the European Prospective Osteoporosis Study were used to determine whether radiographically identified vertebral fractures at baseline influence the occurrence of back pain and disability during follow-up. In this study, 2260 women aged 50 years and over were recruited from population registers in 18 European centres. An interviewer-administered questionnaire at baseline and about 5 years later included questions about back pain and various activities of daily living. Lateral spine radiographs were performed at baseline and follow-up, and prevalent and incident vertebral fractures were defined using established morphometric criteria. The data were analysed by logistic regression, with back pain (or disability) present or not at follow-up as the dependent variable.

INTERPRETATION. Altogether, 242 women had one or more prevalent vertebral fractures at baseline, and 85 developed an incident fracture during follow-up. Relative to unaffected women, a number of activities were impaired in women with prevalent, incident or both types of vertebral fracture (Table. 1.5). However, after adjustment for age, centre and frequency of back pain at baseline, compared with those without a baseline vertebral fracture, women with a prevalent fracture were no more likely to report back pain at follow-up (odds ratio [OR] 1.2; 95% CI 0.8–1.7). There was a small increase

Table 1.5 Association between individual back pain-specific activities and vertebral fracture at follow-up

		Fracture status	
	Prevalent	**Incident**	**Prevalent and incident**
Activity	**OR (95% CI)***	**OR (95% CI)***	**OR (95% CI)***
Reach a book from a high shelf	1.6 (1.1–2.3)	1.4 (0.7–2.6)	2.5 (1.2–5.6)
Lift a heavy object of at least 10 kg	1.7 (1.2–2.4)	1.5 (0.8–2.8)	3.6 (1.3–10.2)
Wash and dry yourself all over	1.1 (0.7–1.7)	0.9 (0.4–1.9)	2.4 (1.1–5.5)
Bend forward and pick up a light object from the floor	1.3 (0.9–1.9)	1.2 (0.6–2.3)	2.3 (1.0–5.2)
Wash your hair over a basin	1.4 (1.0–2.0)	1.5 (0.8–2.9)	2.1 (0.9–4.9)
Sit for 1 hour on a hard chair	1.4 (1.0–1.9)	0.9 (0.5–1.7)	2.7 (1.2–6.4)
Stand continuously for 30 minutes in a queue	1.4 (1.0–2.0)	1.2 (0.6–2.3)	2.0 (0.8–4.8)
Raise yourself in bed from a lying position	1.3 (0.9–1.8)	1.0 (0.5–1.9)	1.7 (0.7–3.9)
Take your socks off your feet	1.3 (0.9–1.9)	1.3 (0.7–2.6)	1.7 (0.7–3.8)
Bend from seated and pick up a small object	1.3 (0.9–1.8)	0.7 (0.3–1.5)	1.9 (0.9–4.2)
Lift box containing six litre bottles on to a table	1.7 (1.1–2.4)	1.3 (0.7–2.5)	1.5 (0.6–3.7)
Run 100 metres fast without stopping	1.4 (0.9–2.1)	1.1 (0.5–2.3)	2.4 (0.7–8.5)

*Odds ratio (95% confidence interval) with adjustments made for age, centre and baseline value of the outcome variable.
Source: O'Neill *et al*. (2004).

in the risk of back pain among those with a pre-existing fracture who also sustained an incident fracture during follow-up (OR 1.6; 95% CI 0.6–4.1), though the difference was not statistically significant.

Comment

This study revealed no significant increase in the level of back pain an average of 5 years after identification of a radiographic vertebral fracture unless women suffered a further fracture during follow-up. This does not mean, however, that there was no continuing problem because the analysis was adjusted for the baseline level of back pain already present in these women. Indeed, as shown in Table 1.5, there was substantial (if not always statistically significant) impairment in many back pain-specific activities of daily living at follow-up in the women with vertebral fractures, whether those fractures were new or old. Moreover, this analysis does not address short-term back pain and/or disability following a vertebral fracture, which can be substantial [9].

Quality of life in ambulatory post-menopausal women: the impact of reduced bone mineral density and subclinical vertebral fractures

Romagnoli E, Carnevale V, Nofroni I, *et al*. *Osteoporos Int* 2004; **15**: 975–80

BACKGROUND. Osteoporosis does not always manifest itself clinically. In fact, because low bone density is asymptomatic, patients may be unaware of their condition. Conversely, women with reduced bone mineral density (BMD) could experience decreased quality of life if they feared falling or future fractures. To investigate quality of life in post-menopausal women presenting for osteoporosis screening, the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUAL-EFFO) was administered to 361 asymptomatic, ambulatory women referred to a mineral metabolism centre in Italy. The participants underwent BMD measurements by dual energy X-ray absorptiometry (DXA) of the lumbar spine and/or femoral neck, as well as X-ray examination to identify subclinical vertebral fractures by semi-quantitative methods. Subjects were then subdivided by BMD values into three groups (normal BMD, osteopenia and osteoporosis) according to the World Health Organization definition [10]. Differences between groups were assessed by *t* tests or one-way analysis of variance, and multiple logistic regression was used to identify the independent determinants of reduced quality of life.

INTERPRETATION. Significant differences among the BMD categories were found only for the quality of life domains which explore general health perception ($P<0.01$) and mental function ($P<0.001$). When the 150 osteopenic and 145 osteoporotic women were further segregated according to whether or not they had vertebral fractures (Table 1.6), a significant difference was found only in osteoporotic patients for the quality of life domains related to physical function ($P<0.01$), social function ($P<0.001$), general health perception ($P<0.02$) and total QUAL-EFFO score ($P<0.01$). Multiple logistic regression analysis of the whole sample demonstrated that both vertebral fracture and low femoral BMD impaired quality of life perception. Conversely, quality of life characteristics did not distinguish either the BMD category or the presence of vertebral deformity.

Comment

Although QUAL-EFFO was not able to discriminate between patients with or without osteoporosis or subclinical vertebral fractures, this analysis showed that some aspects of quality of life (especially impairments in physical functioning and general health perception) appear to be impaired in patients with reduced hip BMD, although results were stronger with respect to fractures. Additional studies are needed to define the mechanisms whereby low BMD is associated with reduced quality of life.

Table 1.6 Scores* for five QUAL-EFFO domains and total QUAL-EFFO score in osteopenic and osteoporotic patients grouped according to the presence or absence of prevalent vertebral fractures

	Osteopenic patients			Osteoporotic patients		
	Vertebral fractures			Vertebral fractures		
	No	Yes	*P*-value	No	Yes	*P*-value
Number of patients	120	30		93	52	
Pain	46.9 ± 20.4	51.2 ± 22.0	0.31	49.8 ± 21.4	53.4 ± 23.7	0.35
Physical function	34.0 ± 11.0	38.0 ± 13.5	0.09	33.8 ± 12.3	41.2 ± 15.5	0.002
Social function	44.4 ± 13.3	44.4 ± 14.1	1.00	40.7 ± 11.3	50.3 ± 17.1	<0.001
General health perception	62.1 ± 15.0	65.8 ± 17.5	0.24	62.9 ± 16.7	70.4 ± 17.3	0.011
Mental function	51.3 ± 13.8	51.3 ± 15.6	1.00	49.1 ± 15.6	48.8 ± 15.0	0.91
Total QUAL-EFFO score	43.1 ± 10.6	45.7 ± 12.1	0.24	42.5 ± 11.0	48.0 ± 13.2	0.008

*The scores were transformed to a 0–100 scale and are presented as mean ± SD.
Source: Romagnoli *et al.* (2004).

Osteoporosis and health-related quality of life outcomes in the Alameda County Study population

Kotz K, Deleger S, Cohen R, Kamigaki A, Kurata J. *Prev Chronic Dis* [serial online] 2004. Available from URL: http://www.cdc.gov/pcd/issues/2004/jan/03_0005.htm

BACKGROUND. As noted above, less obvious (but perhaps equally serious) health outcomes may be associated with osteoporosis *per se*, including cognitive decline, depression, poor perceived health and less social support. Moreover, fear of fracture among individuals with osteoporosis can lead to limitation of activities, which can greatly reduce quality of life. To identify associations between having osteoporosis in 1994 and subsequent health-related quality of life outcomes in 1999, 1171 women members of the Alameda County Study were assessed for osteoporosis by self-report, as well as for specific outcomes in 1999 that were not present in 1994. Odds ratios for these outcomes in the 92 women who reported osteoporosis compared with the 1079 who did not were determined by logistic regression analysis.

INTERPRETATION. After controlling for age, ethnicity, education, financial strain and physical activity, subjects with osteoporosis in 1994 were more likely in 1999 to report new problems with frailty, difficulties with balance and weakness, problems with

Table 1.7 Association between osteoporosis in 1994 and physical health outcomes reported in 1999 for women in the Alameda County Study

Models	Odds ratio (95% CI)
Frailty	
Model 1*	2.0 (1.1–3.8)
Model 2†	1.9 (1.03–3.6)
Model 3‡	1.7 (0.9–3.2)
Difficulty with physical domain (problems with balance and weakness)	
Model 1	3.0 (1.5–5.6)
Model 2	2.9 (1.5–5.6)
Model 3	2.5 (1.3–4.9)
Problems with activities of daily living	
Model 1	3.3 (1.8–6.2)
Model 2	3.3 (1.8–6.3)
Model 3	2.8 (1.5–5.4)
Fair/poor perceived health	
Model 1	2.2 (1.2–4.3)
Model 2	2.3 (1.2–4.4)
Model 3	1.8 (0.9–3.5)

*Model 1 controlled for age, ethnicity, education and financial strain; †Model 2 = model 1 + physical activity; ‡Model 3 = model 2 + chronic medical conditions.
Source: Kotz *et al.* (2004).

activities of daily living and only fair/poor perceived health, as shown in Table 1.7. In addition, there was evidence of less enjoyment of life generally (i.e. never go out or experience entertainment [OR 2.18; 95% CI 1.06–4.50] and do not enjoy free time much [OR 2.88; 95% CI 1.12–7.37]). With further control for chronic medical conditions, the odds ratios were reduced but remained significant for difficulty with balance and weakness (OR 2.48; 95% CI 1.26–4.87) and problems with activities of daily living (OR 2.80; 95% CI 1.46–5.35).

Comment

It is generally presumed that the adverse outcomes of osteoporosis relate almost exclusively to the associated fractures. However, women with low bone density are at increased risk of death independently of fractures [2], and this report emphasizes that there may also be other adverse outcomes. Interpretation of these data is hampered by a number of study limitations, the most prominent of which is ascertainment of osteoporosis by self-report. Doubtless, many women in this age group (mean age in 1994, 62.6 years) who did not report the condition would have been found to have osteoporosis had DXA measurements been made. However, any such misclassification probably weakened relationships with the adverse outcomes reported here. These results further indicate that the effects of osteoporosis on health-related quality of life are not dependent only on the associated fractures. More detailed studies are needed to determine whether frailty, depression and poor health are causes or consequences of osteoporosis.

Cost of osteoporosis

The cost of managing the large number of osteoporotic fractures that occur each year is great, although details have been sketchy. Fortunately, better estimates are now being made of the expenditures associated not only with hip and spine fractures but also with the other osteoporotic fractures [**11**]. While the focus in the past has been on direct expenditures for medical and surgical services and nursing home care, attention is now being given to the indirect costs of osteoporosis, such as those associated with premature death [**12**]. However, little progress has yet been made with respect to the value to be placed on patients' pain and suffering. Moreover, almost nothing is known of the costs of treating osteoporosis and/or osteoporotic fractures in many parts of the world, or of the costs entailed in specific subsets of patients who present with complex management issues.

The burden of osteoporosis in Latin America

Morales-Torres J, Gutiérrez-Urena S, Osteoporosis Committee of Pan-American League of Associations for Rheumatology (PANLAR). *Osteoporos Int* 2004; **15**: 625–32

BACKGROUND. As the numbers of fracture-prone elderly people increase, so will the economic burden of osteoporosis worldwide. Dramatic increases in hip fractures are projected for Latin America [6], but knowledge of the magnitude of the osteoporosis problem in most Latin American countries remains extremely limited. With the objective of achieving a better understanding of the impact of this disease in Latin America, information from 20 countries was collected from diverse published and electronic sources. In addition, selected bone specialists from 18 countries were asked for information about the problem (i.e. demography, morbidity, mortality and direct costs) through a questionnaire.

INTERPRETATION. The population of the Latin American/Caribbean region in 2000 was 524 million. On average, 5.5% of the population was 65 years old or older, but with life expectancy higher than 70 years in most countries significant growth in the elderly population is anticipated. Studies using the World Health Organization criteria for osteoporosis [**10**] report that 12–18% of women aged 50 years and older have vertebral osteoporosis and 8–22% have osteoporosis in the proximal femur. Community-based studies in Argentina reported 263–331 hip fractures per 100 000 annually among people 50 years of age or older, while hospital-based studies in Colombia, Chile, Brazil, Mexico, Panama, Peru and Venezuela reported between 40 and 362 hip fractures per 100 000. The prevalence of vertebral fractures among community-dwelling women aged 50 years and more in Mexico is 19%. Data on other fractures are rare. Direct costs of a hip fracture ranged from $4500 to $6000 compared with national gross income per capita in the region, which ranges from $410 to $7550 (Table 1.8). The costs of bone densitometry, where it is available, and osteoporosis treatment expenses are also variable. With few exceptions, these costs are somewhat lower than those in the USA, but the per capita income in these countries is far less.

Table 1.8 Estimated costs (in US dollars) associated with hip fractures and diagnosis and therapy of osteoporosis in some countries; therapy costs are considered on a monthly basis

Country	Hip fracture (direct costs of acute episode)	Axial BMD testing	Treatment			National gross income per capita in 2000
			Calcium	Alendronate	Calcitonin	
Argentina	5500	90	10	64	140	7550
Brazil	5500	40	7	60	80	4350
Chile	5500	90	10	40	70	4610
Mexico	5500	80	8	50	75	4440
Panama	6000	100	10	68	110	3080
Uruguay	4500	80	10	40	200	6220
Venezuela	4500	40	5	60	60	3680
USA	8500	120	10	70	120	29 340

Source: Morales-Torres and Gutiérrez-Urena (2004).

Comment

Osteoporosis causes considerable morbidity, mortality and resource utilization in industrialized nations. Its burden is relatively well-known in Europe and North America, but poorly studied in the rest of America. This study aimed to document the burden of osteoporosis in Latin America. Despite the provisional nature of some of the findings, it is clear that potential expenses are enormous, given the age-driven increase in osteoporotic fractures that is anticipated in this region, especially relative to the limited resources available to deal with this problem. More information is needed to identify the determinants of variation in the burden of osteoporosis across these countries with ethnically diverse populations.

A retrospective analysis of health care costs for bone fractures in women with early-stage breast carcinoma

Zhou Z, Redaelli A, Johnell O, Willke RJ, Massimini G. *Cancer* 2004; **100**: 507–17

BACKGROUND. Breast carcinoma is the most common cancer in Western women, and metastases to bone are prevalent. Resulting pathological fractures can be devastating because of decreased mobility from femoral fractures or, in some patients, spinal cord compromise with vertebral body collapse. Thus, measures to reduce morbidity from skeletal involvement in breast carcinoma are important for maintaining patient quality of life and for mitigating substantial financial consequences of metastatic bony involvement. This issue is becoming more critical with increased use of adjuvant therapy (in particular, new aromatase inhibitors) for extended periods in women with early-stage breast cancer. Development of an economic model to measure

the extent of this problem requires reliable prevalence and cost data, but few such data are available. To estimate the costs of fracture care in women aged 65 years or older who had early-stage breast carcinoma, and to compare these with the healthcare costs for fractures incurred by older women without breast cancer, data from the 1997–1998 Medicare 5% national sample were analysed.

INTERPRETATION. Overall, 2486 of 20 887 women with early-stage breast cancer experienced at least one fracture over the 2-year study period, and 20% of them required hospitalization. Hospitalization, as opposed to outpatient treatment, was most frequent for femur fractures. Among those with fractures, average costs were greater in the women who were hospitalized ($26 033 versus $1385). Compared with women of the same age without breast cancer but who had fractures, there was little difference in fracture cost stratified by hospitalization or no hospitalization. However, compared with women with early-stage breast cancer but no fractures, those who fractured experienced much greater costs (Table 1.9). For older women with early-stage breast carcinoma, the excess direct costs for fracture were estimated at $45 579, of which 57% came from treating the fracture, 25% from other excess treatment costs, and 18% from excess long-term care costs.

Comment

This study purports to show that the average cost of treating fractures in patients with breast cancer is no greater than fracture treatment costs in women of the same age without breast cancer. However, the analysis considered all fractures, including minor ones, not only those attributed to skeletal metastasis. Moreover, these were early-stage breast cancers, and only 12% of all fractures observed were coded as pathological fractures. Nonetheless, treatment costs were substantially greater in breast cancer patients who fractured compared with those who did not. This is likely to present a growing problem as women live longer with breast cancer and as they are treated more aggressively with agents that impair bone metabolism [**13**]. Similar problems may be seen in men with prostate cancer.

Conclusion

The reports reviewed here add to the growing body of evidence that osteoporotic fractures exact a terrible toll on the population with respect to morbidity and cost, and to a lesser extent on mortality—a toll that will increase dramatically as the elderly population grows worldwide [**6**]. If the impact of osteoporosis is to be reduced, more attention must be devoted to the design and implementation of effective control programmes. Fortunately, encouraging evidence is now emerging that feasible control problems are effective in reducing fractures and their associated costs in the general population [**14**].

Table 1.9 Excess cost (US dollars) for bone fractures stratified by age group in patients with early-stage breast carcinoma who did or did not have a fracture

	Fracture from any cause		No fracture		Excess costs	
Age group (years)	**No.**	**Mean cost ± SD**	**No.**	**Mean cost ± SD**	**Mean**	***P*-value**
Hospitalized for specific fracture						
65–69	44	63 854 ± 69 590	44	29 916 ± 38 259	38 168	0.002
70–74	113	16 854 ± 88 178	13	30 241 ± 53 446	33 613	<0.001
75–79	153	71 463 ± 69 639	153	33 077 ± 43 568	38 387	<0.001
80–84	160	70 591 ± 47 197	160	32 656 ± 40 267	37 935	<0.001
≤85	64	69 130 ± 52 198	64	31 112 ± 47 694	38 017	<0.001
Subtotal	534	69 033 ± 66 350	534	31 855 ± 44 875	37 179	<0.001
Never hospitalized for any fracture						
65–69	318	27 141 ± 68 052	323	18 160 ± 26 762	8981	0.029
70–74	534	26 390 ± 36 957	547	21 527 ± 31 009	4863	0.019
75–79	551	30 224 ± 42 815	555	25 906 ± 36 479	4317	0.071
80–84	432	31 067 ± 37 450	437	29 921 ± 48 518	1146	0.696
≥85	117	34 503 ± 47 320	121	27 213 ± 33 921	7399	0.168
Subtotal	1952	29 116 ± 45 727	1983	24 394 ± 36 839	4722	<0.001

Source: Zhou *et al.* (2004).

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2

Risk factors for osteoporosis and fracture

DIPAK ROY, TERENCE O'NEILL

Introduction

Osteoporosis is an important clinical and public health problem through its association with fragility fractures. Fractures occur in anyone if sufficient force is applied; they are considered osteoporotic if they occur as a result of mild or moderate trauma (typically falls) and are associated with a reduction in bone strength. One of the major determinants of bone strength is the amount of bone (bone mass or mineral density), though other factors are important, including bone turnover, microarchitecture and geometry.

Studying risk factors for osteoporosis and fragility fractures is important for several reasons. A knowledge of risk factors can help in understanding the pathogenesis and mechanisms of disease occurrence, they may be used to help identify individuals who are at high risk and in whom measures to reduce risk might be considered, and they can help inform the development of population-wide strategies for prevention. Currently many genetic, environmental and constitutional factors have been shown to influence both bone mass and fracture risk. In this chapter we review recently published papers which look at environmental and constitutional factors, with a focus on those with potential clinical or public health interest. We have not included papers looking at genetic factors as these are considered elsewhere in this publication.

In the first section we include papers which look at the effect of various metabolic factors on bone health. These are potentially important as dietary modification/supplementation can influence levels of these factors and may reduce fracture risk. In the second section we include papers which look at the impact of various medical therapies on bone mass and fracture risk. In the third section we look at lifestyle and anthropometric risk factors for incident vertebral fracture and fractures in childhood—areas where there is currently a paucity of published data. In the final section we review the occurrence of osteoporosis in other disease states, including HIV infection.

Metabolic factors

Homocysteine as a predictive factor for hip fracture in older persons

McLean RR, Jacques PF, Selhub J, *et al. N Engl J Med* 2004; **350**: 2042–9

BACKGROUND. Homocysteine is an amino acid intermediate formed during the metabolism of methionine. Homocystinuria is an autosomal recessive disorder resulting in high plasma concentrations of homocysteine. Clinical features of homocystinuria include severe occlusive vascular disease and osteoporosis. Mild elevation in plasma homocysteine in the general population is common and recognized as a risk factor for thrombo-embolic disease [1]. The association, however, between elevated homocysteine levels and osteoporosis has received little attention. Two papers published in the same issue of the *New England Journal of Medicine* address the issue. In the first paper, using data from the Framingham study, the authors looked at the association between total homocysteine concentration and the risk of hip fracture in men and women.

INTERPRETATION. A total of 825 men and 1174 women, aged 59–91 years, who had had blood taken between 1979 and 1982 were followed from the time of sample until June 1998 for the occurrence of an incident hip fracture. Mean total homocysteine concentration was 13.4 μmol/litre in men and 12.1 μmol/litre in women. Median follow-up was 12.3 years for men and 15.0 years for women. There were 41 hip fractures among men and 146 among women. After adjusting for age, height, weight, smoking status, caffeine and alcohol consumption, educational level and use of oestrogen in women, the risk of hip fracture was increased by 59% in men and by 26% in women for each increase of 1 SD in the log-transformed total homocysteine concentration. Men and women in the highest quartile had a greater risk of hip fracture than those in the lowest quartile—the risk was almost four times as high for men and 1.9 times as high for women (Fig. 2.1).

Comment

The findings suggest that total homocysteine concentration is associated with the risk of hip fracture. The major strength of the study was its prospective design, with blood for homocysteine levels collected prior to the occurrence of hip fracture. Limitations of the study include the lack of dietary data. Folate and vitamins B_6 and B_{12} are major determinants of the homocysteine level, and inadequacy of one or more of these vitamins rather than the homocysteine concentration itself may have been responsible for the observed effect. No bone mass data were available for the study participants at baseline and the authors were unable to assess whether the effect of homocysteine on hip fracture was mediated through bone mineral density. Finally, the study was restricted to Caucasian men and women and the results may not be generalizable to other racial and ethnic groups. If the results are confirmed, the finding has potentially important implications for fracture prevention. Mild elevation of plasma homocysteine is not uncommon in the general population and

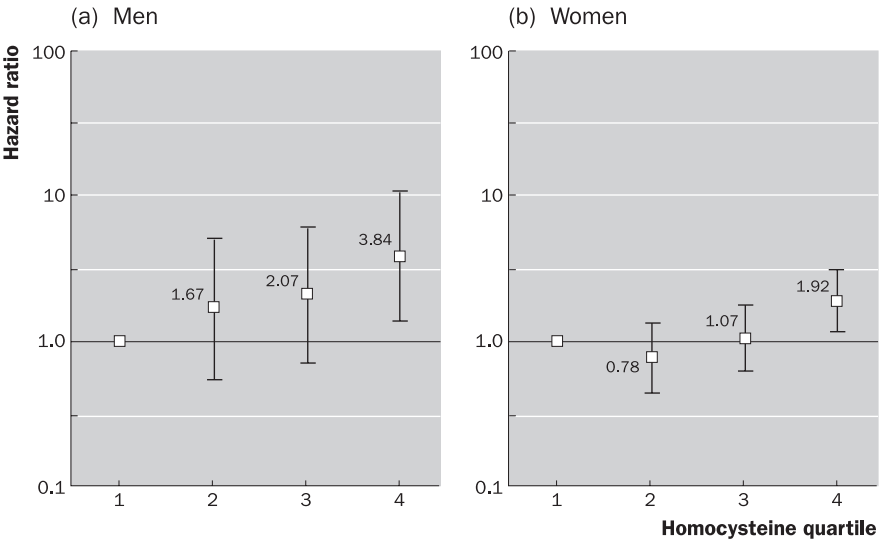

Fig. 2.1 Multivariable-adjusted hazard ratios for the risk of hip fracture according to the quartile of total homocysteine concentration. The y axis is on a log scale. The reference group is quartile 1. The I bars denote 95% confidence intervals (CI). Source: McLean *et al*. (2004).

is readily modifiable by dietary intervention with folic acid and B_{12} |**2**|. However, randomized trials would be necessary to determine whether or not dietary modification reduces the risk of fracture.

Homocysteine levels and the risk of osteoporotic fracture

van Meurs JBJ, Dhonukshe-Rutten RAM, Pluijm SMF, *et al*. *N Engl J Med* 2004; **350**: 2033–41

BACKGROUND. In this paper the authors looked at the relationship between circulating levels of homocysteine and the incidence of fracture in two independent prospective studies of Dutch men and women aged 55 years and over.

INTERPRETATION. The authors studied the association between circulating homocysteine levels and the risk of incident osteoporotic fracture in 2406 men and women, aged 55 years of age and older, who were participants in two separate population-based prospective Dutch studies, the Longitudinal Aging Study Amsterdam (LASA) and the Rotterdam study. Within the Rotterdam study two independent cohorts were studied, in one of which information about dietary intake was obtained using a food frequency questionnaire. During 11 253 person-years of follow-up, osteoporotic fractures occurred in 191 subjects. The overall multivariable-adjusted relative risk of fracture was

1.4 for each 1 SD increase in the natural-log-transformed homocysteine level. The risk was similar in both the LASA and the Rotterdam study cohorts. A homocysteine level in the highest age-specific quartile was associated with a 1.9-fold increase in the risk of fracture. The associations appeared to be independent of bone mineral density (BMD) and other potential risk factors for fracture, including in the Rotterdam cohort dietary intake of calories, protein, calcium and vitamins. In LASA, adjusting for 25-hydroxyvitamin D levels did not alter the risk estimates.

Comment

The data are consistent with the data from Framingham and suggest that elevated levels of homocysteine are associated with an increased risk of osteoporotic fracture in older men and women. Strengths of the study include the prospective design and the availability of bone mass and dietary data. Adjustment for dietary intake of calories, protein, calcium and vitamins or for serum 25-hydroxyvitamin D level did not appear to influence the strength of the observed association, suggesting that the relationship between homocysteine and fracture risk is not due to nutritional deficiency (though the possibility cannot be completely excluded). The lack of association with bone mass suggests that bone fragility is unrelated to bone mass. The authors speculate that homocysteine may lead to an increase in fracture risk through interference in collagen cross-linking, as has been suggested as a mechanism for the occurrence of fracture in homocystinuria [3].

Low plasma vitamin B_{12} is associated with lower BMD: the Framingham Osteoporosis Study

Tucker KL, Hannan MT, Qiao N, *et al. J Bone Miner Res* 2005; **20**: 152–8

BACKGROUND. Vitamin B_{12} is an important cofactor involved in DNA synthesis. Vitamin B_{12} has been associated with osteoblast activity and bone formation and patients with pernicious anaemia have been shown to have a greater risk of fracture [4]. Recent studies suggest that a low plasma concentration of vitamin B_{12} is associated with reduced bone mass in women [5,6]. The aim of this study was to determine the association between plasma vitamin B_{12} and BMD in men and women.

INTERPRETATION. The authors examined the association between plasma vitamin B_{12} and BMD in 2576 adults who were participants in the Framingham Offspring Osteoporosis Study (1996–2001). BMD was measured by DXA (dual energy X-ray absorptometry) at the hip and spine. Mean BMD was estimated for four categories of plasma vitamin B_{12} concentration based on commonly used cut-offs, using analysis of covariance, and adjusted for age, body mass index, physical activity, alcohol use, smoking status, total calcium and vitamin D intake, season of bone measurement and, for women, menopause status and current oestrogen use. Both men and women with plasma vitamin B_{12} levels less than 148 pM had lower BMD than those with vitamin B_{12} above this cut-off. These differences were significant ($P < 0.05$) for men at most hip sites and for women at the spine. Furthermore, the results persisted after adjustment for protein intake and plasma homocysteine.

Comment

Vitamin B_{12} deficiency or marginal status is prevalent in older adults [7]. The results from this study are consistent with data from two recent population studies suggesting that vitamin B_{12} status is important for the maintenance of BMD [5,6]. The study was large, population-based and included both men and women. Further prospective data are needed to determine the temporal nature of the relationship between vitamin B_{12} levels and both bone mass and fractures, and to determine whether the association is due to direct effects of vitamin B12 or whether vitamin B_{12} is simply a marker for dietary intake or absorption of other important nutrients. Vitamin B_{12} deficiency is readily preventable with supplements or fortified foods. The results of this and previous studies raise the possibility that supplementation, or dietary assessment and modification, may help prevent bone loss in some elderly men and women.

Serum vitamin A concentration and the risk of hip fracture among women 50 to 74 years old in the United States: a prospective analysis of the NHANES I follow-up study

Opotowsky AR, Bilezikian JP. *Am J Med* 2004; **117**: 169–74

BACKGROUND. The role of vitamin A (retinol and its metabolites) in bone metabolism is poorly understood. Overt vitamin A toxicity is associated with increased bone resorption and hypercalcaemia. Some studies suggest an association between high dietary vitamin A intake or serum vitamin A concentration, low bone mass and an increased fracture risk, while others have found no evidence of a linear association [8–13]. In a recent study, both low and high intake of vitamin A were linked with low bone mass [14]. The aim of this study was to determine the influence of serum vitamin A levels at the relative extremes of the normal range on the risk of hip fracture in women.

INTERPRETATION. The data were collected as part of the first National Health and Nutrition Examination Survey (NHANES) follow-up study. The authors used data on 2799 women aged 50–74 years. There were 172 incident hip fractures during the 22-year follow-up period. Using Cox regression analysis, the authors analysed the relation between baseline serum vitamin A (retinol and retinyl esters) concentration and the risk of hip fracture. Adjustments were made for age, weight, serum albumin, cholesterol, alcohol use, physical activity, hormone replacement therapy, previous fracture history, dietary calcium intake and race. Overall there was no linear relation between serum vitamin A concentration and the risk of hip fracture in the multivariate analysis (hazard ratio [HR] 1.0). Analysis using quintiles, however, revealed a U-shaped relationship between serum vitamin A and hip fracture. The fracture risk was significantly higher among subjects in the lowest (HR 1.9) and highest (HR 2.1) quintiles compared with those in the middle quintile (Fig. 2.2).

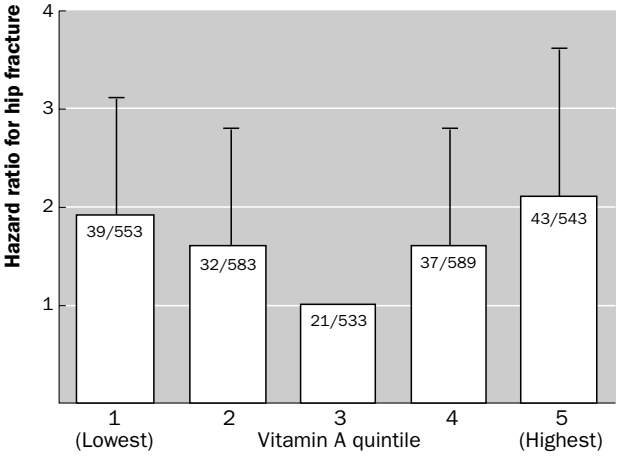

Fig. 2.2 Hazard ratios (error bars represent 95% confidence interval) for hip fracture by serum vitamin A quintile compared with risk in the middle quintile, using multivariate Cox regression analysis. Results presented are adjusted for age, weight, serum cholesterol, serum albumin, alcohol use, non-recreational and recreational physical activity, hormone replacement use, history of fracture, dietary calcium intake, and race. Numbers within the bars represent absolute numbers of hip fractures sustained in a given quintile (*N*) over the total number of participants (*n*) in that quintile. Source: Opotowsky and Bilezikian (2004).

Comment

Most recent research has focused on the potential adverse effects of high vitamin A intake and serum vitamin A levels on bone. The results of this study suggest that there may be a U-shaped relationship between serum vitamin A concentration and hip fracture, with both high and low levels linked with an increased risk. The strengths of the study were its size and prospective design. Limitations include the lack of detailed data about vitamin supplements, including type, dose and duration of use, and the lack of data concerning smoking, which may affect the metabolism of vitamin A. Further prospective data are needed to confirm or refute these findings.

Medical therapies

A meta-analysis of prior corticosteroid use and fracture risk

Kanis JA, Johansson H, Oden A, *et al. J Bone Miner Res* 2004; **19**: 893–9

BACKGROUND. Corticosteroid therapy has an adverse effect on bone fragility, with epidemiological data suggesting an increased risk of hip, forearm and vertebral

fracture. Data from the UK General Practice Research Database suggest a rapid increase in fracture risk after starting corticosteroids and rapid reduction in risk after they are stopped. This suggests that the risk may partly be independent of BMD [15]. The aim of this analysis was to determine the risk of fracture associated with corticosteroid therapy in men and women in an international setting and whether it is influenced by other risk factors, including BMD and previous fracture risk.

INTERPRETATION. Subjects included in the analysis were drawn from seven prospective population studies in North America, Europe and Australia. In total, 42 500 men and women contributed 176 000 person-years of follow-up. The effects of ever having used corticosteroids, BMD, age and sex on all fractures, osteoporotic fracture and hip fracture risk were examined using Poisson regression in each cohort. The results from the different studies were merged from the weighted β coefficients. After adjusting for BMD, previous corticosteroid use was associated with a significantly increased risk of any fracture, osteoporotic fracture and hip fracture (Table 2.1). The relative risk of any fracture ranged from 2.0 at the age of 50 years to 1.7 at the age of 85 years. For osteoporotic fracture, the range of relative risk was 1.7–2.6 and for hip fracture 2.5–4.4. There was no significant difference in risk between men and women. The risk was marginally but not significantly upwardly adjusted when BMD was excluded from the model. Furthermore, the risk was independent of prior fracture. In the three cohorts that documented current use of corticosteroids, BMD was reduced at the femoral neck but fracture risk was still only partly explained by BMD.

Comment

The results of the study confirm findings from previous studies which show that corticosteroids are linked with a substantial increase in the risk of fracture [**15**]. In addition, the study suggests that the effect is largely independent of BMD or prior

Table 2.1 Risk ratio of any fracture and 95% confidence interval (CI) associated with ever having used corticosteroids according to age and adjusted for BMD

	Any fracture		Osteoporotic fracture		Hip fracture	
Age (years)	**Risk ratio***	**95% CI**	**Risk ratio**	**95% CI**	**Risk ratio**	**95% CI**
50	1.98	1.35–2.92	2.63	1.68–4.13	4.42	1.26–15.49
55	1.83	1.35–2.47	2.32	1.63–3.30	4.15	1.50–11.49
60	1.67	1.33–2.09	2.00	1.52–2.62	3.71	1.67–8.23
65	1.56	1.29–1.88	1.81	1.43–2.27	2.98	1.55–5.74
70	1.55	1.30–1.86	1.76	1.42–2.19	2.44	1.37–4.36
75	1.64	1.37–1.97	1.70	1.36–2.11	2.22	1.35–3.63
80	1.62	1.31–2.00	1.59	1.26–2.02	2.13	1.39–3.27
85	1.66	1.26–2.17	1.71	1.29–2.28	2.48	1.58–3.89
All ages	1.57	1.37–1.80	1.66	1.42–1.92	2.25	1.60–3.15
All ages†	1.53		1.61		2.13	

*Ever use versus no use.
†Ever use versus population risk.
Source: Kanis *et al.* (2004).

fragility fracture and that the risk is mediated by other factors, though the nature of these remain uncertain. Strengths include the large population-based sample and the international setting. Limitations of the study include variability in how the question about steroid use was constructed and the documentation on characterization of fracture events between cohorts. However, the effect of this heterogeneity would be to tend to weaken rather than strengthen the observed associations. The authors suggest that, because exposure to corticosteroids confers risk over and above that provided by BMD, intervention thresholds for treatment should be less stringent than for individuals of the same age with osteoporosis caused by gonadal deficiency.

Are inhaled corticosteroids associated with an increased risk of fracture in children?

van Staa TP, Bishop N, Leufkens HGM, Cooper C. *Osteoporos Int* 2004; **15**: 785–91

BACKGROUND. Inhaled steroids are widely used in the long-term management of asthma in children. Data concerning the relationship between inhaled corticosteroid therapy and bone mass are inconsistent [16–18]. The aim of this study was to determine the association between inhaled corticosteroids and fracture risk in children.

INTERPRETATION. The data for the study were obtained from the UK General Practice Research Database, which contains the general practitioner medical records of around 6% of the total registered population of England and Wales. The database includes information about both medical diagnoses and medications prescribed. Children aged 4–17 years with a non-vertebral fracture (n = 23 984) were matched by age, sex, general practice and calendar time to a child without fracture. There was a significant increase in the risk of non-vertebral fracture in children using inhaled corticosteroids (odds ratio 1.19) which disappeared after adjustment for indicators of asthma severity (Table 2.2). With an average daily beclomethasone dose of 200 μg or less, the crude fracture risk relative to non-users was increased, at 1.10; with a dose of 201–400 μg it was 1.23 and over 400 μg it was 1.36 (Table 2.2). The increased risk persisted after removing from the analysis children treated with oral corticosteroids. The excess risk, however, associated with beclomethasone disappeared after adjustment for indicators of asthma severity.

Comment

The results from this study are similar to findings which have been observed in adults suggesting an increased risk of fracture in patients with respiratory disease taking inhaled steroids [**18**]. As in adults, however, the increased risk appears to be related to the underlying illness rather than being directly attributable to inhaled corticosteroid therapy. Strengths of the study include the large sample and the prospective design. Limitations include the lack of information about height, weight, lifestyle factors and of detailed information about the severity of the

Table 2.2 Use of inhaled corticosteroids and risk of fracture

Use of inhaled corticosteroids	No. of cases	No. of controls	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Non-use	20 646	21 051	Reference	Reference
Current use	1464	1266	1.19 (1.10–1.29)	1.03 (0.93–1.15)
Number of prior prescriptions				
1	211	154	1.40 (1.14–1.73)	1.27 (1.02–1.58)
2–5	527	430	1.26 (1.11–1.43)	1.10 (0.95–1.27)
6	726	682	1.10 (0.98–1.22)	0.93 (0.81–1.06)
Daily dose (beclomethasone dipropionate or equivalent), μg/day				
200	444	413	1.10 (0.96–1.26)	0.96 (0.83–1.12)
201–400	552	462	1.23 (1.08–1.39)	1.07 (0.93–1.24)
>400	216	165	1.36 (1.11–1.67)	1.17 (0.93–1.45)
Recent use	1131	972	1.20 (1.10–1.31)	1.07 (0.96–1.18)
Past use	743	695	1.11 (0.99–1.24)	1.06 (0.95–1.19)

*Adjusted odds ratios are based on multivariate conditional logistic regression models including current, recent and past use of bronchodilators, previous asthma hospitalization, past use of non-steroidal anti-inflammatory drugs, history of seizures and number of prescriptions issued by the general practitioner in the preceding year. CI, confidence interval.
Source: van Staa *et al.* (2004).

underlying disease. The mechanism by which the risk of fracture is increased in children with respiratory disease is unclear, though the authors speculate whether children with asthma have weaker bones because of reduced levels of physical activity in association with increased weight for height.

Use of beta-blockers and risk of fractures

Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. *JAMA* 2004; **292**: 1326–32

BACKGROUND. There is accumulating evidence that the sympathetic nervous system is involved in the regulation of bone metabolism. Adrenergic receptors are present on both osteoblasts and osteoclasts, and treatment with the β-blocker propranolol increases bone formation in mice [19,20]. However, there are few data concerning the influence of β-blockers on the risk of fracture. The aim of this study was to determine whether use of β-blockers either alone or in combination with thiazides is associated with a reduced risk of fracture in adult men and women.

INTERPRETATION. The data were derived from the UK General Practice Research Database, which contains computerized medical records of 683 general practices in England and Wales. The database includes information both about medical diagnoses and medications prescribed. In this analysis 30 601 men and women aged 30–79 years with an incident fracture which occurred between 1993 and 1999 were compared with

120 819 controls matched on age, gender, calendar time and general practice. Conditional logistic regression analysis was used to determine the association between β-blocker and or thiazide diuretic use and fracture risk, and adjustments were made for smoking, body mass index, number of practice visits, and use of other medications. Compared with those who did not use either β-blockers or thiazide diuretics, current use of β-blockers (more than three prescriptions) was associated with a 23% reduction in the risk of fracture, while current use of thiazides was linked with a 20% reduction in risk. Current use of both therapies was linked with a 29% reduced risk.

Comment

The data suggest that current use of β-blockers is linked with a reduced risk of fractures, whether the blockers are taken alone or in combination with thiazide diuretics. The strengths of the study were the large sample and the prospective design. Limitations include the inability to adjust for putative confounders not included in the General Practice Research Database, including lifestyle factors and socio-economic status. Two other studies published recently provide somewhat conflicting results concerning bone mass and the fracture risk associated with β-blockade [**21**,**22**]. Further prospective studies are needed to determine the effect of β-blockade on bone health.

Risk of fracture after androgen deprivation for prostate cancer

Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. *N Engl J Med* 2005; **352**: 154–64

BACKGROUND. The use of androgen deprivation therapy for prostate cancer has increased over the last 15 years. Treatment is linked with low bone mass but the risk of fracture after androgen deprivation therapy has not been well studied [23].

INTERPRETATION. The authors studied the records of 50 613 men who were listed in the linked database of the Surveillance Epidemiology and End Results Program and Medicare (USA) as having received a diagnosis of prostate cancer in the period 1992–1997. The primary outcomes were the occurrence of any fracture and the occurrence of fracture resulting in hospitalization. Cox proportional hazards models were adjusted for characteristics of the patients and the cancer, other cancer treatment received, and the occurrence of fracture or the diagnosis of osteoporosis during the 12 months preceding the diagnosis of cancer. Among the men surviving at least 5 years after diagnosis, 19% of those who received androgen deprivation had a fracture compared with 12.6% of those not receiving androgen deprivation therapy (P <0.001). In the Cox proportional hazards analysis, after adjusting for characteristics of the patient and the tumour there was a statistically significant association between the number of doses of gonadotrophin-releasing hormone received during the 12 months after diagnosis and the subsequent risk of fracture.

Comment

This study suggests that androgen deprivation in the form of orchiectomy or treatment with gonadotrophin-releasing hormone agonists is associated with an increased risk of fracture in patients with prostate cancer. Limitations of the study include the fact that fractures due to bone metastases were not excluded, though the authors comment that these represent only a minority of fractures. Also, because the analysis was restricted to the risk of fracture linked with the number of doses of agonist given in the first year after diagnosis of cancer, it may have underestimated the risk linked with this therapy. The findings nevertheless underscore the need for caution in the use of androgen deprivation therapy in settings without clear evidence of benefit. The authors suggest that trials of therapies to prevent bone loss are needed in individuals in whom androgen deprivation therapy is indicated.

Lifestyle and anthropometric factors

Risk factors for a first incident radiographic vertebral fracture in women ≥65 years of age: the study of osteoporotic fractures

Nevitt MC, Cummings SR, Stone KL, *et al. J Bone Min Res* 2005; **20**: 131–40

BACKGROUND. In contrast to hip fracture, there are few data from prospective studies concerning risk factors for vertebral fracture. Such data are potentially important. Identification of those at risk may help target therapies to prevent the occurrence of fracture. The aim of this study was to determine risk factors for a first vertebral fracture in a cohort of older women.

INTERPRETATION. Subjects were participants in the Study of Osteoporotic Fractures, a prospective study of Caucasian women aged 65 years and over recruited from population-based listings in four US metropolitan areas. At the baseline examination women completed a questionnaire and had spinal radiographs performed. BMD of the wrist and calcaneus was measured at baseline and BMD of the spine and hip approximately 2 years later. Repeat radiographs were obtained at follow-up an average of 3.7 years later. Among the 5822 women without vertebral fracture at baseline, 181 had a first incident vertebral fracture during the follow-up period. In multivariate analysis, older age, previous non-spine fracture, low BMD (all sites), low body mass index, current smoking, low milk consumption during pregnancy, low levels of daily physical activity, having a fall and regular use of aluminium antacids independently increased the risk of a first vertebral fracture. Women using oestrogen and those who engaged in recreational physical activity had a decreased risk. The effects of low body mass index, smoking, use of oestrogen and antacids and previous fracture were mediated partially by BMD. Women in the lower third of wrist BMD with five or more risk factors had a 12-fold greater

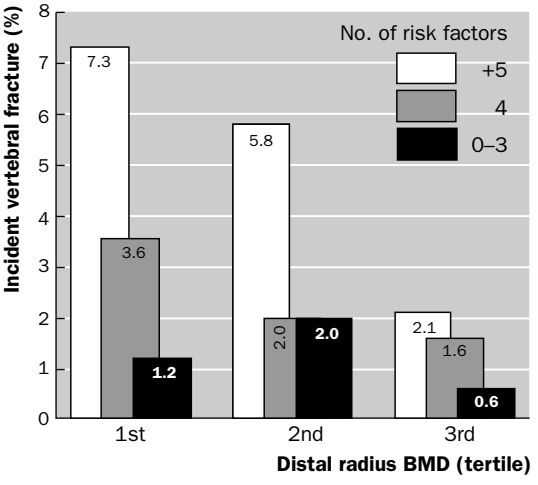

Fig. 2.3 Cumulative incidence of first incident vertebral fracture during 3.7 years of follow-up in women ≥65 years of age at baseline by the number of risk factors present and tertile cut-point of baseline distal radius BMD. Risk factors are age ≥70, a prior non-spine fracture after age 50, body mass index (calculated with knee height) in the lowest 40%, current smoker, low level of physical activity (walks ≤1 block/day and does household chores <1 h/day), does no moderate or high intensity recreational physical activities, fell one or more times in the first 12 months of follow-up, not currently on oestrogen replacement therapy, low milk consumption (<1 glass/day) when pregnant (or teenager for nulliparous women), ever used aluminium-containing antacids weekly, and paternal history of hip fracture. First (lowest) tertile of BMD: 0–3 risk factors, $n = 435$; 4 risk factors, $n = 423$; ≥5 risk factors, $n = 861$. Second tertile of BMD: 0–3 risk factors, $n = 731$; 4 risk factors, $n = 498$; ≥5 risk factors, $n = 728$. Third tertile of BMD: 0–3 risk factors, $n = 1008$; 4 risk factors, $n = 559$; ≥5 risk factors, $n = 542$. Source: Nevitt *et al.* (2005).

risk than women in the highest third of BMD who had zero to three risk factors (Fig. 2.3). The 27% of women at highest risk suffered 60% of the incident fractures.

Comment

The results of this study confirm the high incidence of vertebral fracture in elderly women [**24**]. The strengths of the study are the prospective design, detailed information concerning putative risk factors, use of standardized protocols for acquisition of the spinal radiographs and validated methods for assessment of vertebral fracture. However, the study was restricted to predominantly white elderly women and the results may not necessarily apply to other groups. In contrast to the constellation of risk factors documented for hip fracture in the same population, fall-related risk factors did not appear to play an important role in the occurrence of vertebral fracture [**25**]. This is consistent with a more limited role of falls in the

pathogenesis of vertebral fractures. As was observed with hip fracture, women with multiple risk factors and low BMD were at increased risk of fracture. The combination of risk factors and BMD should be useful for focusing efforts to prevent vertebral fractures.

Associations of birth weight and length, childhood size, and smoking with bone fractures during growth: evidence from a birth cohort study

Jones IE, Williams SM, Goulding A. *Am J Epidemiol* 2004; **159**: 343–50

BACKGROUND. Up to 55% of all children break at least one bone before the age of 18 years and fractures are the most common injury of childhood requiring hospitalization [26]. Despite this, there are relatively few data concerning risk factors for fractures sustained during childhood and adolescence. The aim of this study was to examine the effects of birth weight and length, anthropometric variables during growth, breast-feeding, smoking and sports participation on the risk of fracture during childhood and adolescence.

INTERPRETATION. Subjects were participants in the Dunedin Multidisciplinary Health and Development Study. This is a longitudinal study of health, development and behaviour of children born in Dunedin over a 12-month period (1972/1973). Information about height, weight, fracture status and aspects of lifestyle was collected at birth and at ages 3,5,7,9,11,13,15 and 18 years from parents and or participants. There were 229 fractures in girls and 393 in boys between birth and age 18 years. Fracture risk was elevated (per SD unit increase) in relation to birth length (prepubertal fractures only [relative risk 1.28]), weight at age 3 years (relative risk 1.14), weight from age 5 to 18 years (relative risk 1.15), height at age 3 years (relative risk 1.13) and height from age 5 to 18 years (relative risk 1.13). Birth weight, maternal smoking, breast-feeding and sports participation had no effect on fracture risk. Among teenagers, however, personal daily smoking increased the risk of fracture (relative risk 1.43).

Comment

In this study, children who were born long or who were tall and heavy throughout growth had an increased risk of fracture during their childhood and adolescence, as did adolescents who were daily smokers. An important strength of the study was that information concerning fractures was obtained at regular intervals, minimizing recall bias. Also, follow-up rates during the 18 years of the study were excellent. A limitation of the study was the absence of data concerning bone mineral content or BMD; consequently it was not possible to determine the effect of birth size or later growth variables on bone mass, size or density in the cohort. There is evidence that the incidence of fractures in childhood may be rising in some populations [27]. The results of this study suggest that strategies to reduce the number of fractures in children should include measures to reduce obesity and teenage smoking.

Disease associations

Reduced bone density in HIV infected women

Dolan SE, Huang JS, Killilea KM, Sullivan MP, Aliabadi N, Grinspoon S. *AIDS* 2004; **18**: 475–83

BACKGROUND. Bone mass is reduced in HIV-infected men receiving potent antiretroviral therapy [28]. Relatively little is known, however, about bone mass in HIV-infected women. Previous research has suggested reduced bone density among HIV-infected women with the AIDS wasting syndrome [29]. In this paper the authors investigated bone density in normal-weight, ambulatory HIV-infected women.

INTERPRETATION. Eighty-four HIV-infected women and 63 HIV-negative female controls were recruited through community advertisements and primary care providers. Inclusion criteria for HIV-infected participants included age between 18 and 60 years, previously diagnosed HIV infection, without a change in or initiation of an antiretroviral regimen within 6 weeks of enrolment and a body mass index between 20 and 35 kg/m^2. Those taking therapies which may have affected bone mass, including steroids, were excluded. All subjects had bone mass measurements at the spine, hip and total body site. All completed a 4-day food record and had blood sampling after a 12-hour overnight fast. Mean age for the HIV-infected and control subjects was 41 years. Mean duration of disease among those with HIV was 8 years and the majority (>90%) reported a prior history of antiretroviral exposure. Bone density was significantly lower in those with HIV compared with the controls at the lumbar spine (1.02 vs 1.07 g/cm^2), total hip (0.93 vs 0.99 g/cm^2) and femoral neck (0.82 vs 0.87 g/cm^2). Based on the

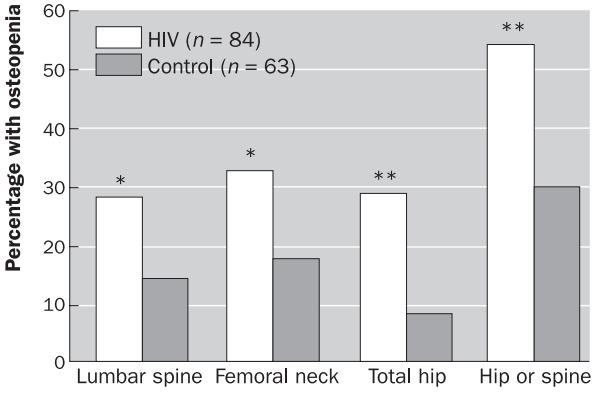

Fig. 2.4 Percentage of HIV-infected versus control subjects with osteopenia at the hip or spine. *P<0.05; **P<0.01 versus control subjects. Source: Dolan *et al.* (2004).

World Health Organization (WHO) classification, osteopenia was present in 54% of the HIV-infected subjects compared with 30% of the controls, while osteoporosis was present in 10% of those with HIV and 5% of those without HIV (Fig. 2.4). Total body fat and percentage body fat were lower in the HIV subjects, while lean mass was similar in those with and without HIV. Total calorie intake and protein, fat and calcium intakes were similar in the two groups. Serum 1,25-hydroxyvitamin D levels were reduced in those with HIV compared with controls. Bone density was not different at any site with respect to current or previous antiretroviral therapy or duration of therapy.

Comment

HIV infection is an increasing public health problem worldwide. In this paper ambulatory normal-weight HIV-infected women had reduced bone density compared with non-HIV control subjects. The mechanism underlying the occurrence of bone loss in those with HIV is unknown, though this study suggests that it may in part be related to altered nutritional status and body composition. Longitudinal studies are needed to better define the natural history of bone loss and the mechanisms underlying it in women with HIV. The authors suggest that in the interim consideration should be given to screening HIV-infected women at high risk of osteoporosis, particularly among those at or entering the menopause.

Aortic calcification and the risk of osteoporosis and fractures

Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. *J Clin Endocrinol Metab* 2004; **89**: 4246–53

BACKGROUND. Previous studies suggest an association between aortic calcification and osteoporosis [30,31]. Most studies have, however, used conventional radiography, which is an insensitive method for determining small vascular calc ifications, and absorptiomety techniques to determine bone mass, which are inaccurate in the presence of extra-osseous calcium in the beam path of the region of interest. The aim of this study was to determine whether there is an association between computed tomography (CT) measures of aortic calcification and bone density, and the number of fragility fractures in healthy post-menopausal women, and to determine whether the rate of change in vascular calcification is associated with the rate of change in bone mass.

INTERPRETATION. The study population comprised patients who had one or more CT bone density determinations at the Department of Radiology, Loma Linda University Medical Centre between 1984 and 1998. Medical records of these subjects were reviewed. A total of 2348 ambulatory, post-menopausal women aged 50 years and over of European descent, who did not smoke and had low alcohol intake were included. Aortic calcifications were inversely related to bone density and directly related to fractures. After adjusting for age and potential confounders, measures of aortic calcification predicted 26% of the variance in bone density. Compared with women without calcification, the odds ratios for vertebral and hip fracture in those with

calcification were estimated to be 4.8 and 2.9, respectively. In a subgroup of 228 women who had repeat CT measurements performed a mean of 2.1 years later, the percentage of yearly increase in aortic calcification accounted for 47% of the variance in the percentage rate of bone loss. Women in the highest quartile for gain in aortic calcification had four times greater yearly bone loss (5.3 vs 1.3%) than women of similar age in the lowest quartile.

Comment

The results of this study confirm a strong association between aortic calcification, bone mass and fracture risk. Strengths of the study include the large sample and the use of CT to obtain graded measures of both skeletal and vascular calcification. However, subjects were selected from patients who had undergone bone density determination, which may explain the high prevalence of osteoporosis in the cohort. Further research is needed to understand the mechanism regulating mineral deposition in connective tissues. From a clinical perspective, the identification of vascular calcification in women – either on quantitative CT or plain film imaging – should be considered a risk factor for subsequent bone loss and fracture risk.

Conclusion

Combinations of risk factors that include age, bone mass and history of fracture can help determine the risk of future fracture and can be used to target therapy at individuals who are most likely to benefit. Knowledge of risk factors may also help in the identification of areas for potential intervention. Many risk factors, e.g. smoking and physical immobility, may be modified and changes in these factors may substantially reduce an individual's risk of fracture. Diet is readily modifiable either by dietary change or by supplementation. Until recently, most clinical and research interest focused on the impacts of calcium and vitamin D on bone health. There is now good evidence that other dietary factors are important [32]. Data reviewed here concerning the adverse effect of hyperhomocysteinaemia on the risk of fracture are potentially important as levels may be readily modified by supplementation with folate and vitamin B12 [2].

Various medical therapies have been linked with bone loss and fracture risk. Data from the UK General Practice Research Database continue to provide important information about the impact of a variety of medical therapies, including, in this review, inhaled steroids and β-blockade. Recent papers also provide further insights into the adverse effect of other therapies, including oral steroids and androgen depletion therapy. Finally, evidence continues to accrue about the adverse effect of HIV infection on bone health.

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3

Pathophysiology of osteoporosis

ÖSTEN LJUNGGREN

Introduction

Osteoporosis is a main risk factor for fragility fractures. In the clinic the diagnosis of osteoporosis is based on bone densitometry. This is also the main technique when investigating effects of therapies on patients. It is therefore important to evaluate how well measures of bone mineral density (BMD) predict fracture. An important recent publication concerning this describes a meta-analysis of 12 clinical cohorts with a total of 39 000 men and women [1]. This analysis revealed that BMD is a risk factor for fracture of substantial importance and has similar predictive ability in men and women. It is not only the absolute amount of bone but also the rate of decline in BMD that is a good predictor of fracture [2]. This probably reflects an aspect of bone tissue other than the absolute amount of bone tissue—the turnover rate. The cellular basis of the development of osteoporosis, or the presence of a high-turnover state, is the activity of the bone cells: the resorbing osteoclasts and the bone-forming osteoblasts. By studying how these cells interact we will eventually understand the pathogenetic mechanisms that underlie osteoporosis. The discovery of the receptor activator of NFκB (RANK)/RANK ligand system some years ago demonstrated how the osteoclasts are regulated. This important discovery was part of an era when the high turnover in post-menopausal osteoporosis was elucidated and when the focus was on the basis of antiresorptive treatment. During recent years the discovery of the LRP5/Wnt signalling pathway has again opened up new understanding about how bone cells interact. In this case the focus is on the anabolic activity of the osteoblasts [3]. Numerous articles on this subject are now emerging in the literature, and this pathway has already been shown to be involved in various instances of metabolic bone disease. It also gives hope for the development of new, potent anabolic drugs. In this chapter recent papers on the regulation of bone cells are reviewed. Two main areas are covered: new insight into primary osteoporosis, and aspects of secondary osteoporosis.

Primary osteoporosis

Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children

Hartikka H, Makitie O, Mannikko M, *et al*. *J Bone Miner Res* 2005; **20**: 783–9

BACKGROUND. Juvenile osteoporosis is a condition with unknown aetiology. The gene encoding LRP5 has recently been shown to affect bone mass accrual during growth and to be involved in the osteoporosis–pseudoglioma syndrome. Mutations in the genes for collagen type I are known to cause osteogenesis imperfecta, characterized by increased bone fragility. The authors of this paper investigated 20 children with juvenile osteoporosis for mutations in the genes for collagen type I and LRP5.

INTERPRETATION. In these patients, no mutations were detected in the type I collagen genes, thereby making the diagnosis of osteogenesis imperfecta unlikely. However, two missense mutations (A29T and R1036Q) and one frame-shift mutation (C913 fs) were found in the LRP5 gene in three of the patients. The frame-shift mutation was also seen in the proband's father and brother, who were both found to have significant osteoporosis. R1036Q was observed in the proband's mother and two brothers, who all had osteoporosis. These results indicate that heterozygous mutations in the LRP5 gene can cause osteoporosis in both children and adults.

Comment

Juvenile osteoporosis poses a diagnostic problem in the clinic. The diagnosis is most often based on clinical findings. Suspicion of osteogenesis imperfecta might call for further investigations into the genes for collagen type I. However, in some patients with osteogenesis imperfecta no mutations in the collagen genes are found. This investigation, showing that some patients with juvenile osteoporosis have mutations in the LRP5 gene, adds to our understanding of this condition. It opens up the possibility of finding the correct diagnosis for some of these patients.

Low plasma vitamin B_{12} is associated with lower BMD: the Framingham Osteoporosis Study

Tucker KL, Hannan MT, Qiao N, *et al*. *J Bone Miner Res* 2005; **20**: 152–8

BACKGROUND. Vitamin B_{12} is important for DNA synthesis and may therefore also affect bone formation. It has been linked to osteoblastic activity in clinical studies, and also in cell culture. In this paper the relationship between plasma levels of vitamin

B_{12} and BMD was investigated in 2576 adult participants in the Framingham Osteoporosis Study. BMD was measured by dual energy X-ray absorptiometry at the hip and spine. Plasma vitamin B_{12} was analysed by radioimmunoassay. Adjustments were made for age, BMD, physical activity, alcohol use, smoking status, total calcium and vitamin D intake, and, for women, menopausal status and oestrogen use.

INTERPRETATION. The results showed that both men and women with vitamin B_{12} concentrations below 148 pmol/l had lower average BMD than those with vitamin B_{12} above this cut-off. These differences were significant for men at the hip and for the women at the spine. It is concluded that vitamin B_{12} deficiency may be an important modifiable risk factor for osteoporosis.

Comment

Low BMD is a major risk factor for fracture. In the absence of underlying diseases, BMD is determined by genes and the environment. Currently, huge efforts are being made to identify the genetic background of fragile bone. Environmental factors might be of greater clinical importance since it is possible to influence these. The search for risk factors in clinical cohorts is therefore always of great interest. In this rather large cohort there is good evidence that low vitamin B_{12} levels are associated with osteoporosis. This is an interesting finding. Its cause is, of course, not yet proven and the mechanism of action on bone cells is not known. However, if this finding should hold true in other investigations and vitamin B_{12} deficiency comes to be recognized as a major risk factor for osteoporotic fractures, this would be an important step forward because the deficiency is easy to investigate and to correct.

Low bone formation in pre-menopausal women with idiopathic osteoporosis

Donovan MA, Dempster D, Zhou H, McMahon DJ, Fleischer J, Shane E. *J Clin Endocrinol Metab* 2005; **90**: 3331–6

BACKGROUND. Osteoporosis in younger patients is often caused by diseases or drugs. A minority of these patients, however, do not have any obvious cause for their osteoporosis. These patients are given the diagnosis of idiopathic osteoporosis. The underlying cause of this disorder is not known. In order to further understand this disease, it is important to find out whether it is due to enhanced turnover or suppressed bone formation. In younger men with idiopathic osteoporosis, histomorphometric studies have shown that these patients have a decreased bone formation rate due to osteoblastic dysfunction. In this paper, pre-menopausal, otherwise healthy women with idiopathic osteoporosis were investigated with histomorphometry.

INTERPRETATION. Iliac crest bone biopsies were taken from nine women with assumed idiopathic osteoporosis and 18 healthy controls matched for age, sex and race. Compared with controls, differences in bone remodelling were identified,

particularly in the cancellous bone. There was a trend towards lower trabecular number and increased separation in women with idiopathic osteoporosis. Patients with idiopathic osteoporosis also had lower bone formation parameters, including a 10% reduction in wall width, an 18% reduction in mineral apposition rate, and a 42% reduction in mineralized perimeter. The bone formation rate was 52% lower. All these measures indicate that bone resorption and formation are uncoupled in women with idiopathic osteoporosis. As in men with idiopathic osteoporosis, the disease is probably due to osteoblast dysfunction.

Comment

Idiopathic osteoporosis in younger individuals has been studied most in men. In this group of patients biopsy materials have demonstrated that the low BMD in otherwise healthy men is due to impaired bone formation. The present study has extended this observation to younger females. In the clinic it is often difficult to determine the cause of low BMD in pre-menopausal women. The finding that these patients are similar to men in that their idiopathic osteoporosis is due to impaired bone formation poses the hypothesis that we are dealing with a new entity in which depressed osteoblastic activity is a common feature in idiopathic osteoporosis. Perhaps we will see similarities with idiopathic juvenile osteoporosis, in that a proportion of patients will turn out to have disturbances in the LRP5 pathway.

Regulation of bone mass, bone loss and osteoclast activity by cannabinoid receptors

Idris AI, van 't Hof RJ, Grieg IR, *et al*. *Nat Med* 2005; **11**: 774–9

BACKGROUND. Accelerated osteoclastic bone resorption has a central role in the pathogenesis of osteoporosis and other bone diseases. Identifying the molecular pathways that regulate osteoclast activity provides a key to understanding the causes of these diseases and to the development of new treatments.

INTERPRETATION. In this paper results from mice with inactivation of cannabinoid type 1 (CB1) receptors were investigated. These mice had increased bone mass and were also protected from ovariectomy-induced bone loss. Further experiments demonstrated that pharmacological antagonists of CB1 and CB2 receptors prevented ovariectomy-induced bone loss *in vivo* and caused osteoclast inhibition *in vitro* by promoting osteoclast apoptosis and inhibiting the production of several osteoclast survival factors. These studies demonstrate that the CB1 receptor has a role in the regulation of bone mass. It might also affect ovariectomy-induced bone loss. The CB1- and CB2-selective cannabinoid receptor antagonists are therefore a new class of osteoclast inhibitors that may be of value in the treatment of osteoporosis and other bone diseases in the future.

Comment

Research during the last two decades has demonstrated a variety of factors regulating bone cells. The most important advances have been the discovery of the RANK/RANK ligand system activating osteoclasts, and the LRP5/Wnt signalling system regulating osteoblastic activity. These systems have been shown to participate in a variety of skeletal diseases. It is therefore enormously interesting to note that there are still important regulatory mechanisms in bone yet to be discovered. In this paper a totally novel and unexpected pathway is described. The data presented are robust but, as always, further studies will reveal whether this is important in the pathophysiology of osteoporosis and whether it will offer possible strategies for future therapy.

Cholestane-3beta,5alpha,6beta-triol inhibits osteoblastic differentiation and promotes apoptosis of rat bone marrow stromal cells

Liu H, Yuan L, Xu S, Wang K, Zhang T. *J Cell Biochem* 2005; **96**: 198–208

BACKGROUND. There is evidence in the literature that oxidized lipids, long recognized as a risk factor in atherogenesis, also contribute to osteoporosis. The underlying mechanism is not understood in detail. A possible effect of atherogenesis-related factors, including oxysterols, on the differentiation and survival of bone marrow stromal cells (MSCs) would therefore be very important in understanding a possible link between atherosclerosis and osteoporosis. Liu *et al.* studied the effect of oxysterol cholestane-3β,5α,6β triol (Triol) on the osteoblastic differentiation and apoptosis of primary rat bone MSCs and the related mechanisms.

INTERPRETATION. Triol inhibited MSC osteoblastic differentiation, as demonstrated by inhibition of alkaline phosphatase activity, osteocalcin secretion and matrix mineralization. Treatment with Triol also promoted MSC apoptosis, characterized by condensed or fragmented nuclei and active externalization of phosphatidyl serine to the cell surface. These results suggest that Triol might contribute to the decreased bone formation by inhibition of osteoblastic differentiation and promotion of apoptosis of MSCs. The data provide insights about common factors underlying the pathogenesis of atherosclerosis and osteoporosis.

Comment

Osteoporosis and atherosclerosis are two major risk factors for severe morbidity in the general population. Both diseases may be influenced by drug therapy and lifestyle interventions. There are several results showing that these two diseases also share common risk factors. If this proves to be the case, it will be of great importance when constructing treatment guidelines and general recommendations. The findings in this paper are interesting since they open up questions about whether interference with blood lipids would also decrease the risk of fracture. The

mechanism is still not known, but a guess is that this finding will be followed by several *in vitro* studies.

Hypovitaminosis D, impaired bone turnover and low bone mass are common in patients with peripheral arterial disease

Fahrleitner-Pammer A, Obernosterer A, Pilger E, *et al. Osteoporos Int* 2005; **16**: 319–24

BACKGROUND. Hypovitaminosis D is common in patients with peripheral arterial disease (PAD) Subsequent secondary hyperparathyroidism and osteomalacia might contribute to bone pain and myalgia and thereby aggravate the clinical symptoms of claudication. In this study, 95 patients with angiographically confirmed PAD and 44 matched healthy controls were compared regarding BMD, bone pain, myalgias and several laboratory variables, such as serum vitamin D, crosslaps and parathyroid hormone (PTH).

INTERPRETATION. The data show that 25-hydroxyvitamin D_3 levels are significantly lower in patients than in controls. Patients had higher serum levels of PTH, alkaline phosphatase and crosslaps than controls. Age-adjusted bone density was lower in patients with severe disease. From these data it was concluded that patients with PAD are at high risk of osteoporosis and osteomalacia and should be monitored and treated for vitamin D deficiency.

Comment

This is another paper showing that cardiovascular disease and osteoporosis may share common pathogenetic mechanisms. A low serum level of vitamin D_3 is suggested to be a major risk factor for fractures and osteomalacia. The finding in this paper points to connection between cardiovascular disease and osteoporosis with regard also to hypovitaminosis D.

Secondary causes of osteoporosis

Normocalcemic hyperparathyroidism in patients with osteoporosis

Monchik JM, Gorgun E. *Surgery* 2004; **136**: 1242–6

BACKGROUND. It is important to diagnose primary hyperparathyroidism (PHPT) in patients with osteoporosis because they might benefit from surgery. The prevalence of PHPT and the optimal diagnostic procedure are not known. Screening patients for serum calcium alone will fail to diagnose PHPT in patients with intermittent or no

discrete elevation of serum total calcium. This paper presents data from a retrospective study of 140 PHPT patients with a pre-operative bone density measurement.

INTERPRETATION. Of these patients, 46% had osteoporosis prior to surgery. Fifteen of the patients with osteoporosis and PHPT were normocalcaemic. The authors conclude that screening patients with osteoporosis for PHPT by measuring only serum calcium will fail to identify a significant proportion of patients who will benefit from surgery. Ionized calcium and intact PTH should be the basis for screening in these patients. It is not clear what levels of 25-hydroxyvitamin D_3 the patients had. It is of great importance to rule out secondary hyperparathyroidism due to low levels of vitamin D, especially in patients with a combination of normal calcium and elevated PTH.

Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis

Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. *Arch Intern Med* 2005; **28**: 393–9

BACKGROUND. There is an increased prevalence of osteoporosis among patients with coeliac disease. However, the relative prevalence of coeliac disease among osteoporotic and non-osteoporotic populations is not known. The benefit of screening the osteoporotic population for coeliac disease therefore remains controversial. In this investigation 840 individuals, 266 with osteoporosis and 574 matched controls without osteoporosis, were evaluated by serological screening for coeliac disease. Individuals with positive serology were offered endoscopic biopsy to confirm the diagnosis.

INTERPRETATION. The prevalence of biopsy-proven coeliac disease among osteoporotic patients was 3.4%. Among the non-osteoporotic population it was 0.2%. The authors conclude that the prevalence of coeliac disease among patients with osteoporosis is much higher than in controls. This difference in prevalence justifies a recommendation for serological screening of all patients with osteoporosis for coeliac disease.

Comment

The search for underlying causes of fragile bone always poses a problem in the clinic. It is debated how many laboratory variables should be collected prior to diagnosis. In these two papers, estimates of the proportion of patients that had hyperparathyroidism and coeliac disease are presented. Also, with regard to PHPT it is clearly shown that the diagnosis requires the measurement not only of serum calcium but also of intact PTH.

Secreted frizzled-related protein 1 modulates glucocorticoid attenuation of osteogenic activities and bone mass

Wang FS, Lin CL, Chen YJ, *et al. Endocrinology* 2005; **146**: 2415–23

BACKGROUND. Glucocorticoid treatment causes osteoporosis. Recently, secreted frizzled-related protein 1 (SFRP1) and LRP5, a Wnt protein antagonist and a co-receptor, have been found to regulate bone turnover. Excess glucocorticoids promote bone loss. It is not known whether there is a biological role for SFRP1 and LRP5 in regulating glucocorticoid attenuation of bone density.

INTERPRETATION. Supraphysiological levels of glucocorticoids increase the expression of SFRP1 but not of LRP5 in primary mesenchymal cells in culture. This was also demonstrated in osteoblasts in the metaphyseal trabecular endosteum and chondrocytes in calcified cartilage *in vivo*. The increase in SFRP1 expression was mediated transcriptionally. The inhibitory action of glucocorticoids on osteogenic differentiation appeared to be regulated by SFRP1 mediation of β-catenin destabilization, because knocking down SFRP1 by RNA interference prevented the attenuation of osteogenesis. These findings suggest that SFRP1 modulates glucocorticoid-induced bone loss. The authors suggest that it may be possible to use the regulation of Wnt/SFRP signal transduction as an alternative strategy for the prevention of glucocorticoid-induced osteoporosis.

Comment

The deleterious effect of glucocorticoids on bone has been well recognized for decades. However, the pathogenetic mechanism is still not known in detail. It is believed that impaired osteoblastic activity is a key element in this process, and previous data suggest that enhanced apoptotic activity in osteoblasts is a predominant cause. The finding in this investigation opens up our understanding further. If proven by future research, this will indeed link glucocorticoid-induced osteoporosis to the Wnt/SFRP pathway. This mechanism, although only recently described, is already recognized as a major regulator of osteoblastic activity and offers a tempting explanation of this form of osteoporosis.

Overexpression of the human interleukin 1a gene causes osteopenia in mice

Aoki Y, Ichimura S, Kikuchi T, *et al. J Rheumatol* 2005; **32**: 320–4

BACKGROUND. Osteoporosis is a major complication of chronic inflammatory diseases such as rheumatoid arthritis. The authors investigated bone metabolism in transgenic mice that overexpress human interleukin 1a. Bone mineral density, ultrastructure assessed by microcomputed tomography, histomorphometry and blood biochemical data were examined.

Interpretation. The results show that the femoral BMD of transgenic mice was 27.7% lower than in wild-type littermates. Microcomputed tomography revealed a marked reduction in the trabecular bone. Cortical thinning was also observed. It was concluded that overexpression of human interleukin 1a causes osteopenia in mice. Analysis of biochemical markers suggested that the systemic osteopenia in these mice occurred primarily as a result of decreased bone formation, with a reduction of bone mineralization rather than increased osteoclastic bone resorption.

Comment

Cytokines such as interleukin 1 were among the first agents known to cause bone resorption. It was initially thought that these were paracrine factors stimulating resorption in areas of inflammation. In parallel with this was the observation that patients with inflammatory diseases may develop generalized osteoporosis as a result of the underlying disease. Also in the field of post-menopausal osteoporosis there is a large quantity of data suggesting that cytokines such as interleukin 1 and tumour necrosis factor might be involved in an endocrine fashion. In this report it is demonstrated that mice overexpressing interleukin 1 develop systemic osteoporosis, which might explain in part the systemic effect of rheumatoid arthritis on the skeleton. Interestingly, it appears to be decreased bone formation rather than increased resorption that underlies the bone phenotype in these animals.

Conclusion

In this review on the pathophysiology of osteoporosis many of the reports focus on osteoblastic activity. This is an expanding field and we are now beginning to understand the processes behind insufficient osteoblastic activity. This is a crucial part of bone loss since bone resorption with adequate coupling of bone formation does not lead to osteoporosis. In several areas of metabolic bone diseases we now see that impaired osteoblastic activity is a major component. This is also vital as we strive to invent anabolic treatment regimes for osteoporosis. Among the other areas of interest, the connection between osteoporosis and cardiovascular disease is intriguing. This field opened up when it became apparent that osteoprotegerin has effects both on bone and on vessels. We have now expanded our understanding with data on the direct effects of lipids on bone cells and on the importance of vitamin D status. This area of research is important in terms of general health strategies in the population. Finally, the discovery that cannabinoid receptors are involved in bone cell metabolism might open up a new area of investigation in the field of metabolic bone diseases.

It may be that there are numerous important signalling pathways ahead of us to discover. Or perhaps understanding RANK/RANK ligand and LRP5 signalling is the main part of bone cell interaction. Future studies will tell. In the meantime, the data that we already have enable us to search for potent drugs that can counteract the development of osteoporosis.

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4

Genetics of osteoporosis

BENTE LANGDAHL

Introduction

The genetics of osteoporosis has gained tremendous interest over the last decade. Interest in this field increased significantly on the appearance of the paper on the impact of vitamin D receptor genotypes on markers of bone turnover and bone mass by Morrison *et al.* in 1994 [1].

The genetic background of an individual was first recognized as an important risk factor for the development of osteoporosis in the 1970s. Smith *et al.* found in a twin study that bone mass of the distal forearm was determined partly by genetic factors; the estimate of heritability was 75% in adolescents and 49% in adults [2]. Similar findings have been demonstrated for bone mineral density (BMD) of the lumbar spine and hip [3,4]. The pattern of inheritance of osteoporosis fits best with a model including several genes, each with modest effects, rather than a few genes with large effect [5,6].

Unravelling the genetics of osteoporosis can be approached by two different methods. One is linkage analysis. Linkage is defined as the tendency of two or more genes at specific loci to be inherited together as a result of their physical proximity on a single chromosome [7]. Linkage studies may be total genome searches or localized searches, in which polymorphic markers are selected randomly throughout either the whole genome or the areas of interest. The basic element of the analysis is the identification of markers, where patients share alleles of these markers more commonly than they share the same alleles with healthy family members. The probability that a marker locus is linked to a disease locus is expressed by the lod (log of the odds) score.

The other method makes use of candidate gene studies. Candidate gene studies are based on the assumption that, if a gene locus is involved in the pathogenesis of osteoporosis, the allele frequencies of a genetic variant differ between patients with osteoporosis and unaffected people. The advantage of this type of analysis is that the power of detecting an association in diseases with a complex genetic background, such as osteoporosis, is better than in linkage analysis. However, only linkage analyses can discover new genes.

The methods discussed above can be applied to both human and animal studies.

Once a new gene or a new polymorphism has been identified as associated with a bone phenotype, much work is still to be done before the polymorphism can be

classified as a genetic risk factor for osteoporosis. First of all, the findings should be confirmed in other populations, and subsequently meta-analyses should be performed. It is also important to investigate interactions between the genetic variant and other genes and polymorphisms, sex, lifestyle, environment and medical treatments. Even when all these issues have been dealt with, we still cannot be sure that the polymorphism investigated is the true pathological factor—it could still be caused by linkage disequilibrium between the investigated polymorphism and the true disease-causing polymorphism. Studies of functionality of the polymorphism are therefore also needed (Table 4.1).

In the following I have chosen studies among the many papers on the genetics of osteoporosis that have been published over the last 2 years and that exemplify the issues discussed above.

Linkage studies in animals and humans

Regulation of bone mass in mice by the lipoxygenase gene Alox 15

Klein RF, Allard J, Avnur Z, *et al. Science* 2004; **303**: 229–32

BACKGROUND. The BMD achieved in early adulthood, called peak bone mass, is a major predictor of the risk of osteoporosis fracture later in life. Linkage analyses in inbred mouse strains have identified linkage between peak bone mass and several chromosomal regions, but the underlying genes have not been identified. Recent studies have also suggested that the genetic variants that are associated with complex genetic traits such as osteoporosis probably influence the regulation of gene expression rather than alter the gene transcript. Chromosome 11 is a region that has

Table 4.1 The different types of studies used in investigations of the genetic background of osteoporosis

- Linkage studies
  - Animals
  - Humans
- Candidate gene studies
  - Genes from monogenetic diseases
- Genes with known effects on bone tissue or calcium metabolic pathways
- Meta-analyses
- Studies on interaction between genetic variants and
  - Other genetic variants
  - Sex
  - Lifestyle
  - Environment
  - Medical treatments
- Studies on the function of identified genetic variants

been associated with bone mass in mice in several studies and the authors of this paper therefore chose to look for genes and genetic variants in this region.

INTERPRETATION. A mouse strain with low bone mass was genetically modified by replacing the normal chromosome 11 with chromosome 11 from a mouse strain with high bone mass. This resulted in higher bone mass and bone strength in the genetically modified mice compared with their normal littermates. Microarray analyses were used to examine gene expression in the normal and the genetically modified mice, and the only gene that was differently expressed was *Alox15* (Arachidonate 15-lipoxygenase). The mouse strain with low bone mass expressed significantly more ALOX15 than the strain with high bone mass. Subsequently, it was demonstrated that 15 polymorphisms in the *Alox15* gene differed between the two strains. Mice in which the *Alox15* gene had been knocked out had higher bone mass, and pharmacological inhibition of ALOX15 increased bone mass.

Comment

The *Alox15* gene encodes 12/15-lipoxygenase, an enzyme that converts arachidonic and linoleic acids into endogenous ligands for the peroxisome proliferator-activated receptor-γ (PPAR-γ). Activation of this pathway inhibits formation of osteoblasts. The hypothesis is therefore that increased expression of ALOX15 inhibits the formation of osteoblasts and subsequently leads to reduced peak bone mass. The effects of the *Alox15* gene or polymorphisms within this gene have not been examined in humans.

Loci for regulation of bone mineral density in men and women identified by genome wide linkage scan: the FAMOS study

Ralston SH, Galwey N, MacKay I, *et al*. *Hum Mol Genet* 2005; **14**: 943–51

BACKGROUND. BMD is an important clinical predictor of subsequent osteoporotic fracture and evidence from twin and family studies has suggested that more than 50% of the interindividual variance in bone mass is determined by genetic factors. Many candidate genes have been examined for genetic variants and associations have been found between some of these variants and BMD or the risk of osteoporotic fractures. However, so far these genetic variants only account for a small proportion of the genetic regulation of bone mass and susceptibility to osteoporotic fractures. Only a few of the linkage studies conducted previously have identified loci with significant linkage to BMD and so far only one gene has been identified [8]. Some of these studies, especially animal studies, have suggested that the genes that regulate BMD act in a gender-specific, age-specific and site-specific manner. A large-scale genome-wide linkage scan for BMD in 3658 individuals from 715 families was conducted and subgroup analysis was performed to identify gender-specific, age-specific and site-specific loci for the regulation of BMD.

INTERPRETATION. No regions of linkage were identified when data from all subjects were analysed together. However, subgroup analysis revealed significant loci for femoral neck BMD in men younger than 50 years on chromosome 10q21, with a lod score of 4.42, for lumbar spine BMD in women younger than 50 years on chromosome 20q13, with a lod score of 3.2, and for lumbar spine BMD in women older than 50 years on chromosome 18p11, with a lod score of 4.42. Five additional loci with suggestive linkage were identified on chromosomes 3q25, 4p25, 7p14, 16p13 and 16q23.

Comment

This study provides evidence that the genes responsible for regulation of BMD are gender-specific, age-specific and site-specific. Even though this study included approximately 30% more individuals than had been included in the second largest study conducted previously, loci associated with bone mass could be identified only in subgroups. This underscores the heterogeneity of the genetic background of osteoporosis.

There are some interesting genes within two of the identified loci, 10p21 and 20q13: the *GNAS1* gene, which is involved in pseudohypoparathyroidism and Albright's hereditary osteodystrophy, the *BMP7* gene, which stimulates osteoblasts, and the *DKK1* gene, which is an antagonist of the wnt-LRP5 pathway.

It is difficult, time-consuming and expensive to collect these large numbers of well-characterized families. Hopefully, it will be possible to perform a combined linkage analysis in all the families that have been included in some of the larger linkage studies conducted so far, in order to improve the statistical power of the studies to identify more loci.

Candidate studies based on studies of rare genetic diseases

Polymorphisms in the sclerosteosis/van Buchem disease gene (SOST) region are associated with bone mineral density in elderly whites

Uitterlinden AG, Arp PP, Paeper BW, *et al*. *Am J Hum Genet* 2004; **75**: 1032–45

BACKGROUND. Sclerosteosis is characterized by massive, progressive bone overgrowth throughout life. Van Buchem disease is a similar disorder with a less severe phenotype. Mutations in or upstream from the *SOST* gene, which encodes sclerostin, cause these diseases. The association between the *SOST* gene and the bone phenotype and the fact that SOST is highly expressed in osteoblasts and osteocytes led the authors to consider the SOST gene a candidate gene for osteoporosis.

INTERPRETATION. Eight informative polymorphisms were found in the gene and its surrounding sequences. Two of these, –1396delGGA and A79106G, were associated with changes in BMD; the difference between extreme genotypes was 0.2 SD. Furthermore, an additive effect of the –1396delGGA and the *COLIA1* Sp1 polymorphism on BMD was found. No effect was found on the risk of osteoporotic fractures.

Comment

This study investigated a new candidate gene and found polymorphisms that are associated with changes in BMD. These findings need to be validated in other cohorts and subsequently in meta-analyses. The authors speculate that the polymorphisms influence BMD through an effect on gene expression. It is therefore important that this study is followed by studies of the effect of these polymorphisms on the function of the gene. Confirmation of association with BMD and fracture risk in several populations and at least an indication of a biological explanation of the function of the polymorphisms are needed before a genetic variant will be accepted as a risk factor for osteoporosis.

Association between a polymorphism affecting an AP1 binding site in the promoter of the TCIRG1 gene and bone mass in women

Sobacchi C, Vezzoni P, Reid DM, *et al*. *Calcif Tissue Int* 2004; **74**: 35–41

BACKGROUND. The *TCIRG1* gene encodes a component of the osteoclast vacuolar proton pump and previous work has shown that inactivating mutations of *TCIRG1* cause autosomal recessive osteopetrosis. Furthermore, the *TCIRG1* gene is located in the region of chromosome 11 that has been associated with high bone mass traits in humans. The authors therefore examined this gene for genetic variants in 70 women. Five common polymorphisms were identified and they were further examined in 739 unrelated women aged 45–55 years.

INTERPRETATION. The G1102A polymorphism in the promoter region was located in a consensus recognition site for the AP1 transcription factor. This polymorphism was associated with BMD at both the lumbar spine and the femoral neck in pre-menopausal women. None of the other polymorphisms were associated with bone mass.

Comment

This polymorphism in the promoter of the *TCIRG1* gene seems to be associated with peak bone mass. The underlying mechanism is still unknown, but the working hypothesis is that reduced expression of TCIRG1 protein could lead to less active osteoclasts in the pre-menopausal state. In the post-menopausal state the loss of oestrogen is probably a stronger stimulator of osteoclast recruitment and activity, and the effect of this polymorphism diminishes.

LRP5, low-density-lipoprotein-receptor-related protein 5, is a determinant for bone mineral density

Mizuguchi T, Furuta I, Watanabe Y, *et al. J Hum Genet* 2004; **49**: 80–6

BACKGROUND. Osteoporosis–pseudoglioma syndrome (OPPG) is an autosomal recessive disease caused by mutations in the *LRP5* gene. Other mutations in the same gene have been demonstrated to cause high bone mass. From these findings a new hypothesis developed: variations in the *LRP5* gene may cause variations in BMD in the general population and may therefore be involved in the development of osteoporosis. In this study, 481 healthy Japanese women were examined for the influence of more than 100 genetic variants in several genes, including *LRP5*.

INTERPRETATION. Three polymorphisms within the *LRP5* gene were associated with BMD and the variant allele of one of these, C2220T, was significantly more frequent in patients with osteoporosis, defined as a T-score below –2.5. This polymorphism is anonymous, i.e. no change in amino acids is caused by this polymorphism. Furthermore, the polymorphism is in strong linkage disequilibrium with other polymorphisms within the gene, but none of these polymorphisms is likely to explain the association.

Comment

LRP5 is an interesting and obvious candidate gene because of the findings in monogenetic diseases. However, in this study only weak associations with BMD were demonstrated. Furthermore, no plausible biological explanation has been presented by the authors. Much more work needs to be performed before this polymorphism can be considered a risk factor for the development of osteoporosis.

Polymorphisms in the low-density lipoprotein receptor-related protein 5 (LRP5) gene are associated with variation in vertebral bone mass, vertebral bone size, and stature in whites

Ferrari SL, Deutsch S, Choudhury U, *et al. Am J Hum Genet* 2004; **74**: 866–75

BACKGROUND. The background for this study is the same as for the previous mentioned study. In this study 889 Caucasian men and women were examined for the influence of eight previously reported polymorphisms in the *LRP5* gene.

INTERPRETATION. The G2047A polymorphism in exon 9, which causes a change of amino acid at position 667 from valine to methionine, was associated with bone mineral content (BMC), bone area and height in adult men and with bone gain in boys.

Comment

There are many polymorphisms in the *LRP5* gene, but unfortunately only two polymorphisms were examined in both papers on *LRP5*. Many of the polymorphisms are in linkage disequilibrium with each other and it is therefore not possible to conclude whether it is more likely to be the G2047A polymorphism or the C2220T polymorphism that is causing the association with bone mass and size. However, the fact that the G2047A polymorphism causes an amino acid change makes it my favourite.

Characterisation of common genetic variants in cathepsin K and testing for associations with bone mineral density in a large cohort of perimenopausal women from Scotland

Giraudeau FS, McGinnis RE, Gray IC, *et al*. *J Bone Miner Res* 2004; **19**: 31–41

BACKGROUND. Cathepsin K is a cysteine protease that plays a role in osteoclast-mediated bone degradation. Rare, inactivating mutations in the cathepsin K gene cause pycnodysostosis, an autosomal recessive disease characterized by osteosclerosis and short stature. The authors screened the cathepsin K gene for common genetic variants in 130 individuals.

INTERPRETATION. Two intronic single-nucleotide polymorphisms and four tandem repeats in the 5′ end of the gene were identified and subsequently examined in 3000 peri-menopausal women. None of the genetic variants was associated with bone mass.

Comment

This is a very comprehensive study including 3000 peri-menopausal women and it is therefore not likely that polymorphisms in the cathepsin K gene are associated with peak bone mass. However, on the basis of this study, it cannot be ruled out that these genetic variants might influence post-menopausal bone loss or fracture risk.

Candidate gene studies based on knowledge of the function of genes

A deletion polymorphism in the RIZ gene, a female sex steroid hormone receptor coactivator, exhibits decreased response to estrogen *in vitro* and associates with low bone mineral density in young Swedish women

Grundberg E, Carling T, Brandström H, *et al. J Clin Endocr Metab* 2004; **89**: 6173–8

BACKGROUND. Oestrogen plays an important role in the maintenance of bone mass. It exerts its effect on bone by binding to the oestrogen receptor α (ERα). RIZ1 is a specific ERα coactivator that strongly enhances the effect of oestrogen and ERα interaction. Several polymorphisms have been found in the *RIZ1* gene, among them a deletion of a proline at codon 704. This study examined the effect of this polymorphism on the ability of RIZ1 to coactivate the ERα and the influence on BMD in young women.

INTERPRETATION. The effect of the polymorphisms on coactivation of the ERα receptor was examined *in vitro* by transfecting the same cells with both the ERα receptor gene and the *RIZ1* gene in either the wild-type form or in the homozygosity state with respect to the polymorphism, and then stimulating the cells with oestrogen. The cells with the polymorphic variant of *RIZ1* expressed approximately 50% of that which the cells with the normal *RIZ1* gene did in a reporter construct assay. In a group of young Swedish women, those with the normal *RIZ1* gene had higher BMD at the lumbar spine, the hip, in the total body and at the heel. However, the differences were only significant at the heel.

Comment

The *RIZ1* gene is a good candidate gene for osteoporosis, since it is a coactivator and enhancer of the effect of oestrogen through the ERα receptor. In this study it was demonstrated that the P704 polymorphism diminishes this effect *in vitro* and is associated with reduced BMD. This study is interesting because the functionality of the polymorphism has been addressed and seems to fit with the clinical findings. However, the clinical findings suffer from lack of statistical power and more studies on the effect of this polymorphism on BMD and fracture risk – also in older women and men – are needed before this polymorphism can be considered a risk factor for osteoporosis.

Genetic predisposition for adult lactose intolerance and relation to diet, bone density and bone fractures

Obermayer-Pietsch BM, Bonelli CM, Walter DE, *et al. J Bone Miner Res* 2004; **19**: 42–7

BACKGROUND. Lactose intolerance is caused by deficiency of the enzyme lactase. A T13910C polymorphism near the lactase phlorizin hydrolase gene has previously been demonstrated to be strongly associated with adult lactose intolerance. Calcium intake is strongly associated with intake of dairy products and the hypothesis is therefore that the presence of this polymorphism may cause insufficient intake of calcium and subsequent development of osteoporosis. In this study 258 post-menopausal women were examined for the prevalence of this polymorphism.

INTERPRETATION. In women with the C allele, BMD at the hip was reduced by 7–11% and the risk of fractures was increased. Furthermore, aversion to milk consumption was increased and intake of calcium from dairy products was significantly reduced. However, overall calcium intake was not different between genotypes.

Comment

The association between this genetic marker for lactose intolerance and bone mass and fracture risk is estimated to explain 2–4% of the interindividual differences in BMD at different sites. The surprising finding is, however, that the overall calcium intake is not affected by the presence of this polymorphism, suggesting that the women in this study, whose average age was 62 years, have heard about the importance of calcium and adopted a diet that contains other sources of calcium, or take supplements. The authors speculate that the explanation for the reduced BMD could be low calcium intake earlier in life.

Female pre-menopausal fracture risk is associated with Gc phenotype

Lauridsen AL, Vestergaard P, Hermann AP, Moller HJ, Mosekilde L, Nexo E. *J Bone Miner Res* 2004; **19**: 875–81

BACKGROUND. Gc is a multifunctional plasma protein that is also known as vitamin D-binding protein. Gc has two main functions in relation to bone: it is the major carrier protein of vitamin D in plasma, and deglycosylation converts it into a very potent macrophage- and osteoclast-activating factor. On this basis the authors examined the effect of the different phenotypes of Gc on bone phenotype in 595 peri-menopausal women.

INTERPRETATION. The Gc phenotypes did not affect peri-menopausal bone mass but affected pre-menopausal fracture risk significantly. Among women with the Gc1-1 phenotype, 34% had suffered a fracture, whereas only 27 and 14% of women with the

Gc1-2 and Gc2-2 phenotypes had suffered a fracture, respectively. The differences were more pronounced if only fractures caused by low-energy traumas were included.

Comment

At first glance, it is puzzling that the significant effect on pre-menopausal fracture risk was not also reflected in an effect on bone mass. However, it is well known that strong effects on osteoclast activity – as seen in treatment with, for example, bisphosphonates – with highly significant reductions in fracture risk are reflected in rather small changes in BMD. Furthermore, the existence of fractures in the parents increased the risk of fractures in the offspring independently of bone mass [9], suggesting that fracture risk depends on factors other than BMD.

Meta-analyses

Differential genetics effects of ESR1 gene polymorphisms on osteoporosis outcomes

Ioannidis JP, Ralston SH, Bennett ST, *et al.*; GENOMOS Study. *JAMA* 2004; **292**: 2105–14

BACKGROUND. Several studies have been undertaken to investigate the influence of the oestrogen receptor polymorphisms *Xba*I and *Pvu*II in the first intron and a TA repeat polymorphism in the promoter, but so far the results have been inconclusive. The objective of this study was to generate large-scale evidence on whether these three common polymorphisms are associated with BMD and fracture. The meta-analysis included individual-level data from 18 917 individuals from eight European centres.

INTERPRETATION. None of the three polymorphisms had any effect on BMD. However, the risks of vertebral and all fractures were reduced by 35 and 19%, respectively in women with the XX genotype of the *Xba*I polymorphism. The effect on fracture risk was independent of BMD.

Comment

This study is the first publication of a new collaboration in the genetics of osteoporosis, the Genomos Study. This study uses a combination of existing and in some cases published data and data that were obtained within the collaboration. In this way publication bias within the defined study population is avoided. This study emphasizes the need for large-scale studies to clarify the importance of the associations between genetic variants and osteoporosis that have been found in smaller studies.

Interactions between genes and other genes, sex, lifestyle, environment and medical treatment

Oestrogen receptor α genotype, and interactions between vitamin D receptor and transforming growth factor-β1 genotypes are associated with quantitative ultrasound in post-menopausal women

Koh J-M, Nam-Goong IS, Hong JS, *et al. Clin Endocrinol (Oxf)* 2004; **60**: 232–40

BACKGROUND. Polymorphisms in the genes for ER-α, vitamin D receptor (VDR) and transforming growth factor-β (TGF-β) have been examined in many studies and associations have been demonstrated with bone mass, also in meta-analyses for ERα and VDR. The authors examined the effects of these polymorphisms on ultrasound of the calcaneus and also studied interactions between the polymorphisms. Two hundred and six post-menopausal women participated in the study.

INTERPRETATION. The *Xba*I polymorphism in the ERα gene was significantly associated with stiffness index. None of the remaining four polymorphisms was significantly associated with any of the ultrasound parameters. However, significant interaction was demonstrated between both the *Bsm*I and the *Fok*I polymorphism in the VDR gene and the T29C polymorphism in the TGF-β gene. The F allele of the *Fok*I polymorphism is associated with reduced stiffness index in carriers of the T allele of the T29C polymorphism, whereas in carriers of the CC genotype, the F allele is associated with a high stiffness index.

Comment

This study is relatively small, but underscores the importance of interaction between genetic variants. Because of the interaction, the authors were not able to find any overall effects of either the VDR or the TGF-β polymorphism. It is therefore important to take these interactions into account in designing future studies and to include enough individuals to have statistical power to examine possible interactions.

A polymorphic CYP19 TTTA repeat influences aromatase activity and oestrogen levels in elderly men: effects on bone metabolism

Gennari L, Masi L, Merlotti D, *et al. J Clin Endocr Metab* 2004; **89**: 2803–10

BACKGROUND. Oestrogens play an important role in determining BMD in men. An important source of oestrogen in men is the conversion of androgens to oestrogen by

the aromatases. Furthermore, inactivating mutations in the aromatase *CYP19* gene have been associated with low bone mass in young men. A TTTA repeat polymorphism in the *CYP19* gene is associated with osteoporosis in post-menopausal women. The authors therefore examined the effect of this polymorphism on bone mass in 500 elderly men.

INTERPRETATION. Men with a high number of repeats had higher BMD, lower levels of bone turnover markers and higher serum levels of oestradiol. Furthermore, *in vitro* studies of fibroblasts revealed that fibroblasts from men with a high number of repeats had higher aromatase activity.

Comment

The results presented in this paper are convincing. The polymorphism is associated with activity of the enzyme, serum levels of oestradiol and effects on bone mass and bone turnover. However, this TTTA repeat polymorphism is located in the fourth intron and is most likely not functional. It is probably in linkage disequilibrium with other polymorphisms in the *CYP19* gene or in nearby genes. A possible candidate is a C to T substitution in exon 10 of the *CYP19* gene. This polymorphism is associated with number of TTTA repeats, increased aromatase activity, increased aromatase mRNA levels and a switch in promoter usage from I.4 to I.3 [**10**].

Interactions of interleukin-6 promoter polymorphisms with dietary and lifestyle factors and their association with bone mass in men and women from the Framingham Osteoporosis Study

Ferrari SL, Karasik D, Liu J, *et al*. *J Bone Miner Res* 2004; **19**: 552–9

BACKGROUND. Genetic factors explain 40–70% of the interindividual variation in bone mass; the remaining variation is caused by environmental factors and it is assumed that there is gene–gene, environmental–environmental and gene–environmental interaction. These interactions may explain some of the different findings with the same polymorphisms in different populations. In this study the effect on bone mass of a previously described polymorphism at position –174 in the IL-6 (interleukin-6) promoter was examined in 1574 women and men.

INTERPRETATION. No significant association between this polymorphism and BMD was found in the total population. When including lifestyle and dietary factors in the analysis, a significant association was found between BMD and the GG genotype in elderly women, in oestrogen-deficient women and in women with a low dietary intake of calcium.

Comment

If genetic variants have a large impact on the phenotype of traits that are being investigated, these variants can be detected in most populations. However, if we are

also to unravel genetic variants with minor effects, we will need to take interaction with lifestyle and dietary factors into account. These minor effects are likely to be overcome by a bone-friendly lifestyle in younger individuals. In this study, the negative effect of the C174G polymorphism in the promoter of the IL-6 gene on bone mass was uncovered by old age, oestrogen deficiency or low calcium intake. Interaction with age and calcium intake has also been suggested for the *COLIa1* Sp1 polymorphism [**11**] and the VDR *Bsm*I polymorphism [**12**].

Association of a common polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene with bone phenotypes depends on plasma folate status

McLean RR, Karasik D, Selhub J, *et al. J Bone Miner Res* 2004; **19**: 410–18

BACKGROUND. Homocysteinuria is a disease caused by defect methylation of homocysteine to methionine and is associated with reduced bone mass. The conversion of methylenetetrahydrofolate to methyltetrahydrofolate is mediated by the enzyme methylenetetrahydrofolate reductase (MTHFR). Methyltetrahydrofolate is a cofactor for methylation of homocysteine. MTHFR is therefore considered a candidate gene for osteoporosis. Several studies have been conducted already, most of them showing an association between the rare allele of the C677T polymorphism and reduced bone mass. At least from a theoretical point of view, a possible interaction between the effect of the polymorphism and serum levels of folate might exist. In this study, the authors investigated this possible interaction with respect to BMD and quantitative ultrasound (QUS) in 1632 men and women.

INTERPRETATION. In the overall population no effect of the C677T polymorphism was demonstrated. However, in individuals with low serum levels of folate, BMD and QUS were reduced in individuals with the TT genotype, while the opposite association was found in individuals with high levels of folate.

Comment

Several theories have been suggested for the association between C677T and bone. The increased plasma levels of homocysteine associated with the TT genotype might interfere with collagen crosslinking in newly formed collagen. The TT genotype has also been associated with reduced DNA methylation, which is associated with ageing processes. This study suggests that limitations in the amount of substrate for the MTHFR reaction in combination with an enzyme defect results in reduced bone mass, whereas sufficient amounts of folate, the substrate, can overcome this effect.

Methylenetetrahydrofolate reductase polymorphism interacts with riboflavin intake to influence bone mineral density

Macdonald HM, McGuigan FE, Fraser WD, New SA, Ralston SH, Reid DM. *Bone* 2004; **35**: 957–64

BACKGROUND. The background for this study is the same as for the previous study, except in this study the focus was on the influence of several B vitamins on homocysteine metabolism and interaction with the MTHFR polymorphism. The authors examined the interaction between dietary intakes of folate, vitamin B12, vitamin B6 and riboflavin and the MTHFR polymorphism in 1241 peri-menopausal women.

INTERPRETATION. There was no overall effect of either the MTHFR polymorphism or B-complex vitamins when examined separately. However, in women with low intake of riboflavin the TT genotype was associated with reduced bone mass, whereas in women with a high intake of riboflavin the TT genotype was associated with higher bone mass.

Comment

Riboflavin is converted to riboflavin adenine dinucleotide, which is a cofactor for MTHFR. The binding between this cofactor and MTHFR is reduced by a factor 10 in the presence of the MTHFR polymorphism. A plausible explanation for the findings in this study is therefore that when the intake of riboflavin is low the deleterious effect of the MTHFR polymorphism on bone mass is seen, and that a high intake of riboflavin can overcome this effect.

Polymorphisms in the CYP19 and AR genes—relation to bone mass and longitudinal bone changes in post-menopausal women with or without hormone replacement therapy: the Danish Osteoporosis Prevention Study

Tofteng CL, Kindmark A, Brändström H, *et al.*; Danish Osteoporosis Prevention Study. *Calcif Tissue Int* 2004; **74**: 25–34

BACKGROUND. Previously, polymorphisms in both the androgen receptor (*AR*) and the aromatase (*CYP19*) genes have been associated with bone mass and risk of osteoporotic fractures. The purpose of this study was therefore to investigate possible effects of these polymorphisms on early post-menopausal bone loss and interaction with hormone replacement therapy (HRT). The TTTA repeat and the C1558T polymorphisms in the *CYP19* gene and the CAG repeat in the *AR* were examined in 1792 recent post-menopausal women.

INTERPRETATION. Peri-menopausal bone mass and early post-menopausal bone mass were unaffected by the *CYP19* polymorphisms in untreated women. In HRT-treated women BMD increased significantly more in women with a high number of TTTA repeats.

Comment

Most studies that have examined the effect of the TTTA repeat polymorphism in the *CYP19* gene have found that a high number of repeats is associated with increased aromatase activity. How increased aromatase activity can explain the findings in this study is not clear. One could speculate that the higher endogenous levels of oestrogen due to the increased aromatase activity could lead to upregulation of the number of oestrogen receptors and thereby provide the basis for a better response to exogenous oestradiol. More studies are expected on interactions between genetic variants and treatments affecting bone. This might eventually lead to the recommendation of anti-osteoporotic treatments on the basis of genotype.

Conclusion

The last 10 years have demonstrated that unravelling the specific genetic variants that underlie the genetic influence on bone mass and fracture risk is going to be much more difficult than was assumed when research within this area started out. Osteoporosis is a complex genetic trait, with several genes involved and with interactions between these genes and other genes, sex, lifestyle, environment and medical treatments. Many of the genes and polymorphisms involved have probably not been discovered yet. Furthermore, only a few of the polymorphisms that have been associated with osteoporosis have been characterized with respect to functionality. Much work is therefore still to be done in this area before we can join the evidence from these many studies and make a list of genetic variants that bring about the increased risk of low bone mass and osteoporotic fractures associated with genetic factors.

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5

Glucocorticoid-induced osteoporosis

JEFFREY CURTIS, KENNETH SAAG

Introduction

Glucocorticoids are the most common cause of drug-related secondary osteoporosis, and prolonged exposure to high-dose systemic glucocorticoids has a well-established deleterious effect on bone mass. Expert US and international guidelines make specific recommendations regarding strategies to detect and prevent glucocorticoid-induced osteoporosis (GIOP) [1–3]. In some guidelines, it is advocated that individuals beginning glucocorticoid therapy for more than 3 months at a prednisone dose of 5 mg/day or greater should begin bisphosphonate therapy, calcium and vitamin D in conjunction with modification of lifestyle risk factors for osteoporosis. For prevalent glucocorticoid users, risk stratification using bone mineral density (BMD) testing is often recommended to help guide therapy, treatment being suggested for individuals with a T-score of –1.0 or lower. A graphical overview of suggested GIOP management guidelines is shown in Fig. 5.1 [4].

Despite this guidance, many controversies regarding GIOP remain. Evidence for the deleterious effects of low-dose, intermittent pulse and inhaled glucocorticoids on bone mass is inconsistent and needs further study. Although the fracture risk for post-menopausal Caucasian women has been reasonably well characterized, more uncertainty exists for men and younger patient populations receiving chronic glucocorticoid therapy. Identification of at-risk patients on the basis of glucocorticoid dose and duration has proved difficult, partly because glucocorticoid-treated patients may have a lower fracture threshold than similar but untreated individuals, independent of longer-term changes in BMD. Bisphosphonates have proved highly effective in preventing and treating GIOP, but under-treatment with these agents is altogether too common [5] and long-term adherence rates remain suboptimal. Newer agents have been introduced, and new data on older agents have recently been published that shed light on potential mechanisms and the therapeutic efficacy of drugs used to prevent or treat GIOP.

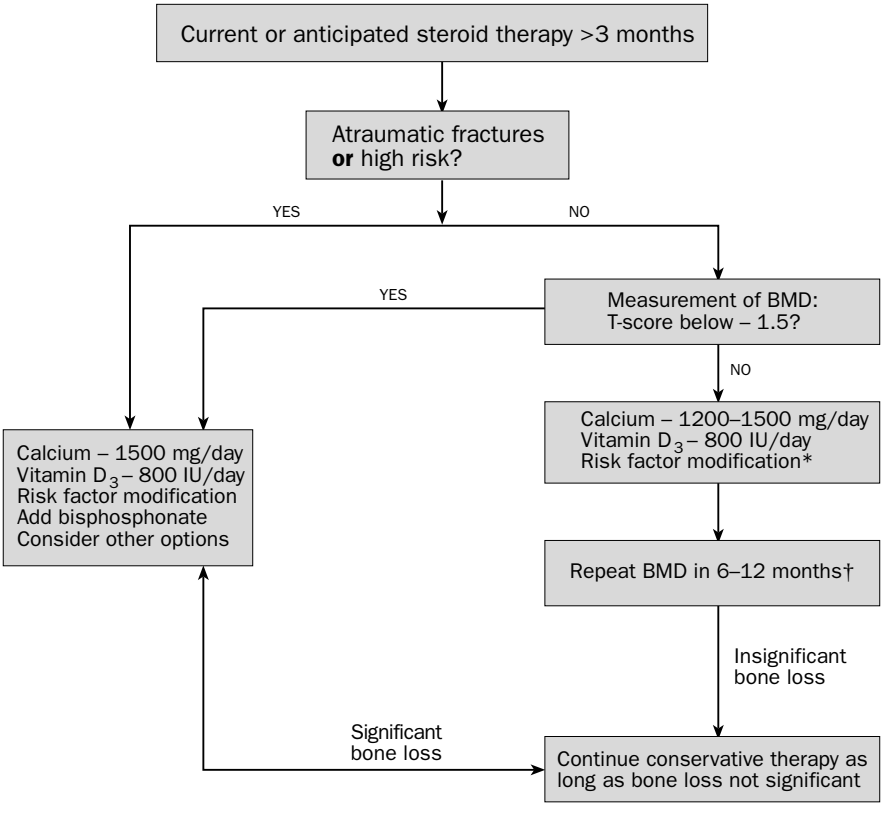

Fig. 5.1 Algorithm for the prevention and treatment of glucocorticoid-induced osteoporosis. *Risk factor modification includes reduction in tobacco, alcohol and caffeine use and increasing weight-bearing exercise. †During the first 2 years of therapy, then less regularly thereafter. Source: Saag (2003) [4].

Bone mineral density loss associated with pulse, low-dose, and inhaled glucocorticoid exposure

The bone loss associated with intermittent pulse, low-dose oral (i.e. prednisolone ≤7.5 mg/day), and inhaled glucocorticoid exposure has been under-studied and remains controversial. Several recent papers provide information that addresses this topic.

Bone loss in patients treated with pulses of methylprednisolone is not negligible: a short-term prospective observational study

Haugeberg G, Griffiths B, Sokoll KB, Emery P. *Ann Rheum Dis* 2004; **63**: 940–4

BACKGROUND. Uncertainty exists regarding the toxicity of repeated short courses of intermittent, pulse glucocorticoid therapy in the absence of oral exposure. In this study, 38 patients with a variety of rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and vasculitis, received sequential courses of intermittent pulse methylprednisolone. The authors measured BMD serially at the spine and hip before and after repeated courses of pulse methylprednisolone. Of the 38 patients, 30 received no antiresorptive therapies, such as oestrogen or a bisphosphonate, and most subjects received concurrent cyclophosphamide. Fourteen were not exposed to concomitant oral prednisolone. The *t* test and analysis of variance (ANOVA) were used to compare changes in BMD at a mean ± SD) of 6 ± 2 months in three groups of patients: (i) intravenous pulse methylprednisolone only; (ii) intravenous pulse methylprednisolone + oral glucocorticoids; and (iii) intravenous pulse methylprednisolone + oral glucocorticoids + an antiresorptive agent.

INTERPRETATION. The 38 patients had a mean age of 48 ± 16 years, and 30 were women. The 14 patients receiving intravenous methylprednisolone only were treated with 5.9 ± 1.7 infusions of methylprednisolone, giving a total prednisolone-equivalent exposure of 4.4 ± 2.0 g. Patients in the intravenous methylprednisolone + oral group had fewer and lower-dose intravenous methylprednisolone infusions but, in conjunction with an average daily prednisolone dose of 10 mg/day, they received a total of 7.6 ± 4.5 g of prednisolone. Average daily prednisolone-equivalent exposure of 31 ± 14 and 31 ± 19 mg/day was similar between the intravenous methylprednisolone and the intravenous methylprednisolone + oral groups. BMD loss was significant in both the pulse methylprednisolone group (–1.7% at the femoral neck and –2.6% at L2–4) and the pulse methylprednisolone + oral group (–4.4% at the femoral neck and –2.1% at L2–4). Compared with pulse methylprednisolone recipients, users of pulse methylprednisolone + oral glucocorticoid had somewhat longer follow-up (325 ± 264 days vs 160 ± 85 days; $P = 0.03$) but did not experience significantly greater bone loss. BMD loss was attenuated in the patients taking calcium ± vitamin D, and BMD actually increased in the 14 patients receiving antiresorptive therapy (+1.6% at the femoral neck and +4.5% at L2–4).

Comment

This study is among the first to provide evidence that intermittent pulse glucocorticoid therapy without concomitant oral glucocorticoid exposure induces significant short-term bone loss. Despite a higher cumulative glucocorticoid dose in the pulse methylprednisolone + daily oral group and a longer follow-up time, bone loss was not significantly greater in this group than in pulse methylprednisolone users. The rapid bone loss observed in the first 6 months following glucocorticoid initiation

and adverse effects on bone quality through decreased bone formation and increased bone resorption [7] may account for the similar magnitudes of deleterious effects on bone observed in these two groups.

GIOP management guidelines are silent for users receiving only intravenous pulses of glucocorticoid therapy. Patients in this study treated with antiresorptive drugs appeared to benefit, and they experienced an increase in BMD at both the femoral neck and the hip. The absence of a fracture outcome, small sample size, lack of a matched control group with similar diseases, and short follow-up time are limitations that need to be noted. However, these data suggest that users of pulse intravenous glucocorticoids have rapid and significant short-term bone loss and should be considered candidates for GIOP prevention using evidence-based therapies such as bisphosphonates.

Effects of low dose prednisone on bone metabolism

Ton F, Gunawardene S, Lee H, Neer RM. *J Bone Miner Res* 2005; **20**: 464–70

BACKGROUND. Although still controversial, modest evidence suggests that low-dose glucocorticoids (e.g. prednisone ≤7.5 mg/day) have a disease-modifying effect in rheumatoid arthritis [8]. However, the relative safety of low-dose oral glucocorticoids is confounded by the effects of systemic inflammation related to the underlying conditions for which glucocorticoids were prescribed. To test hypotheses regarding the effects of low-dose glucocorticoid exposure on the skeleton, this study randomized 50 healthy post-menopausal women without diseases known to affect bone metabolism to 5 mg/day of prednisone versus placebo and examined markers of bone formation (e.g. osteocalcin, bone-specific alkaline phosphatase), bone resorption (e.g. serum collagen N-telopeptide, urinary N-telopeptide/creatinine, free urinary deoxypyridinoline) and BMD changes using dual energy X-ray absorptiometry (DXA). Mixed-model ANOVA was used to compare study end-points and adjustment was made for treatment group, time, vitamin D deficiency (baseline level <15 ng/dl) and several interaction terms. Secondary end-points included changes in blood pressure and self-reported symptoms commonly associated with glucocorticoid use, including changes in mood, appetite and gastrointestinal function.

INTERPRETATION. Baseline characteristics of the 48 women participating were similar except for somewhat lower baseline 25-hydroxyvitamin D levels in the prednisone-treated group (21 ± 8 vs 29 ± 8 ng/ml; P <0.01). No significant changes were observed in bone formation and resorption markers in the placebo group. In contrast, markers of bone formation significantly declined in the prednisone-treated group up to study week 6 (Fig. 5.2). Two of three bone resorption markers were unchanged in the prednisone-treated group, although the third resorption marker, free urinary deoxypyridinoline, declined. No differences in secondary end-points were observed between the two groups.

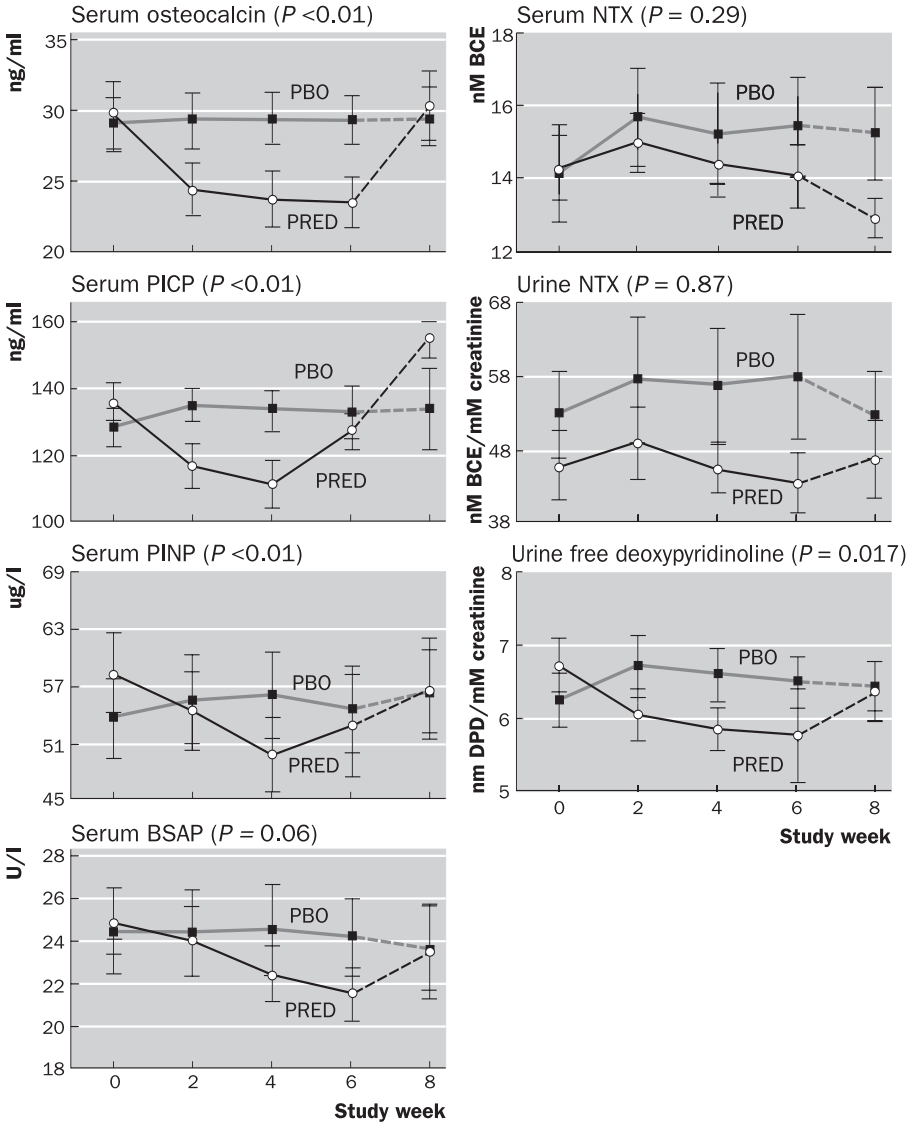

Fig. 5.2 Serial bone formation markers are in the *left column* and bone resorption markers are in the *right column*. Treatment was started after week 0 samples and ended 24 h before week 6 samples. Values are mean ± SE. Source: Ton *et al.* (2005).

Comment

Low-dose glucocorticoids (e.g. prednisone ≤7.5 mg/day) are commonly used in the treatment of rheumatoid arthritis despite uncertainties regarding their effects on bone. This double-blind, randomized, controlled study showed that prednisone even at 5 mg/day adversely affected bone formation in otherwise healthy postmenopausal women. This is concordant with previous studies showing an increased fracture risk in low-dose users [9]. The predominant effect on bone formation markers is consistent with mechanistic studies showing that glucocorticoids principally affect osteoblast function [7].

Although this study was well controlled, it may have limited generalizability in patients with normal gonadal function or in those with inflammatory diseases in which suppression of systemic inflammation with low-dose glucocorticoids may in fact have a positive net effect on bone. However, based on these data, GIOP prophylaxis recommendations may need to be revised to address patients receiving even lower glucocorticoid doses than those specified in some of the existing guidelines.

Loss of bone density with inhaled triamcinolone in Lung Health Study II

Scanlon P, Connett J, Wise R, *et al.*; Lung Health Study Research Group. *Am J Respir Crit Care Med* 2004; **170**: 1302–9

BACKGROUND. Inhaled glucocorticoids are commonly prescribed to patients with chronic obstructive pulmonary disease (COPD). Despite a lack of evidence showing significant long-term improvement in forced expiratory volume in 1 second (FEV1), improvements in symptoms and decreased health services utilization for COPD have been documented [10,11]. The deleterious effect on bone of typical doses of inhaled glucocorticoids remains controversial, with mixed evidence for a decline in BMD and increased fracture risk [12–14]. This discordance may reflect different dosages of inhaled glucocorticoids, limited sample size and duration of follow-up, and the heterogeneity of the treated population. The investigators recruited 412 participants with established COPD, aged 40–69 without 'recent' use of oral glucocorticoids, and measured serial BMD and serum osteocalcin levels (a marker of bone formation). Participants were randomized to six puffs of triamcinolone acetonide twice daily or placebo, and subjects receiving concurrent oral glucocorticoids were excluded. BMD and serum osteocalcin were assessed at baseline and at years 1 and 3. BMD analysis was done using only the 80% of participants with non-missing and technically adequate scans at baseline and 1 and 3 years. Descriptive statistics and general linear models were used for analysis.

INTERPRETATION. The mean age of the 412 participants was 56 years, and 97% were Caucasian. Of the 196 women, approximately 90% were peri- or post-menopausal and 60% were receiving hormone replacement therapy. No significant differences in BMD at 1 year were observed between the two groups. By year 3, inhaled glucocorticoid users had experienced a change of –2.0 ± 4.4% in femoral neck BMD compared with –0.22 ± 4.4% in the placebo group (P<0.001). Lumbar spine BMD decreased by

0.30 ± 3.5% among inhaled glucocorticoid users and increased by 1.5 ± 4.1% in the placebo group at 3 years. Osteocalcin levels had declined at 1 year in both groups and were non-significantly different by year 3. Thirty-eight participants (9%) reported a new fracture. More than half of these were at the spine or hip, and fracture incidence was similar in the two groups. Sixty-eight of the subjects received 'short courses' of oral glucocorticoids during the course of the study ($n = 34$ in each study arm), but even after controlling for this exposure, the association between inhaled glucocorticoid and change in BMD remained significant at both the femoral neck and the lumbar spine.

Comment

This study provides evidence collected in a prospective, randomized trial that 1200 μg/day of inhaled triamcinolone significantly reduced BMD at 3 years compared with placebo. The authors observed greater BMD loss at the femoral neck compared with the lumbar spine, which was unexpected given that trabecular-rich vertebrae often show the earliest changes following glucocorticoid therapy. The paradoxical effect at the lumbar spine, more pronounced for the placebo-treated group, may have been a consequence of artefact due to degenerative changes in the spine. The decline in BMD may also have been attenuated in both treated and placebo groups among women who were concomitantly taking hormone therapy, although the authors did not test this hypothesis specifically.

Although the 38 fractures reported in this study lacked radiographic confirmation, the positive predictive value of self-reported fractures observed in population-based studies typically exceeds 80% [**15**]. Although the modest decline in BMD at 3 years observed for patients receiving inhaled glucocorticoids might cause minimal morbidity in otherwise healthy patients, the relatively high short-term fracture incidence seen in the overall cohort suggests that COPD patients represent a group at high risk of fracture. Despite a paucity of guidance from GIOP management guidelines, BMD monitoring appears prudent, at a minimum, in patients chronically receiving moderate to high doses of inhaled steroids. Alternatively, empirical treatment with an antiresorptive agent for high-risk patients beginning long-term inhaled glucocorticoid therapy (which may be lifelong for many patients) may be reasonable.

Fracture epidemiology in chronic oral glucocorticoid users

A substantial literature describes appreciable BMD loss associated with chronic and high-dose glucocorticoid use. One limitation of conclusions from studies using BMD end-points is the expanding evidence that current glucocorticoid use alters the fracture threshold independently of changes in BMD [**16,17**]. However, well-powered studies that quantify the increased risk of fracture associated with glucocorticoids, especially in low doses, have been much fewer in number.

One population-based study utilizing the General Practitioner Research Database (GPRD; the computerized medical records of approximately 7 million patients treated by general practitioners in the UK) matched 244 235 glucocorticoid users with an equal number of controls receiving non-systemic glucocorticoids. Among these individuals (mean age 57 years), the risks of non-vertebral fractures (relative risk [RR] 1.6; 95% confidence interval [CI] 1.5–1.8), hip fractures (RR 2.3; CI 1.9–2.7) and vertebral fractures (RR 5.2; CI 4.3–6.3) were significantly greater among prednisolone users receiving at least 7.5 mg/day [**18**] compared with controls. A significantly increased risk was also observed at each of these fracture sites among individuals receiving 2.5–7.5 mg of prednisolone per day (Fig. 5.3). Increased fracture risk was seen as early as 3 months after beginning glucocorticoid therapy.

Despite the rigorous methodology used, few studies have replicated these results and uncertainties remain about fracture risk in younger individuals, men and low-dose users. Moreover, despite an expanding epidemiology literature describing fracture risks in large populations, quantification of the absolute fracture risk for individual glucocorticoid users has been elusive, especially for patients living in areas where BMD measurement may not be widely available. Two recent studies address these gaps.

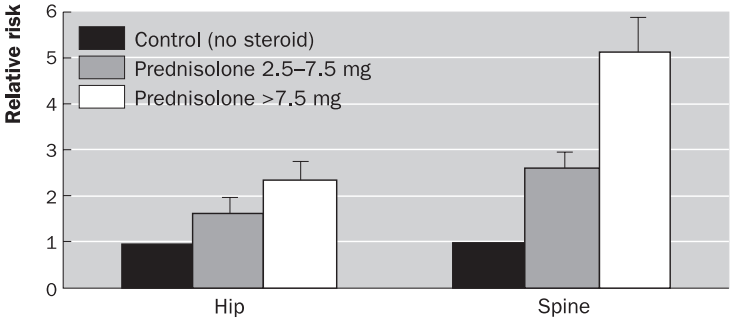

Fig. 5.3 Fracture risk is increased even in low-dose glucocorticoid users. Source: van Staa *et al*. (2000) [**18**].

Oral glucocorticoid use is associated with an increased risk of fracture

Steinbuch M, Youket T, Cohen S. *Osteoporos Int* 2004; **15**: 323–8

BACKGROUND. These authors examined associations between oral glucocorticoids and fractures among managed care enrollees in the US. Using a database that included claims from more than 200 health insurance companies, the 1-year fracture risk among oral glucocorticoid users was compared with that in an unexposed

comparison group. All individuals were between 18 and 64 years of age, and unexposed patients were matched on age (±2 years), sex and index date of their glucocorticoid prescription (versus a random non-glucocorticoid prescription for the control group). No matching or analytical adjustment for disease or the indication for glucocorticoid therapy was made. Because of uncertainties regarding the actual daily glucocorticoid dose, particularly for patients on a glucocorticoid taper, dosage was categorized as low (≤10 mg of prednisone per day) and high (>10 mg/day). Users were also characterized as short-term (≤90 days) versus long-term (>90 days) and sporadic (gaps between prescriptions longer than 20% of total exposure time) versus continuous. Survival analysis compared the fracture hazard between the two groups.

INTERPRETATION. A total of 17 957 oral glucocorticoid users were identified, with mean age 46 ± 0.1 years. Pulmonary diseases were most commonly associated with glucocorticoid therapy (24% of subjects). Combining the high and low glucocorticoid doses, a significantly increased risk of fracture was observed for women in all age groups (RR 2.2; 95% CI 1.9–2.5) and the risk was similar, although smaller, for men (RR 1.5; 95% CI 1.3–1.8). The fracture risks associated with dosage, duration and pattern of use are described in Table 5.1.

Comment

These authors reported an increased risk of hip fracture (RR 1.7; 95% CI 1.0–2.9) and vertebral fracture (RR 2.7; 95% CI 1.8–4.2) among glucocorticoid users receiving up to 10 mg of prednisone daily. An increased risk of wrist/forearm fractures was not observed. Combining all glucocorticoid doses, an increased fracture risk was observed even among individuals as young as 18–30 (RR 1.6; 95% CI 1.2–2.1). Limitations of the study included a lack of radiographic confirmation of fractures and the potential for confounding by disease indication (i.e. patients at higher fracture risk are more likely to receive higher glucocorticoid doses). Dichotomizing the prednisone dose at 10 mg also precluded analysis of whether a lower dose of glucocorticoid might be safe. Nevertheless, this study adds additional weight to the evidence for an increased fracture risk in men and younger women receiving glucocorticoids, even among those receiving lower doses or with a limited duration of exposure.

A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids

van Staa TP, Geusens P, Pols HAP, De Laet C, Leufkens HGM, Cooper C. *Q J Med* 2005; **98**: 191–8

BACKGROUND. Although several studies document an increased fracture risk among glucocorticoid users in large populations, it is often uncertain how to assess an individual's fracture risk and in turn make appropriate treatment decisions among the diverse persons who receive glucocorticoids. With the goal of identifying an

Table 5.1 Relative risk of fracture (95% CI) overall and adjusted for the amount, duration and pattern or oral glucocorticoid use

	Fracture site				
	Hip	**Vertebral**	**Wrist/forearm**	**Non-vertebral**	**Any fracture**
Oral GC use					
Number of fractures	63	119	102	1008	1089
Incidence density per 1000 person-years	1.86	3.53	3.02	30.49	33.01
Overall rate, unadjusted	2.15* (1.39–3.31)	3.30* (2.28–4.77)	1.17 (0.88–1.55)	1.81* (1.63–2.00)	1.89* (1.71–2.09)
Overall rate, covariate adjusted	1.87* (1.19–2.94)	2.92* (2.00–4.27)	1.03 (0.76–1.38)	1.68* (1.52–1.87)	1.75* (1.58–1.94)
Amount					
Low (≤10 mg)	1.73* (1.04–2.90)	2.73* (1.80–4.15)	1.09 (0.78–1.53)	1.81* (1.61–2.04)	1.86* (1.66–2.09)
High (>10 mg)	2.04* (1.22–3.41)	3.15* (2.07–4.79)	0.95 (0.66–1.38)	1.53* (1.35–1.74)	1.62* (1.43–1.84)
Test for trend	$P<0.01$	$P<0.001$	ns	$P<0.001$	$P<0.001$
Duration					
<90 days	1.69* (1.06–2.70)	2.88* (1.96–4.23)	1.07 (0.80–1.44)	1.68* (1.51–1.87)	1.75* (1.58–1.94)
≥90 days	3.41* (1.72–6.75)	3.27* (1.82–5.87)	0.65 (0.33–1.29)	1.69* (1.38–2.07)	1.76* (1.45–2.14)
Test for trend	$P<0.001$	$P<0.001$	ns	$P<0.001$	$P<0.001$
Pattern					
Sporadic	1.68 (0.95–2.99)	2.26* (1.41–3.64)	0.58* (0.36–0.94)	1.06 (0.91–1.24)	1.13 (0.97–1.31)
Continuous	1.98* (1.22–3.21)	3.28* (2.21–4.87)	1.27 (0.93–1.73)	2.01* (1.80–2.24)	2.07* (1.86–2.31)
Test for trend	$P<0.01$	$P<0.001$	ns	$P<0.001$	$P<0.001$

*Relative risk was statistically significant at the 0.05 level compared with unexposed group.
ns, not significant.
Source: Steinbuch *et al.* (2004).

absolute fracture rate for which treatment is cost-effective, several risk models for post-menopausal osteoporosis have been developed previously and have included a variety of factors to derive estimates of an individual's absolute fracture risk [19,20]. Indeed, international attention is shifting to the concept of the absolute risk rather than the relative risk of fracture [21]. However, similar risk models for glucocorticoid users have been unavailable until recently. These authors sought to develop a predictive model that would incorporate age, gender and glucocorticoid dose and provide an estimate of the absolute risk of fracture. This information could be used to guide treatment for individual patients and might also influence health policy decision-making. They used 10 years of data in the GPRD and studied individuals 40 years and older who received at least one glucocorticoid prescription. Glucocorticoid dose and duration were coded using primary care physicians' notes. A variety of covariates were available, including the indication for glucocorticoid treatment, previous fracture, chronicity of glucocorticoid use, tobacco use, and recorded falls in the previous 6 months. The 5-year risk of fracture was modelled using Cox proportional hazards, and the risk coefficients of relevant covariates were converted into an integer risk score and summed to derive an overall score. Model discrimination and calibration were assessed and the model was validated using an external data set (the Health Improvement Network Research Database).

INTERPRETATION. The study cohort consisted of 191 752 individuals who received a mean of eight glucocorticoid prescriptions. Age, female gender, rheumatoid arthritis, the number of other comorbid diseases, a body mass index below 20, a history of falls, taking more than 2.5 mg prednisolone daily and previous fracture all conferred a significantly increased risk of fracture. The results of the risk score derivation (Table 5.2) were used to calculate the absolute fracture risk (Fig. 5.4). Discrimination was examined using receiver operating characteristic (ROC) curves, which plot sensitivity against 1 minus specificity. The area under the ROC curve (a measure of discrimination) was 0.70 for clinical osteoporotic fracture and 0.78 for hip fracture. Validation of the model against an external data set showed similar predictive ability compared with the data set used for model derivation. No specific recommendations regarding treatment thresholds based on absolute fracture risk were offered but were mentioned as an appropriate next step.

Comment

The authors derived a prediction model that was able to provide absolute 5-year fracture risk estimates among chronic glucocorticoid users. Despite the lack of information on BMD, a notable limitation, this work is among the first to provide estimates of fracture risk that are applicable to individual glucocorticoid-treated patients. Other limitations of the study included missing glucocorticoid prescription data for 29% of the subjects, which had to be imputed from patients of similar age and gender, and glucocorticoid dosage modelled as a fixed average daily dose rather than as a time-dependent covariate. Although the study was population-based, the generalizability of these results may be limited to specific patient populations. However, the results provide guidance both for individuals and for groups of patients receiving glucocorticoids and may help clarify thresholds for interventions to prevent GIOP using absolute rather than relative risk estimates.

Table 5.2 Risk score of fracture for glucocorticoid exposure, age, sex, risk factors and indications for glucocorticoid use

	Clinical osteoporotic fracture			Femur/hip fracture			Clinical vertebral fracture		
Age (years)	50	65	80	50	65	80	50	65	80
Daily 7.5 mg	8	6	5	12	8	4	15	14	12
Daily 15 mg	11	9	7	15	10	5	20	18	16
	All ages			All ages			All ages		
Age (for each 10 years of age)	4			8			4		
Male sex	–6			–6			–4		
Body mass index <20	3			6			3		
Body mass index ≥26	–1			–4			–1		
Smoker	1			2			1		
History of fall in 6 months before	8			7			6		
Fracture history before glucocorticoid use	6			5			7		
Other incident osteoporotic fracture during glucocorticoid treatment	–			4			5		
Disease/drug risk factor (for each factor)	2			3			2		
Recent hospitalization for underlying glucocorticoid indication	4			4			9		
Indication for oral glucocorticoid treatment									
RA	1			4			3		
Non-infectious enteritis and colitis	1			2			3		

Source: van Staa *et al*. (2005).

Therapies to prevent or treat glucocorticoid-induced osteoporosis

Substantial evidence supports the use of antiresorptive agents such as bisphosphonates to prevent or treat GIOP. Despite evidence supporting the efficacy of bisphosphonates, approximately one-fourth or more of bisphosphonate users discontinue within 1 year [**22**]. Although newer bisphosphonates may offer still unproven yet potentially more convenient and/or better-tolerated dosing regimens, additional therapies for GIOP are needed. The use of human parathyroid hormone for GIOP suggests promise for this agent in improving BMD and reducing the risk of fracture [**23**], although evidence for its safety and fracture efficacy is still accumulating. As

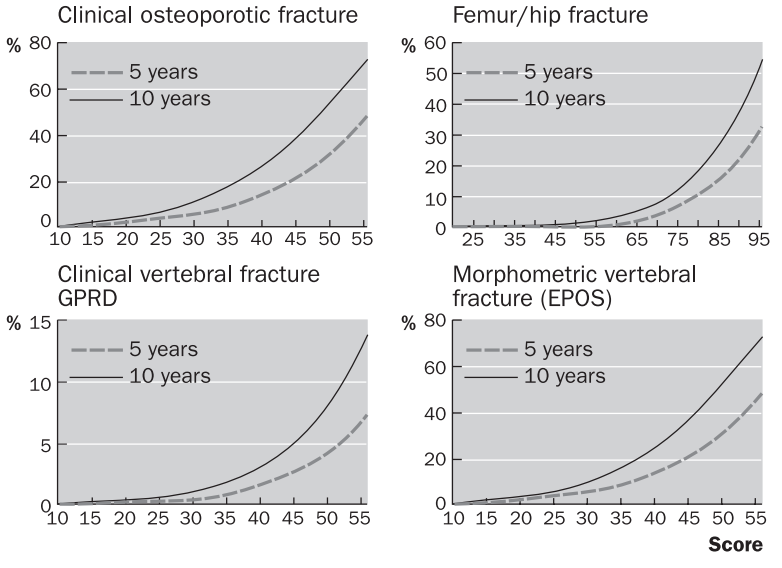

Fig. 5.4 Relation between risk score and risk of fracture for 5- and 10-year periods. Source: van Staa *et al.* (2005).

for post-menopausal osteoporosis, combination therapy for GIOP remains of interest but optimal regimens have not yet been defined.

A search for newer agents that may protect against glucocorticoid-associated bone loss and a closer scrutiny of therapies already available have prompted several recent publications focused on this topic. While some of these newer agents may not be more potent than existing therapies if used alone, they may be better tolerated or used as part of combination therapy with existing agents.

Vitamin K2 inhibits glucocorticoid-induced bone loss partly by preventing the reduction of osteoprotegerin (OPG)

Sasaki N, Kusano E, Takahashi H, *et al. J Bone Miner Metab* 2005; **23**: 41–7

Background. The precise mechanism(s) by which glucocorticoids adversely affect bone metabolism remain unclear. One important pathway involves the interaction of receptor activator of nuclear factor-κ B ligand (RANKL) with its receptor, RANK. Osteoprotegerin, a member of the tumour necrosis factor receptor superfamily, antagonizes this interaction and inhibits the differentiation and function of osteoclasts. Recent work suggests that glucocorticoids suppress osteoprotegerin [24,25] and may thereby promote bone loss in this manner, among other putative

mechanisms. Vitamin K_2 (menatetrenone), approved in Japan for both the prevention and the treatment of osteoporosis, has been shown to reduce fractures [26] and prevent glucocorticoid-associated bone loss [27]. It has been shown to inhibit osteoclastogenesis, promote 1,25-dihydroxyvitamin D3-induced mineralization by human osteoblasts, enhance the expression of osteoprotegerin by upregulating the number and/or activity of bone marrow stromal cells, and inhibit RANKL mRNA expression in stromal cells [28]. This prospective study attempted to elucidate mechanisms of glucocorticoid-associated bone loss and the protective effects of vitamin K_2 in 20 patients scheduled to receive glucocorticoid therapy for glomerulonephritis. Patients received initial doses of approximately 40 mg/day of prednisolone, which was subsequently tapered to 10 mg/day by 12 months. Participants were randomly assigned to receive vitamin K_2 15 mg three times daily or not. Bone formation was assessed using serum osteocalcin and bone-specific alkaline phosphatase, and bone resorption was assessed by measuring serum tartrate-resistant acid phosphatase (TRAP) levels. Lumbar spine BMD was assessed using DXA at baseline and 6 and 12 months after starting glucocorticoid therapy. Differences between treatment groups for bone turnover markers were analysed using ANOVA, and BMD was compared using paired *t* tests.

INTERPRETATION. No baseline differences in bone biomarkers or BMD between treatment groups were observed. Osteoprotegerin declined significantly to 77 ± 4% of the baseline value in the group that did not receive vitamin K_2, compared with no observed change in the group that did receive vitamin K_2 (Fig. 5.5). Bone formation markers had declined in both groups at 3 months but were significantly higher in the vitamin K2-treated group at 12 months compared to baseline, whereas no statistically significant change was observed in the untreated group. The expected increase in the bone resorption marker (TRAP) was significantly attenuated in the vitamin K_2-treated group (Fig. 5.6). A significant decline in BMD was observed in the group that did not receive vitamin K_2 (from 0.66 ± 0.04 to 0.55 ± 0.04 g/cm^2; P <0.001), whereas subjects who received vitamin K_2 experienced no significant changes in lumbar spine BMD at 12 months.

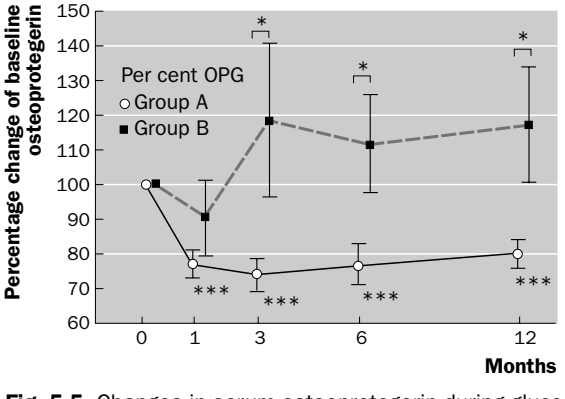

Fig. 5.5 Changes in serum osteoprotegerin during glucocorticoid treatment. Data are expressed as percentages of baseline value (mean ± SEM). *P <0.001 vs baseline value; †P <0.05 between groups. Group A, vitamin K; Group B, placebo. Source: Sasaki *et al*. (2005).

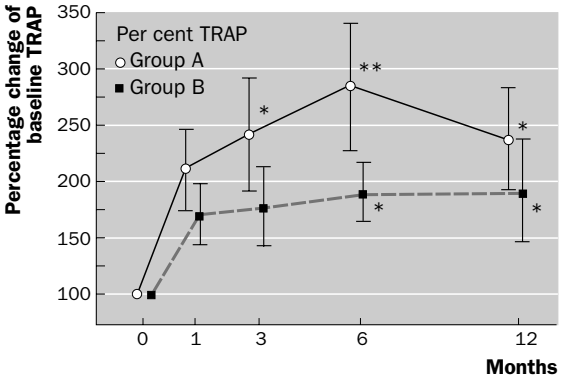

Fig. 5.6 Changes in serum TRAP (a marker of bone resorption) during glucocorticoid treatment. Data are expressed as percentages of baseline value (mean ± SEM). *P <0.05; †P <0.01 vs baseline value. Group A, vitamin K; Group B, placebo. Source: Sasaki *et al*. (2005).

Comment

This study provides support for the efficacy of vitamin K_2 in retarding glucocorticoid-associated bone loss in humans. It also provides evidence for a potential mechanism suggesting that glucocorticoid-associated reduction in osteoprotegerin levels can be attenuated with vitamin K_2. Markers of bone formation had initially declined at 3 months in both the treated and the untreated group, which may be a consequence of high-dose glucocorticoid exposure that could not be mitigated by the use of vitamin K_2. Over time, markers of bone formation rose and were significantly greater in the vitamin K-treated group as patients tapered their glucocorticoid therapy, suggesting that vitamin K_2 may be efficacious only in patients receiving lower glucocorticoid doses. Despite the favourable effects of vitamin K on osteoprotegerin levels (Fig. 5.5), subjects still had significant and sustained increases in bone resorption markers, suggesting that reduced osteoprotegerin levels account only partially for glucocorticoid-induced bone loss. Moreover, osteoprotegerin is not entirely bone-specific, and serum levels can be affected by age, renal function and vascular and other non-skeletal diseases [**29**]. Other factors besides osteoprotegerin that influence osteoclast activity and, in particular, osteoblast activity are also affected by glucocorticoids.

Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies

De Nijs RNJ, Jacobs JWG, Algra A, Lems WF, Bijlsma JWJ. *Osteoporos Int* 2004; **15**: 589–602

Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis

Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY. *Calcif Tissue Int* 2005; **76**: 176–86

Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate

Richy F, Ethgen O, Bruyere O, Reginster J. *Osteoporos Int* 2004; **15**: 301–10

BACKGROUND. Vitamin D analogues have been used for the prevention of GIOP, with mixed evidence for their effectiveness [30]. Biologically active vitamin D analogues promote intestinal calcium absorption and may directly stimulate osteoblasts [31], which possess receptors for vitamin D hormone. Active vitamin D analogues (e.g. calcitriol, alfacalcidol) can conceivably override the tight regulation of vitamin D levels controlled by activity of the 1α-hydroxylase enzyme in the kidney. Three meta-analyses were recently published reporting BMD changes and reduction in fracture risk in glucocorticoid-treated patients. Despite modest differences in the methods used to conduct literature searches, assess study quality, pool results and test for heterogeneity, their results were similar. Changes in BMD were reported as effect sizes (the difference in means between treatment groups divided by the pooled standard deviation). Fracture benefits were reported as relative risk reductions.

INTERPRETATION. In a pooled analysis of eleven studies (De Nijs *et al.*) with follow-up times ranging from 6 to 36 months, the effect size of active vitamin D metabolites compared with a control group consisting of no treatment, placebo, native vitamin D and/or calcium alone was moderate, at 0.35 (95% CI 0.18–0.52). The results from seven studies showed that vitamin D was less potent than bisphosphonates, with a pooled effect size of –1.03 (95% CI –1.71 to –0.36). The pooled estimate of the relative risk reduction for vertebral fractures was 0.56 (95% CI 0.35–0.92) for vitamin D but was significantly inferior to that for newer-generation bisphosphonates. For several of the comparisons, heterogeneity in the results was seen; under these circumstances, random effects models were used to provide the more conservative estimates described above. Using funnel plots, no publication bias was observed.

The two meta-analyses by Richy *et al*. had similar results to that by De Nijs *et al*. The authors used Jadad scores to formally evaluate the methodological rigour of the included studies. The 2004 paper included five trials (median duration 24 months). The effect size for vitamin D to maintain lumbar spine BMD in patients with GIOP was 0.43 ($P<0.001$), which was similar to the estimate (effect size 0.41; $P=0.001$) that included only trials with Jadad scores above 80% (indicating higher-quality studies). In the more recent paper published by the same authors, results from trials of native vitamin D (e.g. ergocalciferol, cholecalciferol) were included. The effect sizes for BMD

preservation for both vitamin D analogues (effect size 0.38; $P<0.001$) and native vitamin D (effect size 0.41; $P=0.002$) were similar and statistically greater than 0. Only two studies provided a direct comparison between active and native vitamin D, which favoured the active form of vitamin D (effect size 0.31; $P=0.02$), largely due to differences at the hip. A significant reduction in vertebral fractures was seen in patients treated with alfacalcidol (rate difference 15%; 95% CI 7–25), based on the results of one superiority trial [**32**].

Comment

Despite enthusiasm for using meta-analyses to combine multiple trials that may be underpowered to detect small differences between treatments, caution in interpretation of their results must be advised. Differences in patient populations, length of follow-up, supplementation with calcium and the dose and preparation of vitamin D used all create variation that potentially compromises the validity of a meta-analysis. In certain situations, the results of a single, well-designed head-to-head trial may be more informative than extrapolating results from indirect comparisons between multiple dissimilar studies. For example, one past head-to-head randomized controlled trial showed no significant differences in efficacy between ergocalciferol and calcitriol for GIOP [**33**].

Despite these limitations, the results of these meta-analyses suggest that active vitamin D does have efficacy in both preserving BMD and reducing fracture risk in patients with GIOP. These results are consistent with an earlier meta-analysis showing efficacy for vitamin D in glucocorticoid-treated patients [**30**]. Compared with bisphosphonates, vitamin D appears less potent in preserving BMD and therefore is not recommended over bisphosphonates for high-risk patients. Although active vitamin D preparations are less costly than bisphosphonates and are usually well tolerated, monitoring for hypercalcaemia and hypercalcuria is advised. Potential advantages of vitamin D include decreased cost and wider availability in some countries. In summary, these data support the use of vitamin D analogues in patients with or at risk of GIOP, especially when more potent antiresorptive agents are not available, not tolerated or are contraindicated.

Five-year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long-term oral and/or inhaled glucocorticoids

Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM. *Thorax* 2004; **59**: 761–8

BACKGROUND. This investigation examined whether etidronate and/or calcium alone or in combination would reverse or reduce bone loss and decrease fractures over 5 years in patients treated chronically with inhaled and/or oral glucocorticoid exposure. This randomized, double-blind, placebo-controlled trial recruited 352

patients with asthma among 40 centres and randomized them to (i) etidronate + calcium carbonate; (ii) etidronate alone; (iii) calcium carbonate alone; and (iv) placebo. Etidronate was given for 2 weeks every 3 months and calcium was provided as calcium carbonate 500 mg daily. Baseline spine radiographs were compared with follow-up radiographs at 5 years and graded using the semi-quantitative methods recommended by Genant *et al.* [34]. Data on glucocorticoid dosage, activity level, BMD and new symptomatic fractures were collected by questionnaire annually from the treating physicians at each facility. Fracture incidence was assessed using contingency tables and Mantel–Haenszel tests. BMD changes were assessed using log-transformed repeated measures ANOVA.

INTERPRETATION. Statistical power calculations for this study demonstrated that 750 patients would be necessary to have 80% power to show a decline in fracture risk from 8% to 3%; however, only 349 patients were recruited and available for analysis. The mean age was 60 ± 7 years and 58% of the cohort was male. Among the 171 patients receiving continuous prednisolone, mean duration of use was 10 ± 5 years at a daily dose of 9 ± 8 mg/day. The mean daily dose of inhaled glucocorticoids was 1517 ± 595 μg daily of beclometasone dipropionate or equivalent used for 7 ± 5 years. Two hundred and five participants had baseline and follow-up X-rays at 5 years. Fifty-seven (16%) of participants had died by 5 years, but no differences between treatment groups were seen. There were 28 new symptomatic fractures and 33 new asymptomatic vertebral fractures, giving a total of 61 new fractures (incidence 17.5%). Individuals with prevalent fracture at baseline (34% of the cohort) had a higher fracture rate (24%) than those without prevalent fractures (14%).

In the primary intention-to-treat analysis, no significant differences in fracture rates were observed between any of the treatment groups. Among women, the odds ratio for new symptomatic fracture was 0.39 (95% CI 0.14–0.99) among those receiving etidronate but was not significant in men. In the etidronate-treated group, BMD at the spine (Fig. 5.7) increased by 4.1% (95% CI 2.0–6.2) but was unchanged at the hip. Most of the change in BMD was seen in the first 2 years, with effects maintained over 5 years. Change in BMD in the calcium group was not significantly different from that in the placebo group. More adverse events were reported among the etidronate users (20 vs 3%; $P = 0.001$), the most common of which was gastrointestinal upset.

Comment

This study is the longest randomized controlled trial for the prevention of GIOP among users of oral and/or inhaled steroids. Fracture incidence was high over 5 years even among individuals receiving only inhaled (and not oral) glucocorticoids (17% rate of new fractures). The trial was not designed to address the controversy regarding whether the increased fracture rate seen in asthma patients was related more to glucocorticoid exposure or the underlying disease itself [**14**].

Etidronate, either alone or with calcium, failed to show a reduction in fracture risk, although it did suggest benefit for women in a *post hoc* analysis. Etidronate significantly increased BMD at the lumbar spine, and a trend suggested more modest benefit at the hip but was not significant. There was no incremental benefit seen with calcium, but the dose of calcium used (500 mg daily) was lower than typically

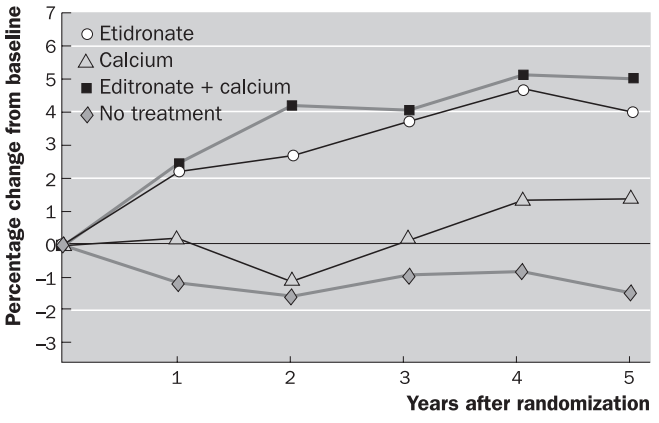

Fig. 5.7 Mean percentage changes in bone mineral density (BMD) from baseline at L2–L4. Source: Campbell *et al*. (2004).

recommended from all sources (1200–1500 mg daily) in some guidelines [1]. Vitamin D supplementation was not provided, nor was vitamin D status assessed. Thus, vitamin D deficiency may have limited the absorption of the modest calcium doses offered. Although bisphosphonates that are more potent and may be better tolerated than etidronate are now available, these data suggest that improvements in BMD associated with this class of medications can be sustained over a longer time frame than previously described in glucocorticoid-treated patients.

Conclusion

Although glucocorticoids have long been recognized to be toxic to bone when used in high doses for prolonged periods, recent data suggest that users receiving intermittent pulse, low-dose and inhaled glucocorticoid exposure experience significant bone loss. Although these losses may be modest over short periods, the high background fracture rate among the individuals who most often receive these therapies underscores the need for more aggressive GIOP prevention strategies. Data showing an increased fracture risk in both genders, even among younger individuals, suggests that clinicians need to be vigilant for all patients prescribed systemic glucocorticoids chronically, and to consider the use of the various preventive therapies for which evidence is rapidly growing.

As is the case with post-menopausal osteoporosis, quantification of the absolute fracture risk over a 5- or 10-year period in glucocorticoid-treated patients remains a desirable goal. Recent data suggest that this is feasible and will allow simple estimation of the fracture risk for individuals—similar to the use of risk scores for patients with cardiovascular diseases. This should not only guide clinicians in

making informed treatment decisions but is also likely to help policy-makers establish treatment thresholds for populations based on the absolute fracture risk.

Although watchful waiting or calcium alone has proved ineffective in preventing or treating GIOP in most patients, the addition of vitamin K and/or vitamin D may be appropriate adjunctive therapies for certain patients, particularly those at lower risk of fracture. Existing data support the use of a bisphosphonate for most at-risk persons, and the benefit of the newer formulations of bisphosphonates (e.g. zolendronic acid, ibandronate) for GIOP is currently under study, as are different formulations of human parathyroid hormone. Combination therapy with two or more osteoporosis medications, used either concurrently or sequentially, remains of high interest and is also under investigation. A refined understanding of the mechanisms by which glucocorticoids affect osteoblasts and/or osteoclasts will probably prove fruitful in identifying future targets for intervention.

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6

Secondary osteoporosis

M SUSAN BURKE, SOLOMON EPSTEIN

Introduction

Primary osteoporosis is due to a slow decline in bone mass and quality because of age-related changes that occur in both sexes, compounded in women by the additional effect of menopause. Osteoporosis exacerbated by medications or other disease processes constitutes secondary osteoporosis, and its spectrum crosses multiple disciplines. Although more commonly seen in men and pre-menopausal women, secondary causes can affect all demographic groups and may account for up to 30% of the osteoporosis seen in women and 64% of that seen in men [1]. The list of secondary causes of osteoporosis or low bone mass is ever-expanding; those currently known are shown in Table 6.1.

The pathogenesis of secondary osteoporosis is diverse, and often involves multiple contributing mechanisms. For example, the low bone mass seen with organ transplantation can be quite complex, resulting from the underlying disease process, the physical inactivity of the patient for months or years prior to transplantation, the patient's age, race or menopausal status, the use of glucocorticoids, heparin and immunosuppressive agents, and baseline calcium, vitamin D and tobacco and alcohol intake. The loss of bone mineral density (BMD) in the months after transplantation can be dramatic; osteoporosis can be seen in almost one half of transplant recipients and vertebral fractures have been reported in up to one third of these patients [2].

Organ transplantation, glucocorticoid use, hyperparathyroidism—such commonly known causes of secondary osteoporosis may be easily identified by most practitioners. Other contributory factors have only more recently been noted to increase the risk of osteoporosis or fracture. Ironically, some of these are the result of treatment of other diseases which in their own right may predispose individuals to bone abnormalities. For example, the use of aromatase inhibitors and gonadotropin-releasing hormone (GnRH) agonists for the treatment of breast cancer and prostate cancer, respectively, affects the contribution of sex steroids to the bone remodelling cycle, allows an imbalance of bone resorption over bone formation, and results in a decrease in BMD and an increase in fractures. Additional medications recently identified as inducing osteoporosis include antipsychotics,

Table 6.1 Secondary causes of low bone mass or osteoporotic fractures

Endocrine
- Acromegaly
- Cushing syndrome
- Hyperthyroidism
- Hyperparathyroidism
- Diabetes mellitus
- Hyperprolactinaemia
- Hypogonadism
- Amenorrhoea/female athlete triad
- Pregnancy
- Hypopituitarism
- Adrenal insufficiency

Gastrointestinal/nutritional
- Eating disorders (anorexia/bulimia)
- Chronic liver disease
- Haemochromatosis
- Malnutrition/inadequate diet
- Malabsorption syndromes
- Inflammatory bowel disease
- Calcium deficiency
- Vitamin B_{12} deficiency
- Vitamin D deficiency
- Sprue
- Gastrectomy/bariatric surgery
- Total parenteral nutrition

Haematological/malignant
- Thalassaemia
- Mastocytosis
- Lymphoma and leukaemia
- Multiple myeloma
- Pernicious anaemia
- Disseminated carcinomatosis
- Tumour secretion of parathyroid hormone-related peptide
- Haemophilia
- Congenital porphyria
- Gaucher's disease

Renal/metabolic
- Hypophosphatasia
- Homocystinuria
- Chronic renal insufficiency/end-stage renal disease
- Hypercalciuria
- Renal tubular acidosis
- Post-renal transplant

Musculoskeletal/connective tissue
- Marfan syndrome
- Ehlers–Danlos syndrome
- Ankylosing spondylitis
- Osteogenesis imperfecta
- Rheumatoid arthritis
- Idiopathic scoliosis
- Lupus

Table 6.1 (continued)

Drug-induced
- Steroids
- Excess thyroid hormone
- Gonadotropin-releasing hormone agonists
  - leuprolide acetate
  - goserelin acetate
  - triptorelin pamoate
- Aromatase inhibitors
  - anastrozole
- Immunosuppressants
  - calcineurin inhibitors
    - ciclosporin
    - tacrolimus
  - Methotrexate
- Anticonvulsants
  - Phenobarbital
  - Phenytoin
  - Valproate
- Phenothiazines
- Heparin (both unfractionated and low molecular weight; long-term use)
- Vitamin D toxicity
- Lithium
- Progesterone (long-acting parenteral form)
- Aluminium
- Tamoxifen (pre-menopausal use)

Other
- Organ transplantation
- HIV/AIDS
- Weight loss
- Smoking
- Stroke
- Amyloidosis
- Chronic obstructive pulmonary disease
- Multiple sclerosis
- Immobilization
- Spinal cord transection
- Elevated homocysteine
- Alcoholism
- Cystic fibrosis
- Congestive heart failure
- Depression
- Porphyria

warfarin and progesterone. Some conditions are a variation of an established reason for secondary osteoporosis. For example, treatment of obesity with bariatric surgery appears to produce a constellation of nutritional deficiencies similar to that produced in the past by partial gastrectomy for peptic ulcer disease, predisposing

these patients to vitamin D deficiency and metabolic bone disease. Finally, some disorders, once considered uncommon, such as coeliac sprue, are now identified as a more prevalent contributor than originally thought.

The challenge for clinicians seeing patients with osteoporosis is to identify those who may have a secondary cause, determine the mechanism of the bone loss and tailor the treatment to the aetiology where possible. There have been several recent reviews discussing the broad topic of secondary osteoporosis [3–5]. The papers chosen for this chapter represent information and studies published in the last year which augment our understanding and approach to these disorders or highlight topical diseases of interest. For the purpose of this review, the topics covered will be divided into recent insight in the broad areas of nutritional/metabolic, drug-induced and disease- and transplant-related causes that result in decreased BMD or osteoporosis.

Nutritional/metabolic causes

Homocysteine as a predictive factor for hip fracture in older persons

McLean RR, Jacques PF, Selhub J, *et al*. *N Engl J Med* 2004; **350**: 2042–9

Homocysteine levels and the risk of osteoporotic fracture

van Meurs JBJ, Dhonukshe-Rutten RAM, Pluijm SMF, *et al*. *N Engl J Med* 2004; **350**: 2033–41

BACKGROUND. Homocystinuria is a rare disease associated with very high homocysteine levels and resultant severe occlusive vascular disease. Patients with this disorder are at risk of early onset of generalized osteoporosis, attributed to inhibition of collagen crosslinking by the elevated homocysteine levels. In addition to the skeletal involvement seen in homocysturics, other studies have implicated high homocysteine levels in age-dependent bone loss. However, the contribution of moderate homocysteine elevation to the incidence of fracture is not known. These two studies, published in the same issue of the *New England Journal of Medicine*, set out to determine the relationship between increasing levels of homocysteine and the incidence of fractures.

INTERPRETATION. McLean *et al*. evaluated a cohort from the Framingham Study, originally comprising 5209 men and women who have been followed since 1948 to assess risk factors for cardiovascular disease. Those who had blood taken between 1979 and 1982 were followed for an incident hip fracture from the date the sample was obtained. A total of 825 men and 1174 women, ranging in age from 59 to 91 years, were

evaluated. The median duration of follow-up was 12.2 years for men and 15.0 years for women. Because homocysteine levels increase with age, age was adjusted for in the regression models. Forty-one hip fractures occurred among the men and 146 among the women. The mean (±SD) plasma total homocysteine concentration in men was 13.4 ± 9.1 μmol per litre and in women it was 12.1 ± 5.3 μmol per litre. Men in the highest quartile of homocysteine had a 3.84-fold increase in hip fractures compared with men in the lowest quartile, while women in the highest quartile had a 1.9-fold increase in hip fracture rate compared with the lowest quartile. However, the differences in absolute risk between the highest and lowest quartiles were more similar (8.8 fractures in men, 9.5 in women per 100 participants at 14 years' follow-up), suggesting that homocysteine's contribution to hip fracture risk is actually fairly similar in the two sexes.

Two separate, prospective population-based studies of subjects aged 55 years or older were investigated by van Meurs *et al*. The first, from the Rotterdam Study, comprised two independent cohorts, one with 562 subjects followed for a mean of 8.1 years, the other with 552 subjects followed for a mean of 5.7 years. The second study evaluated a single cohort of 1291 subjects from the Longitudinal Aging Study Amsterdam who had a mean follow-up of 2.7 years. Fractures in any skeletal locations were recorded as an outcome measure but obvious non-osteoporotic fractures were excluded. Fracture rates per quartile of homocysteine level were calculated, and BMD measurements were also obtained. There were 191 subjects with fracture, mainly of the hip and wrist, during 11 253 person-years of follow-up. The subjects in the highest quartile had twice the risk of fractures as those in the lower quartiles. The relative risk of fracture for each 1 SD increment in the homocysteine level was 1.4 in men and 1.3 in women, and was independent of BMD of the femoral neck or lumbar spine. The risk of fracture in those with the highest homocysteine level was 1.9, similar to the association of fractures with other well-established risks (Table 6.2).

Table 6.2 Relative risks and population-attributable risks for independent risk factors for incident fracture

Factor	Relative risk (95% CI)	Population-attributable risk (95% CI)
		%
Age >75 years	2.3 (1.7–3.1)	31 (25–48)
Bone mineral density, lowest quartile	1.6 (1.1–2.3)	13 (2–25)
Current smoker	1.6 (1.1–2.3)	10 (4–23)
Fall in previous year†	1.9 (1.2–2.7)	20 (10–35)
Dementia and cognitive impairment†	2.5 (1.5–4.1)	15 (7–30)
Homocysteine level, highest quartile	1.9 (1.4–2.6)	19 (10–29)

All relative risks were adjusted for age and sex, except for an age of more than 75 years. CI, confidence interval.
†Only data from cohort 1 of the Rotterdam Study and LASA were used to calculate the population-attributable risk.
Source: van Meurs *et al.* (2004).

Comment

These two studies found a similar association between increased homocysteine levels and the risk of fracture, and van Meurs expanded these findings by showing no association between elevated homocysteine levels and BMD. The authors attempted to isolate the effect of homocysteine by taking into account numerous potentially confounding factors in the various cohorts studied, such as age, sex, height, weight, smoking, alcohol intake, current oestrogen use, creatinine levels, recent falls, diabetes, peripheral arterial disease and calorie, protein and calcium intakes. Although it is still possible that homocysteine may be an innocent bystander [6], perhaps reflecting an uncaptured connection with either some nutritional, hormonal or other factor yet to be defined, it appears fairly likely that it does indeed play some role in increasing the risk of fracture. Further evaluation to determine if restoring homocysteine levels to a normal range by way of folic acid supplementation would result in a decrease in the risk of fracture needs to be performed.

Low plasma vitamin B_{12} is associated with lower BMD: the Framingham Osteoporosis Study

Tucker KL, Hannan MT, Qiao N, *et al. J Bone Miner Res 2005*; **20**: 152–8

BACKGROUND. It is becoming increasingly apparent that many nutrients are important for optimal bone health. Vitamin B_{12} is involved with osteoblast activity and bone formation, and its deficiency in pernicious anaemia has been associated with a greater risk of fracture. The authors examined the relationship between plasma vitamin B_{12} levels and BMD in 2576 community-dwelling adults from the Framingham Offspring Osteoporosis Study. The ages of the participants ranged from 30 to 87, with a mean age of 59.4 for men and 58.4 for women. Analysis was adjusted for age, body mass index, physical activity, alcohol use, smoking status, total calcium and vitamin D intake, season of bone measurement, protein intake, homocysteine concentration, and menopausal status and oestrogen use in women. Vitamin B_{12} levels were divided into four categories: <148 pM (deficient; 4% of cohort); >148–185 pM (marginal deficiency; 8% of men, 7% of women); >185–259 pM (suboptimal 28% of men, 25% of women); and >259 pM (adequate; 59% of men, 63% of women). Mean intake of vitamin B_{12} was higher than the current recommended daily values in all groups.

INTERPRETATION. There was a non-linear association between vitamin B_{12} status and BMD. Men with vitamin B_{12} levels above 259 pM had more than 7% greater BMD at Ward's triangle compared with those with concentrations below 148 pM. Femoral neck and total hip BMD were also statistically higher in those with higher vitamin B_{12} levels, but spine BMD was not statistically different. For women, spine BMD was statistically higher with vitamin B_{12} levels above185 pM compared with the lowest category, and hip BMD approached but did not achieve statistical significance except for the femoral neck area. These statistics remained significant after adjustment for the variables listed above, including protein intake and homocysteine levels.

Comment

Fractures are noted to be increased in patients with pernicious anaemia. Vitamin B_{12} deficiency is associated with low levels of osteocalcin and skeletal alkaline phosphatase [7,8]. Cell culture studies suggest that low vitamin B_{12} concentrations may suppress osteoblastic activity [9]. Although this is a population-based study noting the association of low BMD with low vitamin B_{12} levels in community-dwelling men and women and not a randomized trial, the findings suggest that even those without pernicious anaemia may be at risk of fracture. It is estimated that 5.3–24% of older adults have marginal or deficient levels of vitamin B_{12} [10]. The loss of stomach acidity with ageing results in atrophic gastritis and impaired absorption of protein-bound vitamin B_{12}. The unbound vitamin B_{12} in supplements is better absorbed [11]. Because atrophic gastritis can affect up to 40% of older adults and may be compounded by the increased use of acid-blocking agents [12], it is important to counsel elderly patients to ingest adequate amounts of fortified foods or vitamin B_{12} supplements.

Metabolic bone disease after gastric bypass surgery for obesity

DePrisco C, Levine SN. *Am J Med Sci* 2005; **329**: 57–61

BACKGROUND. Osteoporosis and metabolic bone disease have been reported in patients who had undergone partial gastric resection for peptic ulcer disease. The emergence of histamine 2 blockers and proton pump inhibitors has resulted in far fewer gastric surgeries and their subsequent complications. Gastric bypass surgery for treatment of obesity, though, has increased dramatically in the last several years and can produce similar complications of osteoporosis and osteomalacia if not addressed aggressively in the post-operative period. The authors report on four patients who had either Roux-en-Y gastric bypass or biliopancreatic diversion 9–12 years previously and who presented with symptoms similar to those seen after ulcer surgery.

INTERPRETATION. Patients were women between the ages of 43 and 58. All reported symptoms of fatigue, arthralgias and myalgias for months or years before the correct diagnosis was made. Each had either osteoporosis or osteopenia with hypocalcaemia, low or undetectable 25-hydroxyvitamin D levels, secondary hyperparathyroidism and increased serum alkaline phosphatase. Levels of 1,25-dihydroxyvitamin D were elevated, reflecting its stimulation by elevated levels of parathyroid hormone. In addition to offering adequate calcium and vitamin D supplementation to patients with bariatric surgery, the authors recommend that these patients also have routine monitoring of serum calcium, alkaline phosphatase, parathyroid hormone and 25-hydroxyvitamin D levels to allow the early identification of abnormalities.

Comment

The percentage of the US population with obesity has doubled in the last 30 years, so the number of patients who will undergo bariatric surgery is expected to

increase. This procedure results in improvements in glucose, lipid and blood pressure levels, and most often this is the main focus of follow-up in these patients. As seen with transplant-induced osteoporosis, though, the metabolic bone consequences of gastric bypass surgery may only manifest themselves years after the procedure. Heightened awareness of the potential for delayed bone effects and recognition of the non-specific symptoms of fatigue, myalgias and bone pain in these patients by those providing their care should help prevent this outcome. Routine tests for metabolic bone abnormalities should be the standard of care, given the frequency of the altered vitamin D status and the increasing frequency of these operations.

Drug-induced causes

Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer

Howell A, Cuzick J, Baum M, *et al.*; ATAC Trialists' Group. *Lancet* 2005; **365**: 60–2

BACKGROUND. Five years of therapy with tamoxifen has been the standard adjuvant treatment for hormone-receptor-positive breast cancer in post-menopausal women. However, it is associated with recurrences and side effects, such as thromboembolism and endometrial cancer, which has limited its usefulness. Anastrozole, an aromatase inhibitor, does not possess oestrogen agonist effects and has been used for years to treat post-menopausal women with metastatic breast cancer or metastatic cancer during tamoxifen treatment. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was designed to compare these two agents as adjuvant therapy in 9366 post-menopausal women with localized breast cancer.

INTERPRETATION. Anastrozole significantly prolonged disease-free survival and time to recurrence, and reduced distant metastases and contralateral breast cancer. It was also associated with fewer side effects than tamoxifen, but was associated with increased fractures. There was a total of 340 fractures in the anastrozole group compared with 237 in the tamoxifen group (odds ratio 1.49; $P < 0.0001$). Anastrozole is now recommended as the preferred initial treatment for post-menopausal women with localized oestrogen-receptor-positive breast cancer.

Comment

This study is included to highlight the repercussions that a change from tamoxifen to anastrozole as the standard of care will have on women with breast cancer. It is estimated that approximately 60–70% of breast cancers in post-menopausal women are oestrogen-receptor-positive, so oestrogen deprivation therapy is an

important therapeutic modality. With tamoxifen, pre-menopausal women may experience bone loss while post-menopausal women may benefit from its oestrogen agonist effect on bone. Tamoxifen's effects on the risk of fracture have been conflicting, one study showing a trend towards reducing fractures [13] and the other showing no benefit compared with placebo [14]. In post-menopausal women, aromatase inhibitors such as anastrozole reduce oestrogen levels by inhibiting the enzymatic conversion of androgens to oestrogen. Anastrozole has been shown to result in a decrease in BMD at the spine and hip and an increase in markers of bone resorption and formation at 1 year, with further adverse changes seen in the second year [15]. Because no large trials have compared anastrozole with placebo with regard to BMD or fracture risk, it is not clear whether the fracture differences seen in the ATAC study are due solely to anastrozole's reduction of oestrogen levels, the possible beneficial effect of tamoxifen on bone, or a combination of both factors. Because women with breast cancer have an increased risk of osteoporosis anyway, they should be targeted aggressively for osteoporosis-preventive measures, including smoking cessation, weight-bearing exercises and supplementation with calcium and vitamin D. Those beginning therapy with an aromatase inhibitor should have dual energy X-ray absorptiometry (DXA) performed, and bisphosphonates should be prescribed for those with osteoporosis. Risedronate [16], zoledronic acid [17] and clodronate [18,19] have demonstrated effectiveness in reducing the severity of bone loss or increasing BMD in women with ovarian failure induced by cancer therapy. Until trial results become available with raloxifene in this population, this agent should not be used.

Risk of fracture after androgen deprivation for prostate cancer

Shahinian VB, Yong-Fang K, Freeman JL, Goodwin JS. *N Engl J Med* 2005; **352**: 154–64

BACKGROUND. Prostate cancer is the second leading cause of death from cancer in men, and medical castration with GnRH agonists and anti-androgens has generally replaced orchiectomy as the preferred method of androgen deprivation therapy (ADT). Bone mineral density is dramatically affected with this treatment, analyses demonstrating a 2–8% decrease in lumbar spine BMD and a 1.8–6.5% decrease in femoral neck BMD after 12 months of continuous ADT [20]. The assessment of fracture risk with these agents has been limited. This study examines the risk of fracture with ADT by orchiectomy or GnRH agonist treatment in a large population of men diagnosed with prostate cancer between 1992 and 1997, using data from the linked database of the National Cancer Institute's Surveillance, Epidemiology and End Results program and Medicare.

INTERPRETATION. Records of 50 613 men 66 years of age or older were studied. Excluding fractures that occurred in the first 12 months after diagnosis, fractures were recorded in 19.4% of those receiving ADT compared with 12.6% for those not receiving

such treatment. Patients were further stratified into how many doses of GnRH agonist therapy they received. Those who received nine or more doses and those who had an orchiectomy had lower fracture-free survival compared with those receiving fewer doses of ADT or no treatment (Fig. 6.1). The number needed to harm for the occurrence of fracture from 12 to 60 months after diagnosis of prostate cancer was 28. With the annual incidence of prostate cancer of 220 000, and at least 40% of these men receiving ADT, approximately 3000 excess fractures are expected to occur yearly as a result of ADT.

Comment

The rate of bone loss in men on ADT is higher than that seen in women at menopause. Despite this increased risk, a recent analysis showed that only 8.7% of men receiving ADT for 1 year or longer underwent evaluation by DXA in the previous 3 years [**21**]. Men on ADT should be targeted to receive the same preventive strategies as those offered to women, and BMD measurement and appropriate pharmacological therapy should be considered early in their course of treatment. A less commonly considered therapeutic option for men is discussed in the next article.

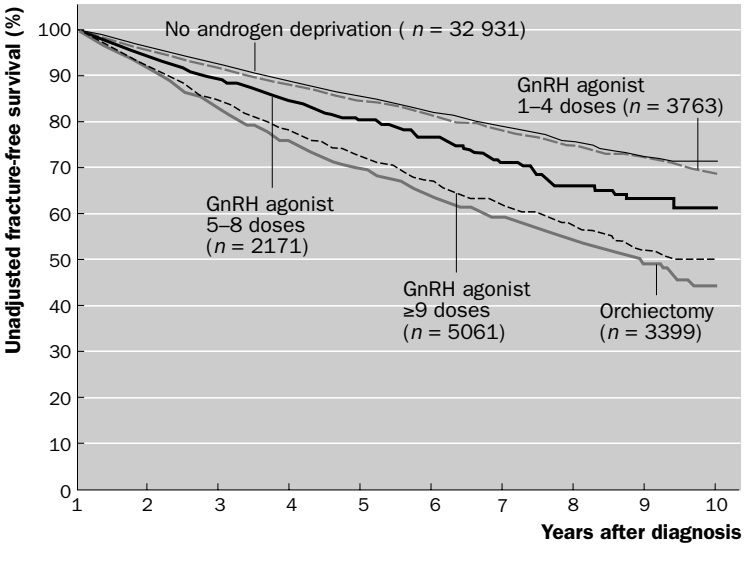

Fig. 6.1 Unadjusted fracture-free survival among patients with prostate cancer, according to androgen deprivation therapy. The survival curves start at 12 months after diagnosis, and androgen deprivation was initiated within 6 months after diagnosis. The number of doses is the number administered within 12 months after diagnosis. GnRH, gonadotropin-releasing hormone. Source: Shahinian *et al*. (2005).

Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial

Smith MR, Fallon MA, Lee H, Finkelstein JS. *J Clin Endocrinol Metab* 2004; **89**: 3841–6

BACKGROUND. Oestrogens play a role in bone formation and resorption in both sexes. Serum oestradiol levels correlate positively with spine BMD and negatively with fracture risk in elderly men, even more so than androgen levels [22–24]. Although raloxifene, a selective receptor modulator that mimics oestrogen's positive effect on bone, has been shown to increase BMD and reduce vertebral fractures in post-menopausal women, its effects on bone metabolism in men is not known. This study investigates the effects of raloxifene on BMD in men who were given a GnRH agonist for prostate cancer for at least 6 months prior to enrolment; the median duration of their disease was longer than 2.5 years. Men were excluded if they had known metastases, disease progression, or bone disease including osteoporosis.

INTERPRETATION. A total of 44 men were randomized to receive raloxifene 60 mg daily or placebo for 1 year. Baseline testosterone levels were in the castration range for both groups. The mean BMD of the posteroanterior lumbar spine, total hip, trochanter and femoral neck increased by 1.0, 1.1, 1.6 and 0.3% respectively in those treated with raloxifene compared with a decrease of 1.0, 1.1, 2.4 and 1.7% at these sites in the men on no treatment. All results except for the spine were statistically significant. A significant decrease in urinary excretion of amino-terminal propeptide of type I collagen and a numeric decrease in deoxypyridinoline were also noted in raloxifene users compared with non-users. There was no significant change in total testosterone, oestradiol or the free oestrogen index, and lipid levels were comparable in each group. One man taking raloxifene had a pulmonary embolus.

Comment

The effect of raloxifene on bone turnover markers in men has been examined in an earlier study. In that study, changes in urine levels of N-teleopeptide of type I collagen (NTX) were directly related to baseline oestradiol levels, individuals with a low baseline oestradiol levels having a greater decrease in NTX [**25**]. This study by Smith *et al.* is the first to evaluate the effects of this selective oestrogen receptor modulator (SERM) on BMD in men. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, similar changes in BMD and biochemical markers with raloxifene in post-menopausal women resulted in a decrease in spine fractures [**26**]. This was a very small study, and further evaluation is clearly necessary to determine if fractures in men would be reduced with this SERM. It is worth noting that venous thromboembolism is increased about 3-fold in women using raloxifene, and one man in this study also had a pulmonary embolism.

Other agents to consider in men with prostate cancer include the bisphosphonates. There are suggestive data from animal studies that increased bone resorption

may lead to an increased likelihood of bony metastases [27]; therefore, decreasing resorption may reduce this likelihood. Several bisphosphonates have been evaluated in men. Oral alendronate 10 mg daily has been shown to increase lumbar BMD by 7.1% and femoral neck BMD by 2.5% in men with primary osteoporosis with or without low testosterone levels [28]. More specific to men receiving ADT, pamidronate 60 mg IV every 12 weeks for 48 weeks protected BMD in men on leuprolide therapy compared with the loss of BMD seen with leuprolide alone [29]. Intravenous zoledronic acid 4 mg every 3 months for 1 year resulted in an increase of more than 5% in lumbar spine BMD compared with a loss of 2% in those not receiving the bisphosphonate [30]. These data suggest that bisphosphonates may build bone to a greater degree than raloxifene in men, and this has already been demonstrated in women [31]. Whether fracture reduction and side effects of treatment would be more favourable with bisphosphonates in either gender remains to be determined. An important message from these studies is that men on ADT are at increased risk of fracture and should be targeted for prevention and treatment.

Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception

Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. *Arch Pediatr Adolesc Med* 2005; **159**: 139–44

BACKGROUND. Injectable contraception with depot medroxyprogesterone acetate (DMPA) results in oestrogen depletion with resulting adverse effects on bone. Although prior studies have shown that DMPA can adversely affect BMD in older pre-menopausal women, few studies have evaluated the effects in adolescents. With up to 10% of adolescent women relying on this form of birth control, the adverse changes in BMD in such a large population could have significant consequences. In this 3-year study, the authors evaluated the effect on hip, spine and total body BMD of DMPA use and discontinuation relative to non-use in 170 women aged 14–18 years.

INTERPRETATION. DMPA users and non-users differed in that the users were more likely to currently smoke, have been pregnant, have an earlier age of menarche, have a lower calcium intake and a higher body mass index, body fat content and percentage. Their baseline BMD was also non-significantly lower at all sites than in non-users. After baseline evaluation, BMD was obtained every 6 months for 24 months, with a range of use between 3 and 62 months. Seventy-one per cent discontinued injections at some point during follow-up and were followed for a mean of 14 months. The mean percentage change in BMD from baseline differed significantly at the hip and spine for those on DMPA, with greater decreases in BMD seen in new users compared with prevalent users. After adjustment, the calculated annualized mean percentage change in BMD was –1.81, –0.97 and 0.73% at the hip, spine and whole body respectively in users compared with –0.19, 1.32 and 0.88% in non-users. In those discontinuing DMPA during this study, the adjusted mean percentage changes were significantly higher for these women at all sites, particularly the whole body, compared with non-users. These findings

suggest that rapid recovery of BMD occurs with discontinuation of DMPA in adolescent women, although this recovery is more modest at the hip than at the other sites.

Comment

Because adolescent women have not yet achieved peak bone mass, the implications of using an agent that reduces BMD in this population are considerable. Various factors that influence the attainment of optimal bone mass before the menopause can affect the future risk of fractures. Although fracture risk generally increases with ageing, there are data to suggest that the relationship between decreased BMD and increased fracture risk also exists in pre-menopausal women [**32**]. DMPA recently received a black box warning in the US because of its effect on reducing BMD, and is not recommended for use for longer than 2 years unless other modalities have been considered. Although this study is reassuring in that discontinuation of DMPA after short-term use resulted in a rebound of BMD, further investigation with larger trials is clearly needed to determine whether this agent can be given safely without increasing the risk of fracture during a woman's lifetime.

Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome

Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA.
N Engl J Med 2004; **351**: 868–75

BACKGROUND. The use of glucocorticoids in both children and adults is associated with dose-related decreases in BMD. However, it is not always clear whether the decreases seen are due solely to the drug or whether the inflammatory cytokines from the underlying process may also exacerbate the bone loss. Glucocorticoid-sensitive nephrotic syndrome is a disorder that occurs in childhood and responds swiftly to glucocorticoids. Although flares can be associated with increases in cytokines, the disease is generally not associated with extensive inflammatory involvement; thus, the effects of intermittent high-dose glucocorticoids on the growing skeleton can be evaluated with this model. In this study, the effect of the cumulative dose of steroids on bone mineral content and body mass index in 60 children and adolescents with glucocorticoid-sensitive nephrotic syndrome was compared with values in 195 control subjects without disease or steroid exposure.

INTERPRETATION. The enrolled subjects received an average of 23 000 mg glucocorticoids (prednisone equivalent). The patients had significantly lower *Z*-scores for height which inversely correlated with lifetime cumulative steroid dose, reflecting the effect of steroids on stature. *Z*-scores for weight and body mass index were higher in the steroid users, and when bone area, age, sex, Tanner stage, race and height were analysed, whole-body bone mineral content showed no difference between glucocorticoid users and controls (Fig. 6.2). The use of appropriate reference data may reduce inappropriate concern and treatment of children receiving intermittent steroid treatment.

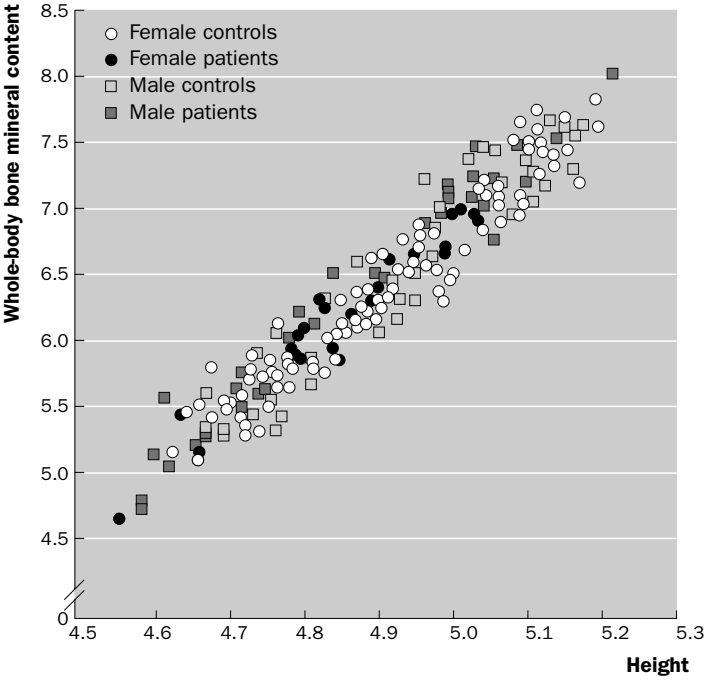

Fig. 6.2 Whole-body bone mineral content relative to height in patients with glucocorticoid-sensitive nephrotic syndrome and control subjects. Values have been log-transformed. Source: Leonard *et al*. (2004).

Comment

This analysis offers some reassurance that administration of pulse steroids in this young population may not be as devastating to bone as once thought, at least as evaluated by measuring bone density and whole-body bone mineral content. It is possible that the young skeleton may have an increased ability to recover during steroid-free intervals. A previous population study of children receiving more than four courses of corticosteroids demonstrated an increase in fracture rate in these children, many of whom were being treated for an inflammatory condition [**33**]. The lack of a significant inflammatory process in glucocorticoid-sensitive nephrotic syndrome may have contributed to the results seen in this study. This was a cross-sectional study, and further studies should be carried out to corroborate these conclusions and to evaluate children with other steroid-requiring disorders. Because there is more to bone quality than just BMD, data on other parameters, such as markers of resorption and formation, should also be gathered to better evaluate the impact of glucocorticoids in a young population.

Superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis

Ringe JD, Dorst A, Faber H, Schacht E, Rahlfs VW. *Rheumatol Int* 2004; **24**: 63–70

BACKGROUND. The treatment of glucocorticoid-induced osteoporosis requires adequate vitamin D supplementation, initiated at the start of steroid therapy. Although plain vitamin D has been demonstrated to be an important supplement in osteoporosis management, its use has not demonstrated similar efficacy in patients with glucocorticoid-induced osteoporosis [34,35]. Alfacalcidol, a pro-drug of calcitriol, is a potent vitamin D hormone that produces positive bone results independently of vitamin D levels [36]. However, it is more expensive than plain vitamin D, and it is not known if it is superior to plain vitamin D with regard to fracture reduction in glucocorticoid-induced osteoporosis. This study was designed to determine the effect of alfacalcidol versus plain vitamin D on BMD and fracture risk. Patients with osteoporosis on long-term glucocorticoid therapy were randomized to receive either 1 μg alfacalcidol ($n = 103$) or 1000 IU vitamin D_3 ($n = 101$) daily for 3 years, and both groups also received 500 mg calcium daily. BMD was measured at study onset and at 12, 24 and 36 months, and patients were evaluated for adverse events and back pain.

INTERPRETATION. A total of 89 patients in the alfacalcidol group and 88 in the vitamin D group completed 3 years of treatment. Lumbar spine BMD increased in both groups at 12 months, but the gains reversed in the vitamin D group at 24 and 36 months compared with a continued moderate increase in the alfacalcidol group. Vitamin D did not change femoral neck BMD significantly, while alfacalcidol demonstrated a moderate superiority in BMD change at this site. Three years of alfacalcidol therapy led to a significant reduction of 61% in vertebral fracture and 52% reduction in all fractures combined compared with vitamin D therapy (Fig. 6.3). A non-significant reduction of 41% in non-vertebral fractures was also seen in the alfacalcidol group. Adverse events were mild in both groups, and back pain was significantly less in the alfacalcidol group.

Comment

A recent meta-analysis demonstrated that vitamin D metabolites reduced bone loss and prevented fractures in osteoporotic patients not on steroids, but could only demonstrate a positive BMD effect in patients exposed to corticosteroids [37]. This is the first study with sufficient power to demonstrate that alfacalcidol reduces fracture risk in corticosteroid-induced osteoporosis. The fact that alfacalcidol could demonstrate a significant reduction in fractures in such a small population indicates the marked increase in fracture risk that patients exposed to steroids have. The dose of vitamin D used, 1000 IU, is a well-accepted supplementary dose and should have resulted in some benefit. Perhaps if it had been compared with a placebo control it might have demonstrated some effectiveness. The fact that it was inferior to alfacalcidol raises the question of why it was not as effective, since they both work

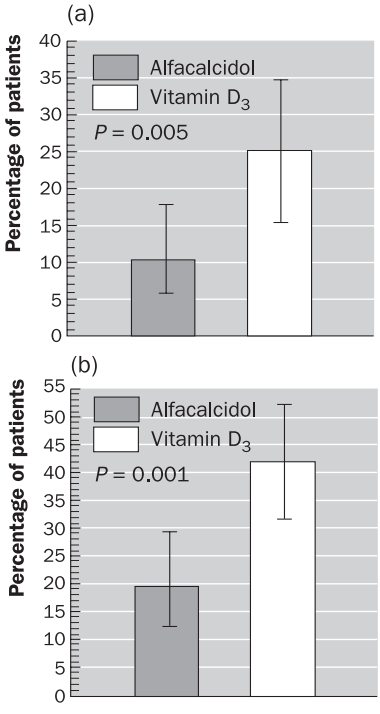

Fig. 6.3 Three-year rate of patients with at least one new vertebral fracture (a), and three-year rate of patients with at least one new non-vertebral fracture (b). Source: Ringe *et al.* (2004).

on the same pathway. Unlike vitamin D, which requires 25-hydroxylation by the liver and 1α-hydroxylation by the kidney, alfacalcidol is already hydroxylated at the 1α position. Glucocorticoids may reduce the amount of D-hormone receptors on effector cells, and this effect may be exacerbated by chronic inflammation. Tumour necrosis factor inhibits renal 1α-hydroxylase, and low serum calcitriol levels can be seen in patients with inflammatory diseases [38]. Administering a D hormone that is already hydroxylated at the 1α site may bypass this adverse effect. This, coupled with the facts that D-hormone analogues have immunoregulating properties and can decrease tumour necrosis factor α (TNF-α) and interleukin-6 (IL-6) levels, may account for alfacalcidol's superiority over vitamin D. These results are also in contrast to those of Sambrook *et al.* [39], who compared ergocalciferol (vitamin D2) 30 000 IU weekly with calcitriol 0.5–0.75 μg/day and found no difference between these two agents in the treatment of glucocorticoid-induced bone loss. However, the different doses and formulations of D compounds used in these two studies may account for the different results seen, although even Sambrook's data suggested superiority of calcitriol over vitamin D in those initiating glucocorticoid therapy.

Because the effect of corticosteroids on bone is one of the most common reasons for secondary osteoporosis, larger studies looking at various vitamin D formulations are clearly necessary to elucidate which would be most protective in this high-risk population.

Disease- and transplant-related causes

Reduced bone mineral density in male renal transplant recipients: evidence for persisting hyperparathyroidism

Roe SD, Porter CJ, Godber IM, Hosking DJ, Cassidy MJ. *Osteoporos Int* 2005; **16**: 142–8

BACKGROUND. In the first year after renal transplantation, BMD decreases by 3–7% [40], and it continues to fall thereafter at a more modest rate. Reasons for this bone loss are complex and include the use of glucocorticoids, immunosuppressive agents, patient age and underlying disease process. Fracture rates in this population vary between 11 and 19%, and rates up to 45% are seen in patients with diabetes [41–43]. Although osteoporosis and fractures are well-recognized complications of renal transplantation, attention to bone health often wanes in the years following transplantation. In this study, the authors investigated the prevalence of osteoporosis in a cohort of 134 male transplant recipients and evaluated factors that may have influenced their bone loss.

INTERPRETATION. The mean age of the population studied was 49.7 years and 96% were white Europeans. The median time after transplantation was 72.4 months. The group was divided into those who were transplanted less than 5 years ago, between 5–10 years ago and more than 10 years ago. Various regimes of immunosuppressive therapies were used, but 93% remained on prednisolone, 87% on ciclosporin, 81% on azathioprine, 13% on mycophenolate mofetil and 10% on tacrolimus. The prevalence of osteoporosis was 24% at the femoral neck, 23% at the ultradistal radius, 17% at the lumbar spine and 13% at the distal one-third radius. In analysing various predictors of BMD (age, body mass index, diabetes, time on dialysis, BMD, biochemical markers and parathyroid hormone), there was a negative correlation with parathyroid hormone at all sites. Only 27.6% of men had a normal parathyroid hormone value. The lowest BMD measurements were seen in men 5–10 years after transplantation. The femoral neck and radius were more severely affected than the spine, suggesting involvement at both cortical and trabecular sites. There was no significant effect of the cumulative corticosteroid or calcineurin inhibitor dose on BMD.

Comment

Osteoporosis is a frequent complication of organ transplantation. Fortunately, this complication is now generally well recognized and addressed in the post-transplant period. However, as patients live longer and become more removed in time from

their surgery, attention to their fracture risk may wane. In this study, the patients 5–10 years out from their transplant had the greatest reduction in BMD, and the majority of patients demonstrated hyperparathyroidism. Because parathyroid hormone may remain elevated after renal transplantation in those with severe pre-transplantation hyperparathyroidism [44], efforts should be focused on addressing this issue aggressively prior to transplantation. What is not known is how best to control the pre-transplantation hyperparathyroidism and whether too aggressive intervention may exacerbate the possibility of adynamic bone disease. Calcimimetic agents, which can directly decrease plasma parathyroid hormone secretion without aggravating disturbances in mineral metabolism, may show promise in this regard, although further evaluation needs to be done with these agents. In the meantime, post-transplantation surveillance should monitor calcium, vitamin D, alkaline phosphatase and parathyroid hormone levels in addition to renal parameters in order to reduce the late post-transplantation bone effects seen in this population.

Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation

Shane E, Addesso V, Namerow PB, *et al*. *N Engl J Med* 2004; **350**: 767–76

BACKGROUND. Because rapid bone loss occurs after cardiac transplantation and the prevalence of fracture rate is very high without treatment, strategies to prevent bone loss need to be instituted early in transplant recipients. Because both alendronate and calcitrol have been shown to be efficacious compared with placebo for glucocorticoid-induced osteoporosis, the safety and efficacy of these two agents were compared in 149 patients who had undergone cardiac transplantation within the previous 30 days. Twenty-seven patients who declined to be enrolled in the study served as a reference group. Alendronate 10 mg or calcitriol 25 μg was administered in a double-blind, double-placebo fashion for 1 year. The primary efficacy end-points were percentage change in BMD at the lumbosacral spine (LS-spine) and femoral neck at 6 and 12 months. The safety end-points were serum calcium and creatinine levels and urine calcium and creatinine clearances. Data on vertebral fractures, parathyroid hormone and serum N-telopeptide levels were also gathered. All patients received glucocorticoids and calcineurin inhibitors, mainly ciclosporin, as well as daily calcium 945 mg and vitamin D 1000 IU.

INTERPRETATION. At 1 year, mean changes in lumbosacral spine BMD in the alendronate, calcitriol and reference groups were –0.7, –1.6 and –3.2% respectively, and the mean changes at the femoral neck were –1.7, –2.1 and –6.2% respectively. There was no statistically significant difference between the active groups. Alendronate was better than the reference group at both sites, while calcitriol was better than the reference group at the hip. The incidence of fractures was not significantly different among the groups. Hypercalciuria was seen in 27% of patients in the calcitriol group compared with 7% in the alendronate group. Although the bone loss and fracture rates with the two agents were comparable, the need to monitor serum and urinary calcium when using calcitriol makes alendronate the more reasonable option in this population.

Comment

Although results for both agents were better than those in the reference group, neither alendronate nor calcitriol was able to fully eliminate the loss in BMD after cardiac transplantation. It is not known whether increased use of tacrolimus, which might allow a lower dose of glucocorticoid to be used, may further reduce the bone loss or even allow an increase in bone mass compared with what was seen in this study. Transplant-related bone loss is a multifactorial process, and these agents may have different sites of action, as suggested by their differing ability to increase BMD at the spine and hip. Studies combining two or more agents and studies with anabolics such as parathyroid hormone may have to be conducted to see if gains in bone density and, more importantly, fracture reduction, can be achieved.

Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis

Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. *Arch Intern Med* 2005; **165**: 393–9

BACKGROUND. Coeliac disease is an autoimmune disorder in which there is an inappropriate response to dietary gliadin, a component of wheat products. It affects over 1 million Americans and can present with anaemia, weight loss, diarrhoea and abdominal cramping, although it can also be silent. The chronic intestinal inflammation and intestinal mucosal atrophy lead to malabsorption of nutrients, including calcium and vitamin D. The resulting secondary hyperparathyroidism leads to an increased prevalence of osteoporosis in those with this disease. Consumption of a gluten-free diet can result in an increase in BMD. However, it is not known whether the prevalence of coeliac disease is higher in patients with osteoporosis than in those without it or whether all osteoporotic patients should be routinely screened with serological testing to rule out this disorder. The present prospective study evaluated the prevalence of coeliac disease in patients with (n = 266) and without (n = 574) osteoporosis by measuring antitissue transglutaminase (TTG) and antiendomysial antibodies (EMA). Patients with positive results were offered intestinal biopsies to confirm the diagnosis. Those with biopsy-confirmed coeliac disease were placed on a gluten-free diet and BMD measurements were obtained after 1 year.

INTERPRETATION. Nine patients (3.4%) from the osteoporosis group had biopsy-proven coeliac disease versus 1 (0.2%) from the group without osteoporosis. All nine osteoporotic patients were receiving pharmacological therapy for osteoporosis and had low T-scores despite medical therapy. Each patient with positive biopsy was positive for both TTG and EMA. Patients with higher levels of TTG, indicative of more severe coeliac disease, also had more severe osteoporosis by T-score (Fig. 6.4). The coeliac disease patients had significantly higher parathyroid hormone levels and lower 25-hydroxyvitamin D levels, although the latter was still within the normal range. Affected patients were instructed on a gluten-free diet and re-evaluated at 1 year. All those with elevated parathyroid hormone and alkaline phosphatase at baseline showed normalization of these levels with diet. Post-treatment T-scores were significantly higher than

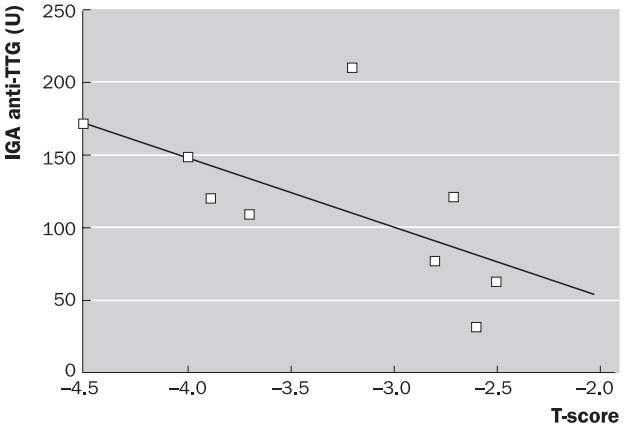

Fig. 6.4 Correlation of T-scores with immunoglobulin A antitissue transglutaminase (anti-TTG) levels in the nine patients with coeliac disease and osteoporosis ($R^2 = 0.37$). Source: Stenson *et al*. (2005).

pre-treatment scores, and the BMD improvement was felt to be greater than expected for patients receiving standard osteoporosis therapy (Fig. 6.5). The authors calculated that it would cost US$1500 at their institution to identify a coeliac disease patient by serological testing. Because there was considerable improvement in BMD with diet and the prevalence of coeliac disease in patients with osteoporosis was high, the authors

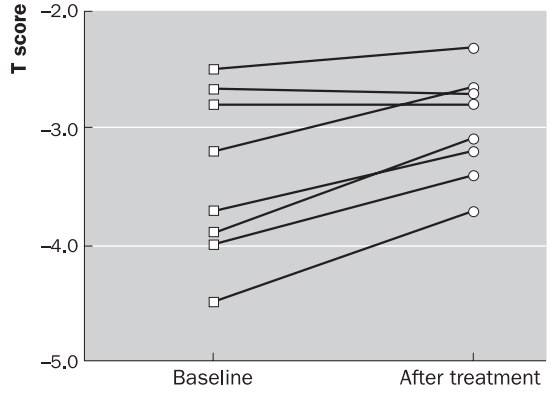

Fig. 6.5 T-scores at baseline and after 1 year of a gluten-free diet in the eight patients with coeliac disease and osteoporosis who completed a year of therapy. Post-treatment T-scores are significantly higher than pre-treatment T-scores by paired samples *t* test ($P = 0.02$). Source: Stenson *et al*. (2005).

suggest that all individuals with osteoporosis undergo screening for coeliac disease. At a minimum, those with elevated parathyroid hormone and evidence of 25-hydroxyvitamin D deficiency should receive testing, especially if any other signs of coeliac disease are present.

Comment

Not all studies have demonstrated an increase in the prevalence of coeliac disease in osteoporosis [**45,46**]. Other studies suggest that the risk of osteoporosis is increased only in those who present with signs and symptoms of classic coeliac disease, in which case the condition should have been considered anyway [**47–49**]. Further studies are needed to determine the cost of mass screening of osteoporotic patients in settings other than a university. Although it is reasonable to consider coeliac disease in patients with elevated parathyroid hormone and low vitamin D levels, it is probably premature to recommend routine screening for coeliac disease in all patients with osteoporosis at this time.

Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism and osteoprotegerin serum levels in patients with ankylosing spondylitis

Franck J, Meurer T, Hofbauer LC. *J Rheumatol* 2004; **31**: 2236–41

BACKGROUND. The pathogenesis of osteoporosis in patients with ankylosing spondylitis is not clear and is confounded by the difficulties faced when assessing BMD in the presence of the spinal abnormalities associated with this disorder. Assessment of bone turnover has yielded contradictory results in ankylosing spondylitis. Osteoprotegerin is a substance produced by a variety of tissues and cell lines that neutralizes receptor activator of nuclear factor-κ B ligand (RANKL), preventing the activation of receptor activator of nuclear factor-κ B (RANK). In inflammatory conditions, activated T cells produce RANKL, which regulates important osteoclast cell functions, including RANK expression. The authors hypothesized that, in the inflammatory condition of ankylosing spondylitis, osteoprotegerin levels differ between affected patients and controls. They compared osteoprotegerin levels with BMD and markers of bone turnover.

INTERPRETATION. There were 264 patients with ankylosing spondylitis and 240 controls, the majority of whom were men. In both groups. osteoprotegerin levels were significantly lower in both men and women with ankylosing spondylitis, especially those with low BMD at the femoral neck and total hip sites. Although osteoprotegerin levels have been shown to increase with ageing as a compensatory mechanism to retard bone loss [**50–52**], this trend was not seen in the ankylosing spondylitis cohort. Patients with ankylosing spondylitis had increased C-reactive protein, erythrocyte sedimentation rate and serum levels of vitamin D, as can be seen with increased inflammatory activity, but these did not correlate with osteoprotegerin levels. Also, the use of non-steroidal anti-inflammatory drugs (NSAIDs) was not found to affect osteoprotegerin levels

significantly. In this study, bone loss in patients with ankylosing spondylitis was associated with low serum levels of sex hormones, high markers of bone resorption and inflammatory activity and low osteoprotegerin levels out of proportion to expected age-related levels.

Comment

The findings in patients with ankylosing spondylitis are consistent with those seen in patients with rheumatoid arthritis, in whom osteoprotegerin levels have also been found to be inappropriately lower than those which would be expected to counteract the increased bone resorption [53]. This may be due to an inhibitory effect of the inflammatory process itself on bone formation. However, NSAIDs did not provide enough of an anti-inflammatory effect to enhance osteoprotegerin levels in this population. It is likely that more potent agents targeting inflammation are needed to allow osteoprotegerin to return to its normal level.

Conclusion

When evaluating patients with low bone mass or a fragility fracture, it is fundamental to their management that secondary causes be considered since these patients will often require a more aggressive treatment approach. For those found to have a secondary cause, however, the World Health Organization definition of osteoporosis (BMD T-score of ≤ -2.5) is not the best criterion to determine when to institute therapy because they frequently have higher fracture rates at higher bone densities than would traditionally be considered for treatment. For this reason, certain guidelines – for example, those for the treatment of glucocorticoid-induced osteoporosis – advise that therapy be instituted early in the course of treatment with this offending agent to help prevent the rapid bone loss that would otherwise occur. Other patients with known secondary causes, especially those with disorders associated with acute rapid severe bone loss (transplant-related, immobilization and stroke) [54] should also be targeted with aggressive pharmacologic measures earlier in their disease process to help prevent bone loss and fractures. Whenever possible, efforts should be directed to correcting the nutritional deficiency, using the lowest dose of the offending agent for the shortest period, and maximizing calcium and vitamin D supplementation. Antiresorptive agents, especially the bisphosphonates, play an important role in the treatment of these disorders. Those with processes affecting bone formation may benefit from an anabolic agent, such as recombinant human parathyroid hormone, to reverse or attenuate the bone loss. In most cases, more studies are needed to determine the best therapeutic regimens for the growing number of secondary causes of bone loss.

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Part II

Bone mass and measurement

7

Quantitative ultrasound measurements and fracture risk: a review

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Introduction

Osteoporosis is a complex multifactorial disease characterized by low bone mass and microarchitectural deterioration of bone tissue that leads to bone fragility and susceptibility to fractures [1]. Low-trauma fracture, being the ultimate consequence of osteoporosis, is a global health concern because of its close association with increased mortality, morbidity, healthcare costs and reduced quality of life [2,3]. One of the major research endeavours in osteoporosis is therefore to identify individuals who are at high risk of sustaining fractures, and to provide appropriate prevention rather than treatment.

Bone mineral density (BMD) is a two-dimensional representation of the mineral content in a given area of bone (g/cm^2), which is commonly measured in the axial and peripheral skeleton using dual energy X-ray absorptiometry (DXA). BMD has been used extensively in predicting fracture risk and to diagnose osteoporosis. Several large-scale epidemiological studies have consistently indicated that individuals with low BMD have a higher risk of fracture [4–8], such that each standard deviation (SD) decline in BMD is associated with a 2- to 3-fold increase in fracture risk [9,10]. The magnitude of the association between BMD and fracture risk is equivalent to that seen between blood pressure and stroke [11]. Because low BMD is associated with higher fracture risk, BMD measurement has been proposed and is used to define osteoporosis [12]. However, the association between low BMD and fracture risk is not discriminatory enough, such that a large proportion of fracture cases do not have low BMD. It should therefore be recognized that normal BMD is not an indication that fracture will not occur, only that the risk is markedly decreased [13].

Fracture is a multifactorial event caused by an accumulation of abnormalities of bone metabolism, which lead to reduced bone strength and deterioration of bone architecture. However, other bone properties, such as tissue elasticity, also play

important roles in the determination of fracture risk. Bone architecture refers to the three-dimensional arrangement of trabecular struts, which can be further quantified in terms of porosity (volume fraction), connectivity (the extent to which structural elements are connected together) and anisotropy (orientation of struts) [14]. Because BMD is a two-dimensional measure, it is not a good indication of bone qualitative properties and does not provide information on the three-dimensional structure of bone. Indeed, although BMD is strongly correlated with bone strength, a previous study suggested that BMD accounts for only 48–77% of the variance in the strength of a bone sample [15].

Bone quality and quantitative ultrasound measurements

Recently the use of quantitative ultrasound (QUS) measurements has been proposed as a way of measuring bone quality and bone microarchitecture [16,17]. The two most common QUS measurements are the speed of sound (SOS) and broadband ultrasound attenuation (BUA); however, in some devices additional parameters, such as the stiffness index (SI), quantitative ultrasound index and amplitude-dependent speed of sound (AD-SOS), could also be calculated as a combination of the primary parameters SOS and BUA [18]. SOS is influenced by the elasticity and the density of bone [19], and is expressed in metres per second (m/s). Higher SOS values are obtained in denser and more elastic bone tissue [17]. BUA, on the other hand, represents the rate of loss of ultrasound intensity versus frequency, which results from the interaction of ultrasound with the propagation medium. BUA is influenced by the thickness, spacing and orientation of the trabeculae [17,20], and is expressed in decibels per megahertz (dB/MHz).

The use of QUS to assess bone properties has several advantages over DXA. Firstly, QUS measurement is non-invasive and can be provided by easily portable scanners at relatively low cost. Moreover, QUS requires less operator skill than DXA, and it is becoming more common in primary care centres and smaller clinics. Compared with DXA, QUS involves no ionizing radiation and is therefore suitable for regular use.

Commercially available QUS machines measure several peripheral skeletal sites: calcaneus [21], tibia [22], radius [23], phalanges [24] and patella [25]; the calcaneus is the most popular measurement site. The ease of accessibility of the calcaneus and its metabolic nature makes it the most favourable site for QUS measurement.

Reliability and concordance of QUS measurements

A physical or biological measurement is useful only if it is reliable and accurate. Recent studies have consistently indicated that QUS measurements are highly

reliable, the coefficient of variation being between 1.9 and 2.6% [26]. The limit of agreement for BUA measured with the CUBA Mark II Ultrasound (McCue Ultrasonics, London, UK) was between –4.4 and 5.0 dB/MHz, which was comparable to that measured with the QUS-2 (Metra) [27].

There are many commercially available devices that can be used to measure BUA and SOS [25]. The concordance in QUS measurements between these instruments has been studied. For example, the coefficient of concordance in BUA measurement between the CUBA and QUS-2 instruments was 0.87, and, on average, BUA measured with the QUS-2 was significantly higher than that measured with the CUBA by approximately 1.9 dB/MHz [27]. In a study comparing QUS measurements between UBIS 5000 (an image-based scanner; Diagnostic Medical Systems, Montpellier, France) and the Achilles+ (GE Lunar, Madison, WI, USA), Nguyen *et al.* observed that the concordance between the two instruments was poor, the coefficient of concordance being 0.05; however, the concordance in SOS and SI between the two instruments was good, the coefficient of concordance being 0.86 and 0.91 respectively [28].

Zochling *et al.* [27] followed a group of 56 individuals for an average of 2.2 years with repeated BUA measurements (CUBA) and observed that the mean (± SD) change was –1.9 ± 8.3 dB/MHz or –5.2 ± 16.5%. They also found that about 50% of subjects had changes that were beyond the random measurement error. However, in that study there was no significant change in SOS during the follow-up period. Thus, it appears that BUA is more sensitive to SOS in terms of change with time.

Correlation between QUS and BMD measurements

BUA is moderately correlated with lumbar spine BMD, the correlation coefficient ranging from 0.3 to 0.5 [29]. However, it appears that the correlation between BUA and total hip or femoral neck BMD is fairly high, the correlation coefficient ranging from 0.7 to 0.8 [30]. Furthermore, the site-matched correlations between QUS and BMD were significantly higher than those for non-matched sites. For instance, SOS measured at the tibia was correlated better with BMD of the mid-tibia ($r = 0.71$); it compared favourably with the theoretical correlation of 0.66 and 0.86 [31–34], but less so with BMD of the lumbar spine ($r = 0.50$–0.54), the hip (0.47–0.52) or the wrist (0.63) [35]. Despite the significant correlation between BMD and QUS measurements, it has also been suggested that differences in the measurement technique itself influence the observed correlation significantly [36]—other studies have shown poor correlation between QUS and BMD [37,38].

When BMD is considered the gold standard and QUS measurements are used to predict BMD, the accuracy of the prediction can be measured as the area under the receiver operating characteristic curve (AUC). Recent studies reported that the AUC at the femoral neck BMD was 0.66 (95% confidence interval 0.62–0.71) and that at the lumbar spine was 0.60 (95% confidence interval 0.56–0.65), which is

comparable with the AUC value of 0.6 (95% confidence interval 0.56–0.65) for AD-SOS measured at the phalanges [39]. Other studies also reported that the AUC value for BUA ranged from 0.72 to 0.85 [34,40–42]. These results suggest that QUS measurements can yield additional information on bone health over and above that given by BMD measurement.

QUS measurements as a predictor of fracture risk

Large epidemiological studies have suggested that each 1 SD lowering of calcaneal BUA (after adjusting for confounders such as sex, age and anthropometric and lifestyle factors) is associated with a two-fold increase in fracture risk [43,44], and that the magnitude of association is independent of BMD. Lower values of SOS were also found to be associated with increased fracture risk, such that each 1 SD lowering of SOS increased the fracture risk by 60% [43], and there is evidence that this association is independent of BMD [19,28,45].

Although numerous studies have suggested that QUS measurement at the heel has a strong ability to discriminate individuals with any fracture from individuals without a fracture, the predictive value of QUS seems to be dependent on skeletal sites. For example, QUS measurements at the patella could predict the risks of vertebral fracture [21] and appendicular fracture [46], and QUS measurement at the distal radius and proximal phalanx has been shown to be a significant predictor of the risk of spinal fracture [47]. However, QUS measured at non-weight-bearing anatomical sites appears to be insufficiently useful in predicting fracture risk [48]. These findings are collectively consistent with the view that the association between QUS measurements and other non-spinal fractures is weak [49].

Between 2003 and 2005, there were 13 studies examining the association between fracture risk and QUS [28,32,43,50–57] (Table 7.1). Most of these studies were in post-menopausal women and measured SOS, AD-SOS, BUA, SI or a combination of them at either the phalanges or the calcaneus. Almost all of these studies reported a significant association between fracture risk and low QUS measurements. The average odds ratio was 1.9, suggesting that each 1 SD reduction in QUS measurement (e.g. SOS, AD-SOS or BUA) increased the risk of fracture approximately two-fold (Fig. 7.1).

Do QUS measurements predict fracture risk independently of BMD? From a theoretical point of view, the modest correlation between QUS and BMD suggests that the prediction of fractures could be improved by combining the use of QUS and DXA [28,58]. Two screening strategies have been suggested: (i) selective BMD screening (based on weight) followed by clinical evaluation for women with medium-low BMD; and (ii) QUS triage followed by BMD evaluation for individuals with medium to low QUS measurements. Both strategies have the same discriminating ability to identify individuals at high risk of fracture as the traditional BMD measure, but the second strategy results in 50% fewer BMD examinations [59]. Because of the low cost and radiation-free nature of QUS, the

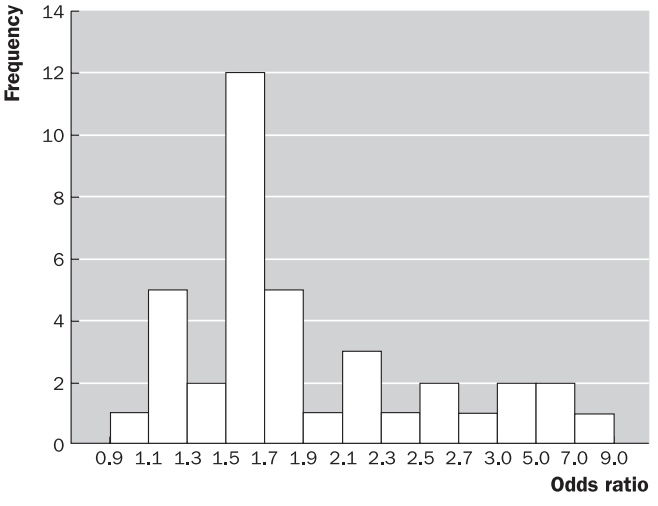

Fig. 7.1 The frequency of reported odds ratios of association between QUS measurements and fracture risk.

second strategy seems to be attractive for mass screening provided that cost-effective conditions for an effective screening programme are met.

An evaluation of clinical and economic outcomes using the second strategy has shown that a sequential measurement that uses QUS followed by DXA scanning of the femoral neck for those with low values of BUA may prevent similar numbers of hip fractures as does testing all women with DXA alone, but reduces the total medical costs by treating fewer women [60]. In Europe, the number of QUS devices exceeds the number of DXA devices, and to use QUS as a pre-screening tool is well accepted because it not only reduces the overall cost but also limits the number of patients exposed to radiation by having a DXA [61].

Limitations

Some limitations of the use of QUS measurement to predict fracture have also been reported. QUS measurements are temperature-dependent [62–64], and the temperature of the bone and soft tissue at the measured skeletal site is the main cause of seasonal variation in QUS measurement. The temperature at the measurement site was associated with lower SOS measurements [65]. On the other hand, the association between variation in BUA and temperature has been inconsistent, perhaps because BUA is dependent on the core temperature of the bone; therefore the temperature of the skin or room temperature alone would not represent the true temperature of BUA, causing an inconsistent finding [65]. Although the true effect of temperature on BUA is not completely understood, the seasonal variation in

Table 7.1 Results of the QUS studies from 2003–2005

Studies	Country	Study type	Subjects	Fracture type	QUS measurement site	Results
Drozdzowska *et al*. (2003) [**50**]	Italy	CC, P	2466 women	Hip, vertebrae, wrist	Phalanges	AD-SOS OR for: hip 3.49 (1.57–7.75); spine 3.25 (1.94–5.45); wrist 2.24 (1.86–2.70); other fracture 1.81 (1.36–2.40)
Guglielmi *et al*. (2003) [**51**]	Italy	CC, H	140 women	Vertebrae	Phalanges	Did not adjust for BMD; age- and BMI-adjusted OR AD-SOS 2.5 (1.5–4.3)
Krieg *et al*. (2003) [**52**]	Switzerland	CS, R	7562 women	Hip, forearm and others	Phalanges Calcaneus	Age- and BMI-adjusted OR Achilles+ for hip BUA 2.3 (1.8–3.0); SOS 2.5 (2.0–3.3); SI 2.7 (2.1–3.5); for forearm BUA 1.5 (1.4–1.6); SOS 1.6 (1.5–1.7); QUI 1.6 (1.5–1.7); other fracture BUA 1.1 (1.0–1.2); SOS 1.1 (1.0–1.2); SI 1.1 (1.1–1.2)
Gluer *et al*. (2004) [**53**]	International, multicentre	L, P	2374 women	Vertebrae	Phalanges Calcaneus	Did not adjust for BMD. Age-adjusted OR Achilles+ BUA 1.6 (1.3–2.0); SOS 1.5 (1.2–2.0); SI 1.5 (1.2–1.8) and AD-SOS 1.5 (1.3–1.9)
Gnudi *et al*. (2004) [**33**]	Italy	CC, H	200 women	vertebrae, hip	Phalanges	AD-SOS for vertebrae 1.6 (1.0–2.4); for hip 0.9 (0.6–1.4)
Gonnelli *et al*. (2005) [**54**]	Italy	CC, H	401 men	Any	Calcaneus	BMD-adjusted OR SOS 6.1 (2.7–9); BUA 7.1 (2.6–14.3); SI 6.1 (2.6–14.3)
Hernandez *et al*. (2004) [**55**]	Spain	CC, P	5195 women	Any	Calcaneus	Age-adjusted OR, BUA 1.56 (1.4–1.6); SOS 1.5 (1.4–1.7); SI 1.6 (1.4–1.7)

Hollevoet *et al.* (2004) [**35**]	Belgium	CC, H	81 women	Wrist	Tibia	Did not adjust for BMD. Did not show OR but AUC of tibia = 0.6
Huopio *et al.* (2004) [**56**]	Finland	L, P	422 women	Any	Calcaneus	Adjusted for age, BMI, BMD OR SOS 1.80 (1.27–2.56); SI 1.72 (1.21–2.45); BUA 1.43 (1.01–2.03)
Khaw *et al.* (2004) [**43**]	EPIC-Norfolk	L, P	14 799 men and women	Any, hip	Calcaneus	OR BUA 1.95 (1.50–2.52); VOS 1.63 (1.34–1.99)
Nguyen *et al.* (2004) [**28**]	Australia	L, P	549 women	Any	Distal radius, proximal phalanges, tibia	BMD-adjusted distal radius SOS 1.76 (1.29–2.41)
Schneider *et al.* (2004) [**32**]	Germany	CC, H	167 women 133 men	Vertebrae	Phalanges Calcaneus	Did not show OR, use AUC and ROC analysis. In women, ability to predict vertebral fracture AUC = 0.794; in men AUC = 0.551 and 0.520 for calcaneal and phalangeal QUS respectively
Varenna *et al.* (2005) [**57**]	Italy	R, P	4832 men	Hip and other non-spinal fracture	Calcaneus	OR adjusted for age and lifestyle factors for hip fracture, BUA 2.24 (1.61–3.08); SI 2.19 (1.56–3.11); SOS 1.71 (1.18–3.24) For other non-spinal fracture, BUA 1.38 (1.12–1.59); SI 1.27 (1.17–1.38); SOS 1.14 (0.96–1.40)

CC, case–control study; CS, cross-sectional study; P, prospective study; L, longitudinal study; H, hospital based; R, retrospective; QUI, quantitative ultrasound index; VOS, velocity of sound.

QUS measurements has been well documented [63]. This seasonal dependence can potentially limit the long-term precision of QUS as a diagnostic tool.

QUS devices can only measure bone at appendicular sites of the skeleton, and this reduces its ability to predict the risk of fracture of the hip or vertebrae, which is perhaps better predicted by site-matched measurement such as femoral neck BMD and lumbar spine BMD [66]. Moreover, body height and therefore bone size has been suggested to have a strong influence on SOS.

Most studies on the association between QUS measurements and fracture prediction have been case–control investigations, with very few longitudinal investigations. Therefore, the magnitude of association between QUS and fracture risk was probably overestimated.

While QUS measurements can predict the risk of hip fracture, this does not mean that QUS can be used to predict fracture for an individual. A statistical model may provide accurate probability estimates but does not necessarily yield good predictions, because the accuracy of estimates is evaluated in a group of patients, whereas dichotomous prediction is concerned with the concordance between predicted and observed outcomes for individual subjects. Even if each SD reduction in SOS is associated with a two-fold increase in the risk of fracture, there is still considerable overlap in the measurements between individuals with and without fracture. For example, in a simulation [67] we have shown that, for a strong association with a typical odds ratio of 1.7, and under the assumptions that the prevalence of vertebral fracture is 16% and the mean SOS for non-fracture individuals is 1530 m/s, the proportion of SOS measurements in fracture and non-fracture cases overlapping is approximately 80% (Fig. 7.2). This overlapping proportion is, as expected, progressively decreased as the odds ratio increases. However, even with an odds ratio of 10 the overlapping proportion is still high (approximately 20%). To achieve complete discrimination between fracture and non-fracture cases, an odds ratio of 30 is required (Fig. 7.1). Therefore, it can be argued that none of the QUS or DXA BMD measurements was an accurate discriminator of fracture. They are useful indicators of fracture risk, not a discriminator of individuals with and without fracture.

Conclusion

Recent advances in the development of ultrasonic methods to assess the skeleton have contributed significantly to the prediction of fracture risk. During the past two decades or so, there has been growing interest in the use of QUS as an alternative tool for screening populations for the risk of osteoporotic fracture. The calcaneus has been the most frequently used site for QUS measurement and gives promising predictive values.

Numerous studies have suggested that QUS measurements can identify individuals who are at increased risk of sustaining a fracture; however, like BMD measurement [68], it cannot discriminate individuals who will or will not sustain a

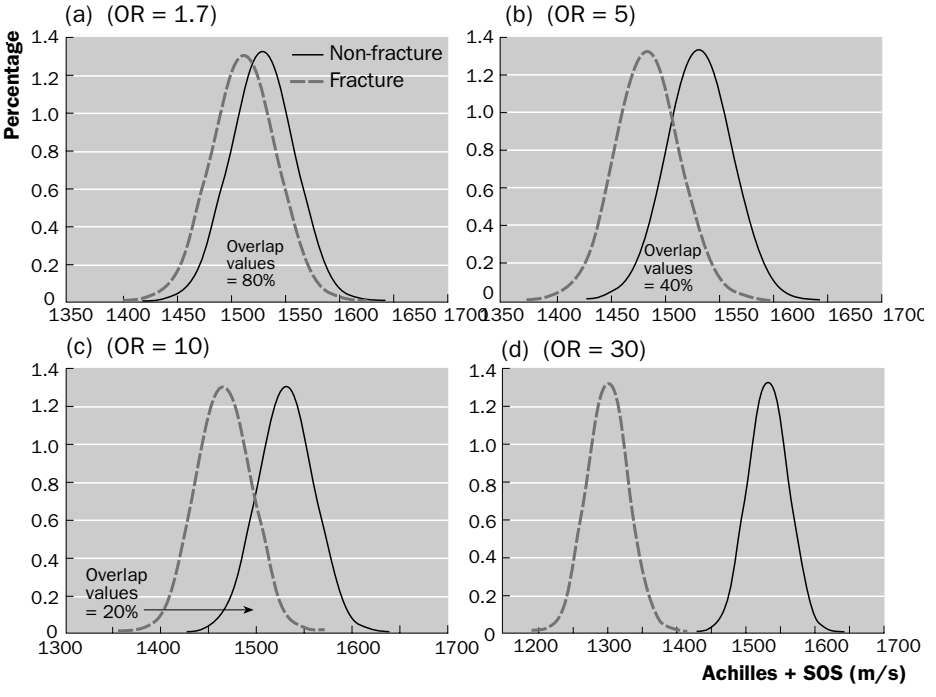

Fig. 7.2 Simulated distributions of SOS (m/s) measured with the Achilles+ in fracture and non-fracture populations for various odds ratios. The simulation was performed with the following parameters: the prevalence of asymptomatic vertebral fracture was set at 16%; the mean SOS for non-fracture cases was 1530 m/s; the mean SOS for fracture cases was set so that it yielded an odds ratio of 1.7 (a), 5.0 (b), 10 (c) and 30 (d). Source: Nguyen *et al*. (2005) [**67**].

fracture in the future. Nevertheless, measurement of QUS is a potential pre-screening tool for the identification of individuals who might be referred for axial DXA measurements.

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8

Update on the role of biochemical markers in the management of osteoporosis

PETER EBELING

Introduction

Several serum and urine biochemical markers of bone resorption and formation have been developed. Biochemical bone markers have been used as intermediate end-points in all major studies of anti-osteoporotic therapies. Bone resorption markers, in particular, may add an independent, predictive value to the assessment of bone loss and fracture risk. There are also potential advantages in monitoring anti-osteoporotic treatment in the short term in addition to bone densitometry, to identify rapidly non-responders to therapy, or non-compliance. Recent publications underscore the importance of increased bone remodelling in the pathogenesis of microarchitectural deterioration that results in osteoporotic fracture. Anticatabolic treatments for osteoporosis reduce fracture risk by decreasing bone remodelling and increasing bone density. The major component of vertebral fracture risk reduction is through a reduction in bone remodelling. This decrease is also important for non-vertebral fracture risk reduction. It is therefore important to demonstrate a reduction in bone turnover to the normal pre-menopausal range when monitoring efficacy of anticatabolic therapy. Bone turnover markers are useful in monitoring compliance with therapy. This review highlights the most recent evidence regarding the use of bone turnover markers in the management of osteoporosis.

Osteoporosis is one of the most common and serious diseases of the musculoskeletal system. The lifetime fracture risk of a female aged 60 years is 56%, compared with 29% in a man of the same age. As a result of fragility fractures, the individual experiences pain, decreased mobility and a reduced quality of life. The onset of the disease is silent and insidious, the diagnosis often only being made after there is irreversible damage resulting from a fragility fracture. Thus, it would be highly desirable to develop sensitive and reliable methods for the early diagnosis and monitoring of treatment for this debilitating disease. The effective monitoring of treatment efficacy might also aid in long-term compliance with anti-osteoporotic therapy.

Advances in bone biochemistry and physiology have provided important insights into the pathogenesis of osteoporosis. Both post-menopausal and age-related bone loss are due to increased bone remodelling, with a relative imbalance between bone formation and bone resorption that favours the latter. Recker *et al.* [1]. dramatically confirmed this in a recent study of bone remodelling, determined by bone histomorphometry in pre-menopausal, early post-menopausal and late post-menopausal women. Activation frequency doubled at the menopause and was even higher in older normal women. Surprisingly, it was not increased further in untreated osteoporotic women than in older post-menopausal women. This underscores the importance of the contribution of increased trabecular bone remodelling at the tissue level to reduced bone strength. Anticatabolic therapy for osteoporosis normalizes this increased bone remodelling, preserves bone microarchitecture and increases bone mineral density (BMD), reducing the risk of subsequent fragility fractures.

Early biochemical changes in osteoporosis include the increased release of bone collagen degradation products by the action of osteoclasts. Osteoclast numbers and activity may be increased. The production of molecules released from either osteoblasts or by the bone matrix is also increased. The rate of release of these products of bone cells or their actions indicates abnormalities of bone and mineral metabolism. Biochemical assays for these molecules may be used to detect increased bone turnover, predict the risk of osteoporotic fractures, and monitor treatment efficacy and patient compliance. A number of biochemical assays readily detect these molecules, released from the bone matrix and as a result of bone collagen degradation, in both serum and urine. Several of these biochemical markers of bone turnover have the potential to serve both as aids in the decision to treat patients with low bone density and as effective and early indicators of the response to anticatabolic and anabolic therapy.

In this chapter, the most recent evidence regarding the potential utility of biochemical markers of bone turnover in the management of patients with osteoporosis is reviewed. To facilitate the understanding of the rationale and the value of biochemical bone turnover markers in osteoporosis management, Table 8.1 shows the biochemical markers of bone turnover currently available.

The type I collagen fragments ICTP and CTX reveal distinct enzymatic pathways of bone collagen degradation

Garnero P, Ferreras M, Karsdal MA, *et al*. *J Bone Miner Res* 2003; **18**: 859–67

BACKGROUND. Specific serum and/or urine immunoassays are used to measure the two bone resorption markers ICTP (pyridinoline cross-linked C-terminal telopeptide of type I collagen) and CTX (C-terminal telopeptide of type I collagen), fragments of type I collagen. Because the relative abundance of ICTP and CTX varies according to the aetiology of bone pathology, these two collagen fragments may be generated through different pathways of collagen digestion.

Interpretation. The release of ICTP and CTX from bone collagen by the proteinases reported to play a role in the solubilization of bone matrix, cathepsin K and metalloproteinases, was studied. Cathepsin K released large amounts of CTX, but did not result in detectable release of ICTP. By contrast, the matrix metalloproteinases (MMPs) released ICTP but did not result in a detectable release of CTX. The release of ICTP and CTX from bone cultures in the presence of well-established inhibitors of these proteinases and of matrix solubilization was also studied. An inhibitor of cathepsin K inhibited the release of CTX, but did not inhibit the release of ICTP. MMP inhibitors inhibited the release of both ICTP and CTX, in agreement with the likely role of MMPs in the initiation of bone resorption. MMP inhibitor treatment of mice bearing bone metastases led to a significant reduction in both serum ICTP and CTX and a decrease in the number of osteolytic lesions.

Table 8.1 Potential biochemical markers of bone turnover in osteoporosis

Bone formation	Bone resorption
Serum	Serum
Osteocalcin	Pyridinoline cross-linking telopeptides (C- and N-telopeptides, CTX, NTX, ICTP)
Bone-specific alkaline phosphatase	Free pyridinoline and deoxypyridinoline
Procollagen type I C-/N-extension peptide (PICP, PINP)	Tartrate-resistant acid phosphatase
	Bone sialoprotein
	Urine
	Pyridinoline cross-links
	Pyridinoline
	Deoxypyridinoline
	Pyridinoline cross-linking telopeptides (C- and N-telopeptides, CTX, NTX)

Source: Ebeling and Akkeson (2001 [2]).

Comment

The generation of ICTP and CTX depends on two different collagenolytic pathways mediated by either cathepsin K or MMPs. The cathepsin K pathway predominates in post-menopausal osteoporosis, Paget's disease and osteolytic metastases. However, the ICTP-generating MMPs are important in malignant causes of increased bone resorption, including metastatic breast and prostate cancer, and multiple myeloma. Specific antagonists of cathepsin K and MMPs may prove to be effective anticatabolic agents in non-malignant and malignant bone diseases in the future.

Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate

Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. *J Bone Miner Res* 2003; **18**: 1051–6

BACKGROUND. A decrease in fracture risk with anticatabolic therapy for osteoporosis results from a decrease in bone remodelling and an increase in bone density. The antifracture efficacy of anticatabolic therapies is only partially explained by increases in BMD. Early decreases in bone resorption may also be important.

INTERPRETATION. This prospective study examined changes in the levels of biochemical markers of bone resorption with risedronate treatment for osteoporosis as a surrogate for the decrease in fracture risk. Greater decreases in bone resorption markers were associated with greater decreases in vertebral (and non-vertebral) fractures. The authors tested this hypothesis by measuring two markers of bone resorption, urine CTX and urine NTX (N-terminal telopeptide of type I collagen), in osteoporotic patients studied in European, Australian and North American risedronate vertebral fracture trials. They studied 693 women with at least one vertebral deformity (mean age, 69 ± 7 years) who received 1000 mg calcium (and up to 500 IU vitamin D if required) and placebo or risedronate 5 mg daily for 3 years.

Baseline CTX and NTX levels were related to the incidence of vertebral fracture over 1 or 3 years, while only baseline NTX levels were related to non-vertebral fracture incidence over 3 years. The reductions in urinary CTX (median 60%) and NTX (51%) at 3–6 months with risedronate therapy were significantly associated ($P<0.05$) with the reduction in vertebral fracture risk (75% over 1 year and 50% over 3 years). The changes in NTX and CTX accounted for 49 and 55%, respectively, of risedronate's effect in reducing the risk of vertebral fractures in the first year and approximately two-thirds (CTX, 67%; NTX, 66%) over 3 years compared with placebo.

The relationships between vertebral fracture risk and changes from baseline in CTX and NTX were not linear ($P<0.05$). There was little further improvement in fracture benefit below a decrease of 55–60% or a T-score of ≤0.5 for CTX and 35–40% or a T-score of ≤1.5 for NTX, suggesting a threshold of reduced bone resorption and vertebral fracture risk reduction.

The changes in CTX and NTX also accounted for 77 and 54%, respectively, of risedronate's effect in reducing the risk of non-vertebral osteoporosis-related fractures over 3 years compared with placebo. However, no threshold existed for reduced bone resorption and non-vertebral fracture risk reduction. This may have been related to a real difference in the relationship between these two types of fracture, or it could be related to limited study power because of smaller numbers of patients with non-vertebral fractures.

Comment

Baseline levels of bone resorption markers were related to the incidence of both vertebral and non-vertebral fractures. The decrease in bone resorption in patients taking risedronate accounts for the major proportion of the reduction in fracture

risk. There may be a level of bone resorption reduction below which there is no further fracture benefit for reduction in the risk of vertebral fracture risk; however, it is important to note that the same is not true for reduction of the risk of non-vertebral fracture.

Biochemical markers for prediction of 4-year response in bone mass during bisphosphonate treatment for prevention of post-menopausal osteoporosis

Ravn P, Thompson DE, Ross PD, Christiansen C. *Bone* 2003; **33**: 150–8

BACKGROUND. This study with alendronate also examined the role of short-term changes in biochemical markers of bone turnover in the prediction of long-term response in bone mass during anticatabolic therapy. This study included younger post-menopausal women with normal bone density who were treated with two doses of alendronate (2.5 or 5.0 mg/day). In addition, change in BMD rather than fractures was the study end-point.

INTERPRETATION. In the Danish cohort ($n = 306$) of the Early Post-menopausal Intervention Cohort (EPIC) Study ($n = 1609$) of oral alendronate for the prevention of post-menopausal osteoporosis, bone markers (urine CTX [uCTX]; urine NTX [uNTX]; serum total osteocalcin measured by enzyme-linked immunosorbent assay [ELISA]; and serum total osteocalcin measured by radioimmunoassay [RIA]) were measured at 6-month intervals. The correlation between 6-month change in uCTX and 4-year change in spine and hip BMD was $r = –0.41$ and $r = –0.42$, respectively ($P<0.001$). The corresponding values for the other bone markers were $r = –0.53$ and $r = –0.42$ for uNTX, $r = –0.46$ and $r = –0.47$ for total osteocalcin (ELISA), and $r = –0.43$ and $r = –0.41$ for total osteocalcin (RIA) (all $P<0.001$).

Receiver operating characteristic curves were used to analyse the ability of the bone markers, measured at 6 months, to predict a change in spine BMD greater than 0% at 4 years. The best performance (defined as the maximum value of [sensitivity plus specificity]) was found at the cut-off values of a –29% change from baseline in uCTX, a –45% change from baseline in uNTX, a –13% change from baseline in total osteocalcin (ELISA), and a –15% change from baseline in total osteocalcin (RIA). At these values the corresponding sensitivity was 66% for uCTX, 76% for uNTX, 70% for total osteocalcin (ELISA) and 83% for total osteocalcin (RIA). The specificity was 80% for uCTX, 75% for uNTX, 71% for total osteocalcin (ELISA) and 55% for total osteocalcin (RIA).

The positive predictive value was 82% for uCTX, 80% for uNTX, 77% for total osteocalcin (ELISA) and 71% for total osteocalcin (RIA). The negative predictive value was 64% for uCTX, 70% for uNTX, 64% for total osteocalcin (ELISA) and 71% for total osteocalcin (RIA). The two bone resorption markers, CTX and uNTX, tended to have better performance, on the basis of higher positive and negative predictive values.

Comment

The predictive ability of the bone markers was dependent on the chosen cut-off level for the bone markers, which was dependent on the marker. Interestingly, the

cut-off levels for uCTX and uNTX were higher (less negative) than those for maximal vertebral fracture reduction by risedronate in the study of Eastell *et al.* Bone markers predicted a change in spine BMD greater than 0%, with a high positive predictive value (70–80%) and a high specificity (68–80%). There was a trend towards better performance in this respect for the bone resorption markers than for the bone formation markers.

Long-term variability of markers of bone turnover in post-menopausal women and implications for their clinical use: the OFELY study

Garnero P, Mulleman D, Munoz F, Sornay-Rendu E, Delmas PD. *J Bone Miner Res* 2003; **18**: 1789–94

BACKGROUND. Concern over the biological variability of bone markers has limited their use in individual patients. In this prospective study, serum osteocalcin (a bone formation marker) and CTX (a bone resorption marker) were measured every year for 4 years. Women were divided into tertiles of bone turnover based on serum levels of either marker at baseline and compared with their bone turnover tertile 4 years later to determine if tracking of bone turnover occurred.

INTERPRETATION. A total of 268 untreated post-menopausal women aged 50–81 years of age (mean ±SD, 63 ± 8 years) from a population-based cohort were studied. Fasting morning blood samples were collected every year for 4 years to measure serum intact osteocalcin and serum CTX as bone formation and resorption markers, respectively.

Serum osteocalcin levels increased minimally while CTX levels remained stable during follow-up (+1.2%/year, $P = 0.003$ for osteocalcin and –0.13%/year, $P = 0.70$ for CTX). At baseline, women were classified as having low (tertile 1), intermediate (tertile 2) or high (tertile 3) bone turnover. Agreement of classification between baseline and 4-year measurements was only moderate, with kappa scores of 0.51 (95% confidence interval [CI] 0.43–0.59) and 0.52 (0.44–0.60) for osteocalcin and CTX, respectively. However, fewer than 10% of women in tertile 1 or 3 of either marker at baseline were found in the opposite tertile 4 years later (Fig. 8.1). When the two markers were combined, only 2% of women with high bone turnover at baseline were classified as having low turnover 4 years later. Among women classified as having high bone turnover at baseline (tertile 3), 70–80% were also found to have high turnover 4 years later. There was more change in the women in tertile 2, of whom only 51 and 43% for osteocalcin and CTX, respectively, remained in the same tertile at the second measurement.

Comment

Serum levels of bone formation and resorption markers are relatively stable over 4 years in older post-menopausal women. Seventy to eighty per cent of women classified as having high bone turnover at baseline on the basis of one or both markers were similarly classified by the same methods 4 years later. However, in 20–30%

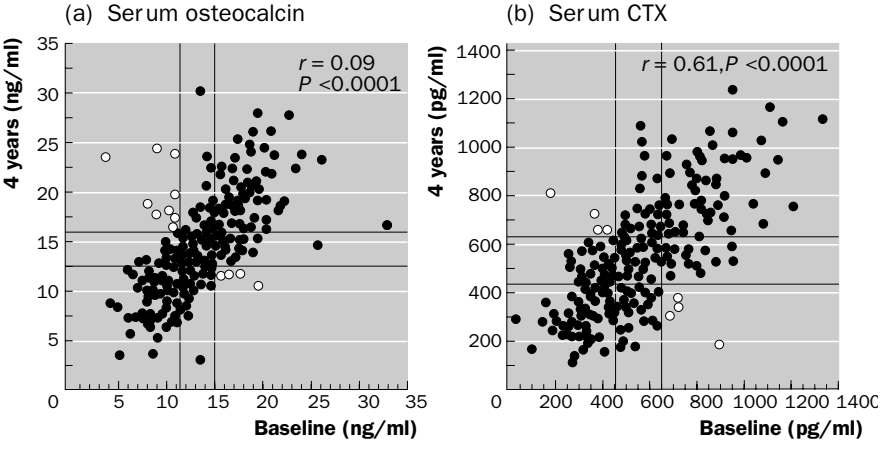

Fig. 8.1 Correlation between measurements of (a) serum osteocalcin and (b) serum CTX performed at a 4-year interval in 268 healthy untreated post-menopausal women. The vertical and horizontal dotted lines represent the cut-off values of bone marker levels at baseline and at 4 years between tertiles 1 and 2 and between tertiles 2 and 3. The top left quadrant includes women who were classified as having low turnover (T1) at baseline but high turnover (T3) 4 years later. The bottom right quadrant includes women classified as having high turnover at baseline but low turnover 4 years later. Source: Garnero *et al.* (2003) with permission of ASBMR.

of these women with high bone turnover the risk of fracture would be classified incorrectly. This suggests that further investigation would be required to reduce the number of false-positive patients who would be treated unnecessarily if the decision was made on a single bone marker measurement. For women with intermediate levels, their classification may be improved by performing a second measurement or by combining two bone turnover markers.

Relationship between pre-treatment bone resorption and vertebral fracture incidence in post-menopausal osteoporotic women treated with risedronate

Seibel MJ, Naganathan V, Barton I, Grauer A. *J Bone Miner Res* 2004; **19**: 323–9

BACKGROUND. The antifracture efficacy of bisphosphonates may depend on the level of pre-treatment bone turnover. Earlier studies on post-menopausal osteoporosis have suggested that the therapeutic efficacy of anticatabolic therapies might be influenced by pre-treatment bone turnover. However, all of these studies have used BMD as the primary end-point, so it remains unclear whether this association holds true for incident fractures.

INTERPRETATION. A *post hoc* analysis was made of a subset of the risedronate phase III clinical programmes, using the urinary excretion of deoxypyridinoline (uDPD) as an index of pre-treatment bone resorption (PBR). A total of 1593 women with post-menopausal osteoporosis who had baseline uDPD values and paired spinal radiographs available were pooled, in similar proportions, from the risedronate European, Australian and North American vertebral fracture reduction (VERT) and hip fracture reduction (HIP) trials. Patients from treatment and placebo groups were stratified by the pre-menopausal normative median for uDPD. The four resulting groups were balanced for age, years since menopause, body mass index, baseline femoral neck BMD, and number of prevalent fractures, but baseline lumbar spine BMD was significantly higher in patients with low PBR.

In all groups, the proportion of patients with new vertebral fractures was higher in patients with baseline uDPD levels above the normative median. The incidence of vertebral fracture was significantly lower in groups assigned to risedronate than in those assigned to placebo. This effect was independent of PBR: in patients with high PBR, the relative risk of vertebral fracture after 1 year of risedronate was 0.28 ($P = 0.03$ compared with controls; absolute risk reduction 7.1%). In patients with low PBR, the relative risk of fracture after 1 year was 0.33 ($P < 0.001$; absolute risk reduction 4%). After 3 years, the relative risk of fracture was 0.52 ($P = 0.042$; absolute risk reduction 8.3%) in patients with high PBR and 0.54 ($P = 0.002$; absolute risk reduction 7.1%) in patients with low PBR. Results were similar after adjusting for age, baseline lumbar spine BMD and prevalent fractures. The number needed to treat to avoid one vertebral fracture at 12 months was 15 in the group of patients with high PBR and 25 in patients with low PBR. Risedronate significantly increased lumbar spine BMD. During the first year of treatment, women with high PBR gained lumbar spine BMD at a faster rate than patients with low PBR.

Comment

The efficacy of risedronate in reducing incident vertebral fractures in women with post-menopausal osteoporosis is largely independent of pre-treatment bone resorption rates. Risedronate reduced incident vertebral fractures in women with post-menopausal osteoporosis independently of the pre-treatment bone resorption rate. However, increases in spinal BMD were greater in women with higher pre-treatment bone resorption rates.

Biochemical markers of bone metabolism and prediction of fracture in elderly women

Gerdhem P, Ivaska KK, Alatalo SL, *et al*. *J Bone Miner Res* 2004; **19**: 386–93

BACKGROUND. Osteocalcin fragments may provide better information on different aspects of bone turnover than the intact molecule. Tartrate-resistant acid phosphatase (TRACP) isoform 5b provides information on different aspects of bone resorption other than that provided by pyridinium cross-links.

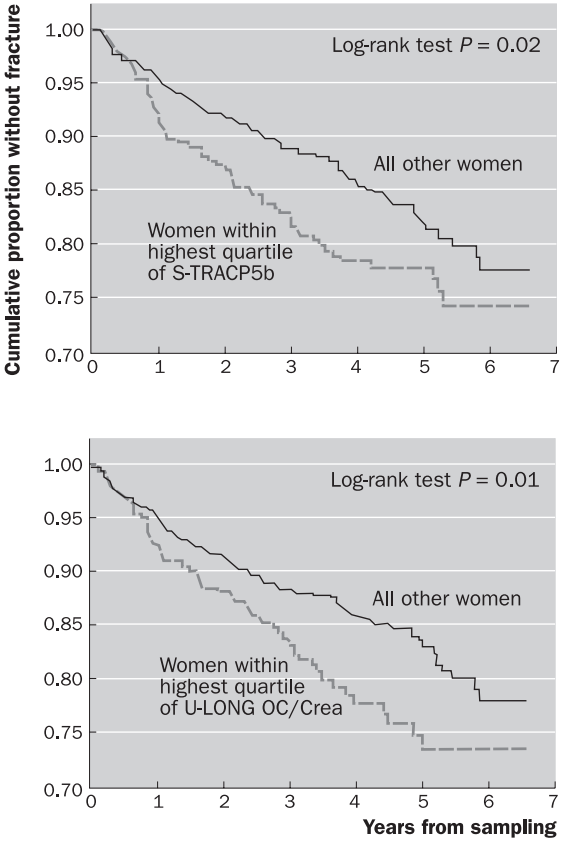

Fig. 8.2 Proportion of subjects without any prospective fracture (Kaplan-Meier). Women within the highest quartile of sTRACP5b, or uLongOC/Crea (the long form of urine osteocalcin corrected for urine creatinine concentration) are compared with all other women. *P*-values for log-rank tests are shown. Source: Gerdhem *et al*. (2004) with permission of ASBMR.

Interpretation. Ten bone turnover markers, including two novel assays for osteocalcin fragments, were used to predict fracture in 1040 randomly recruited 75-year-old women. Over an average of 4.6 years (range 3–6.5) of follow-up, 178 of the women sustained at least one fracture. The total number of fractures was 231, the most common fractures being vertebral (49 women) and hip (41 women) fractures. Serum bone-specific alkaline phosphatase and four different forms of serum osteocalcin (sOC) were analysed as markers of bone formation, and serum CTX (sCTX), serum TRACP isoform 5b (sTRACP5b) and urinary free DPD (uDPD) were analysed as markers of bone resorption. Two novel assays for osteocalcin fragments in urine (uOC) were analysed. One measured all urinary osteocalcin fragments, while the other measured

only the longest fragments. Areal BMD was measured by dual-energy X-ray absorptiometry in the femoral neck and lumbar spine.

When women with prospective fractures were compared with women without fractures, sTRACP5b, sCTX, one form of sOC, one form of uOC were higher in women with a fracture of any type (all $P<0.05$), and all bone markers were higher in women with a clinical vertebral fracture (all $P<0.05$). Surprisingly, markers were not significantly elevated in women with hip fracture. When women within the highest quartile of a bone marker were compared with all others, sTRACP5b and one form of uOC predicted the occurrence of a fracture of any type (odds ratio 1.55 and 1.53; $P<0.05$) (Fig. 8.2). sTRACP5b, the two forms of uOC, and sCTX predicted vertebral fracture (odds ratio 2.28, 2.75, 2.71 and 1.94, respectively; all $P<0.05$). The predictive value for clinical vertebral fracture remained significant for sTRACP5b and the two forms of uOC after adjusting for areal BMD of the spine or femoral neck (odds ratio 2.02–2.25; $P<0.05$). However, bone markers were not able to predict hip fracture.

Comment

These results showed for the first time that, in elderly women, biochemical markers of bone turnover can predict fracture, and in particular, clinical vertebral fractures. In elderly women, serum TRACP5b and urinary fragments of osteocalcin are promising new bone markers that allow the prediction of an increased likelihood of vertebral fractures. Bone markers did not predict hip fractures, implying that different mechanisms may exist.

Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk

Sarkar S, Reginster JY, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. *J Bone Miner Res* 2004; **19**: 394–401

BACKGROUND. As noted above, a decrease in fracture risk with anticatabolic therapy for osteoporosis results from a decrease in bone remodelling and an increase in bone density. The antifracture efficacy of anticatabolic therapies is only partially explained by increases in BMD. BMD change has previously been noted to be a poor predictor of the reduction in vertebral fracture risk in raloxifene-treated women, whereas change in bone turnover markers is significantly associated with fracture risk reduction.

INTERPRETATION. The ability of 1-year percentage changes in bone turnover and BMD to predict vertebral fracture risk in 2503 women (one-third of the participants) from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial who had measurements of bone turnover markers was examined. The MORE study was a randomized, placebo-controlled trial of women with osteoporosis treated with raloxifene 60 or 120 mg/day for 3 years.

The prediction of vertebral fracture risk was examined using changes in both BMD and two bone turnover markers: serum osteocalcin and bone-specific alkaline phosphatase (BSAP). Logistic regression models were constructed using 1-year

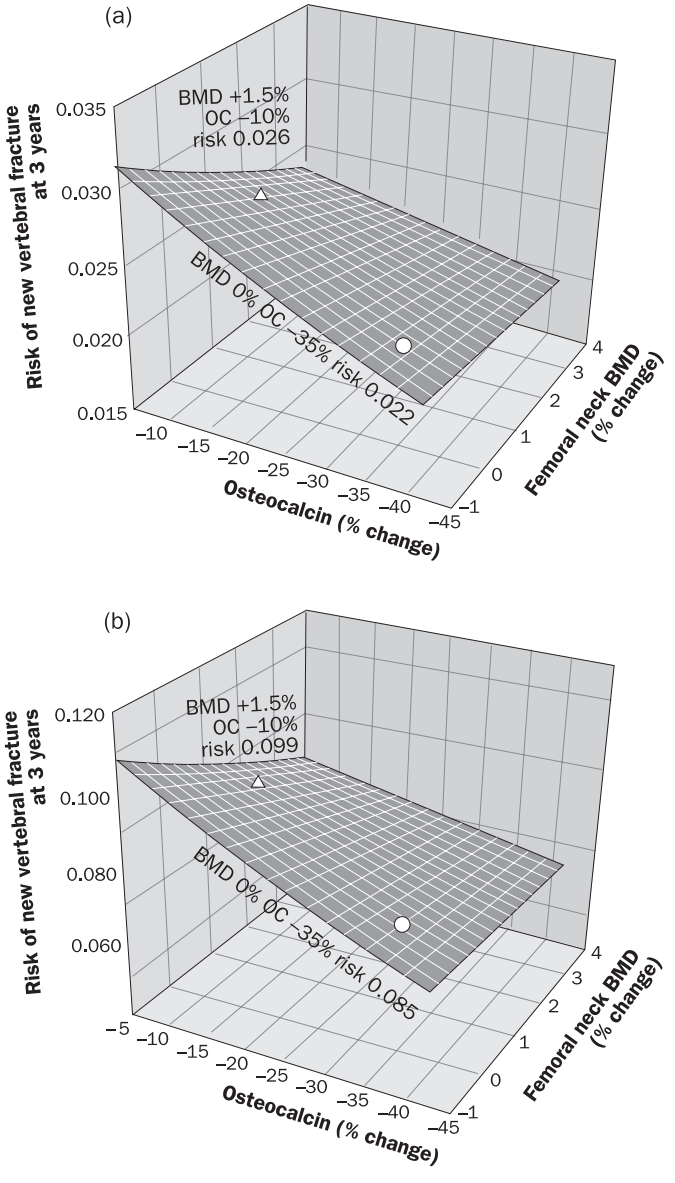

Fig. 8.3 The predicted risk of vertebral fracture for each percentage change in osteocalcin or femoral neck BMD. (a) Women without a prevalent vertebral fracture. (b) Women with a prevalent vertebral fracture. Source: Sarkar *et al*. (2004) with permission of ASBMR.

percentage changes in BMD and bone turnover and relevant baseline demographics to predict the risk of vertebral fracture with both raloxifene doses at 3 years.

The mean percentage decreases in serum osteocalcin, BSAP and increase in femoral neck BMD were –28.2, –29.0 and 1.9%, respectively, at 1 year. The signal-to-noise ratio was best for serum osteocalcin. Prevalent vertebral fracture status ($P<0.0001$), baseline lumbar spine BMD ($P<0.0001$) and number of years post-menopausal ($P=0.0005$) were independent predictors of fracture risk in raloxifene-treated patients. Therapy-by-change in femoral neck BMD ($P=0.02$) and therapy-by-change in osteocalcin (osteocalcin; $P=0.01$) were also significant for all treatment groups, indicating that changes in BMD and osteocalcin had different effects on fracture risk for the placebo and pooled raloxifene groups (Fig. 8.3). The final model included significant baseline variables and change in osteocalcin ($P=0.01$), whereas change in femoral neck BMD was not significant.

Comment

The percentage change in osteocalcin was better able to predict the reduction in vertebral fracture risk than the percentage change in femoral neck BMD in patients treated with raloxifene. However, in post-menopausal women with a femoral neck BMD response greater than 3.5%, a low or high osteocalcin response to therapy did not alter the risk of vertebral fracture. Nevertheless, in most of the women treated with raloxifene the percentage change in osteocalcin was a better predictor of the reduction in vertebral fracture risk than femoral neck BMD. This study confirms that changes in bone turnover are better predictors than BMD of the reduction in the risk of vertebral fracture with raloxifene therapy.

Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial

Bauer DC, Black DM, Garnero P, *et al.*; Fracture Intervention Trial Study Group. *J Bone Miner Res* 2004; **19**: 1250–8

BACKGROUND. The antifracture efficacy of anticatabolic therapies is only partially explained by increases in BMD. This study adds to that of Eastell *et al.* to provide more data on the relationship between short-term changes in biochemical markers of bone turnover and the risk of non-spine fracture among bisphosphonate-treated women. It also helps to define the clinical use of such measurements.

INTERPRETATION. The relationship between 1-year percentage changes in bone turnover after alendronate or placebo treatment and the subsequent risk of hip, non-spine and spine fracture among 6186 post-menopausal women enrolled in the Fracture Intervention Trial (FIT) was examined. The investigators measured serum biochemical markers of bone turnover (bone-specific alkaline phosphatase [ALP], intact N-terminal propeptide of type I collagen [PINP] and serum CTX) and BMD of the spine and hip at baseline and after 1 year of alendronate or placebo treatment. During a mean

follow-up of 3.6 years (range 2.5–4.5 years), 72 hip, 786 non-spine and 336 vertebral fractures were documented. The time of specimen collection was unknown and the specimens were not archived optimally. In addition, not all patients were fasting at the time of specimen collection, a potential limitation in the interpretation of the CTX data.

In the alendronate group, the mean percentage changes in serum bone ALP, PINP and CTX were –31, –51 and –59.2% respectively. The results showed that each 1 SD reduction in the 1-year change in bone ALP was associated with fewer spine (odds ratio 0.74; 95% CI 0.63–0.87), non-spine (relative hazard 0.89; CI 0.78–1.00; $P<0.050$) and hip fractures (relative hazard 0.61; CI 0.46–0.78) (Fig. 8.4). The associations between 1-year change in serum PINP and CTX and fracture risk were of a similar magnitude, but did not reach significance. Fasting or non-fasting status did not affect the relationships between change in CTX and spine and non-spine fractures. Adjustment for baseline BMD had little effect on these relationships.

Alendronate-treated women with at least a 30% reduction in bone ALP had a lower risk of non-spine (relative hazard 0.72; CI 0.55–0.92) and hip fractures (relative hazard 0.26; CI 0.08–0.83) relative to those with reductions of less than 30%. Reductions of 30% or more in bone ALP occurred in 56% of alendronate-treated women. For the absolute fracture risk, the probability of a non-spine fracture was 9.8, 8.7 and 6.8% in placebo-treated patients, alendronate-treated patients with bone ALP below 30% and alendronate-treated patients with bone ALP at least 30%, respectively. For hip fractures, corresponding absolute risks were 1.0, 0.8 and 0.2%.

Comment

Greater reductions in bone turnover with alendronate therapy are associated with fewer hip, non-spine and vertebral fractures, and the effect is likely to be more

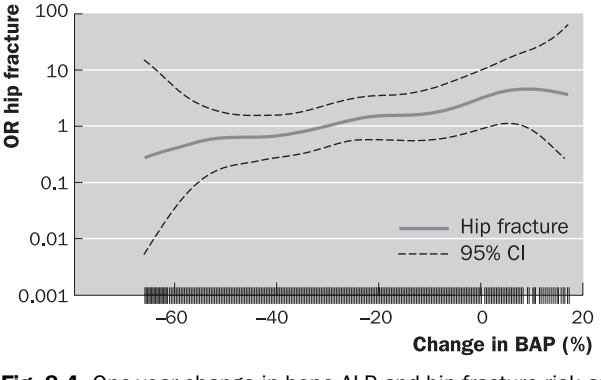

Fig. 8.4 One-year change in bone ALP and hip fracture risk among alendronate-treated women. Percentage change in bone ALP and predicted risk (log odds ratio) of hip fracture (*solid line*) and 95% CI (*dotted lines*). Source: Bauer *et al.* (2004) with permission of ASBMR.

important than that observed in the 1-year change in BMD. With alendronate therapy, a greater reduction in one or more biochemical markers is associated with a lower risk of fracture. There is no evidence of a plateau of antifracture efficacy or that the greatest reductions in bone turnover are associated with loss of antifracture efficacy. This is the largest study relating reduction in bone turnover to fracture risk, but, like the other studies, its main limitation is the use of within-treatment group analyses, which have the same limitations as observational studies, including unmeasured confounding.

Dissociation between global markers of bone formation and direct measurement of spinal bone formation in osteoporosis

Frost ML, Fogelman I, Blake GM, Marsden PK, Cook GJR. *J Bone Miner Res* 2004; **19**: 1797–804

BACKGROUND. Measurements of biochemical markers of bone turnover indicate global bone remodelling throughout the entire skeleton. Bone turnover markers consistently demonstrating increased bone turnover is a feature of patients with osteoporosis.

INTERPRETATION. The non-invasive functional imaging technique of 18F-fluoride positron emission tomography (PET) was used to directly quantitate bone metabolism at specific sites in the skeleton, including the clinically important site of the lumbar spine. The authors compared regional skeletal kinetics in 72 post-menopausal women (mean age 61 years) classified as normal, osteopenic or osteoporotic according to their BMD T-score at the lumbar spine. Each woman had a dynamic PET scan of the lumbar spine after injection of 90 MBq of 18F-fluoride ion and measurements of biochemical markers of bone formation (serum bone-specific ALP [BSALP] and osteocalcin) and bone resorption (urine free DPD cross-links). The arterial plasma input function was derived using aorta arterial activity from the PET image. Time–activity curves were obtained by placing regions of interest over the lumbar vertebrae. They used a previously described three-compartmental bone kinetic model to calculate bone blood flow (K_1) and the net plasma clearance of tracer to bone mineral (K_i), reflecting regional osteoblastic activity (ml/min/ml). The rate constants k_2, k_3, and k_4, which describe transport between plasma, the extracellular fluid compartment and the bone mineral compartment, were also measured.

The net uptake of fluoride to the bone mineral compartment (K_i) was 16.7% lower in the osteoporotic group compared with both the osteopenic and the normal group. The fraction of the tracer in the extravascular tissue space that underwent specific binding to bone mineral ($k_3/k_2 + k_3$) was also significantly reduced in the women classified as osteoporotic. In contrast, levels of BSALP were significantly higher in the osteoporotic group compared with the normal and osteopenic groups, by 35 and 27% respectively. However, serum osteocalcin and urine DPD levels were not increased in women with osteoporosis. A significant negative correlation ($r = -0.41$) was observed between levels of BSALP and the fraction of the tracer that underwent specific binding to bone mineral.

Lower values of K_i, a measure of regional bone formation activity at the lumbar spine,

were seen in post-menopausal women with osteoporosis, whereas levels of BSALP, a measure of total skeletal bone formation, were significantly increased.

Comment

These findings are suggestive of increased global skeletal bone turnover in women with post-menopausal osteoporosis, but with relatively reduced regional bone formation at the predominantly trabecular site of the lumbar spine. Further studies, including bone histomorphometric techniques, are required to confirm these findings. In addition it would be useful to investigate whether different relationships between fluoride kinetics and bone turnover markers are seen at predominantly cortical sites, such as the femoral neck and distal radius.

Fracture-induced changes in bone turnover: a potential confounder in the use of biochemical markers in osteoporosis

Åkesson K, Kakonen SM, Josefsson PO, Karlsson MK, Obrant KJ, Pettersson K. *J Bone Miner Metab* 2005; **23**: 30–5

BACKGROUND. Biochemical bone turnover markers are increased in post-menopausal women with osteoporosis, but it is not clear whether all bone marker interpretations are affected by acute clinical fractures.

INTERPRETATION. Short- and long-term bone metabolic effects of fracture on biochemical markers were assessed by utilizing the clinical fracture model of proximal tibial osteotomy in 14 patients. This model of an induced fracture of a major bone has the advantage of enabling the assessment of pre-fracture bone turnover. Repeat marker measurements were performed at 6–9 weeks, 4–7 months, 9–13 months and 14–17 months after fracture. Serum was assayed for PICP, total ALP and ICTP, and free DPD was measured in urine. Serum osteocalcin was measured using two novel assays, which both measure full-length and fragmented forms of osteocalcin (total osteocalcin), one of the assays specifically detecting only the carboxylated form of osteocalcin. Osteocalcin was also measured in urine using the same assays as those used for serum.

Bone resorption markers increased earlier after fracture than bone formation markers. DPD increased significantly, with a doubling at 6 weeks, while serum ICTP increased by 73% ($P<0.01$ and $P<0.001$). By contrast, serum total osteocalcin increased to a peak 4–7 months after fracture ($P<0.001$), and a similar increase was seen for carboxylated osteocalcin ($P<0.05$) and ALP ($P<0.01$). Bone formation had returned to baseline after a year. Urine osteocalcin increased to a maximum of 84% at 6 weeks, similar to the time course of bone resorption markers.

Comment

Bone turnover is altered within 6 weeks of fracture; the major changes occurred within 6 weeks to 6 months, but they may persist for up to a year. The early initial greater increase in bone resorption than bone formation may contribute to the

increased post-fracture bone loss. Two novel urine osteocalcin assays show a pattern of change similar to those of established markers of bone resorption, which may indicate that they measure bone resorption and the release of previously incorporated osteocalcin from hydroxyapatite crystals in bone. Fracture-induced effects on bone turnover are significant and are thus potential confounders in the assessment of patients with osteoporosis and their response to anticatabolic therapy.

Early changes in biochemical markers of bone formation predict BMD response to teriparatide in post-menopausal women with osteoporosis

Chen P, Satterwhite JH, Licata AA, *et al*. *J Bone Miner Res* 2005; **20**: 962–70

BACKGROUND. Early reductions in biochemical markers of bone turnover with anticatabolic therapy correlate negatively with subsequent increases in BMD. Parathyroid hormone (PTH) is the prototypic anabolic agent that increases bone formation and BMD, and reduces fracture risk. However, it is unclear whether early changes in bone turnover markers predict either the BMD response or fracture risk reduction with PTH therapy.

INTERPRETATION. Whether early changes in biochemical markers predicted subsequent increases in BMD in response to daily human PTH(1–34) (teriparatide) therapy was studied in 1637 women with post-menopausal osteoporosis enrolled in the Fracture Prevention Trial. The women were randomized to receive daily, self-administered, subcutaneous injections of placebo, teriparatide 20 μg/day or teriparatide 40 μg/day. Serum concentrations of two bone formation markers (bone ALP and PICP) and urinary concentrations of two bone resorption markers (free DPD and NTX) were assessed in a trial population subset ($n = 520$) at baseline and at 1, 3, 6 and 12 months. The authors also assessed serum concentrations of another bone formation marker, PINP, in a subset of 771 women at only two time-points: baseline and 3 months. Lumbar spine BMD was measured by dual energy X-ray absorptiometry at baseline and 18 months. Femoral neck BMD was measured at baseline and 12 months.

Baseline bone turnover status correlated positively and significantly with BMD response. The highest correlations occurred for the lumbar spine BMD response to teriparatide 20 μg/day for PICP, PINP and NTX (0.36, 0.41 and 0.40 respectively; $P < 0.05$). The bone formation markers, PICP and PINP, increased within 1–3 months of commencing PTH treatment (Fig. 8.5). Among all the biochemical markers, increases in PICP at 1 month and PINP at 3 months correlated best with increases in lumbar spine BMD at 18 months (0.65 and 0.62, respectively; $P < 0.05$). The relationships between these two biochemical markers and the lumbar spine BMD response were stronger than the corresponding relationships for the femoral neck BMD response. Using receiver operating curve analysis, the increases in PICP at 1 month and PINP at 3 months were the most sensitive (sensitivity 59 and 69%, respectively) and accurate (positive predictive value 93 and 88%, respectively) predictors of the lumbar spine BMD response. Cut-off values for changes in these markers were also calculated.

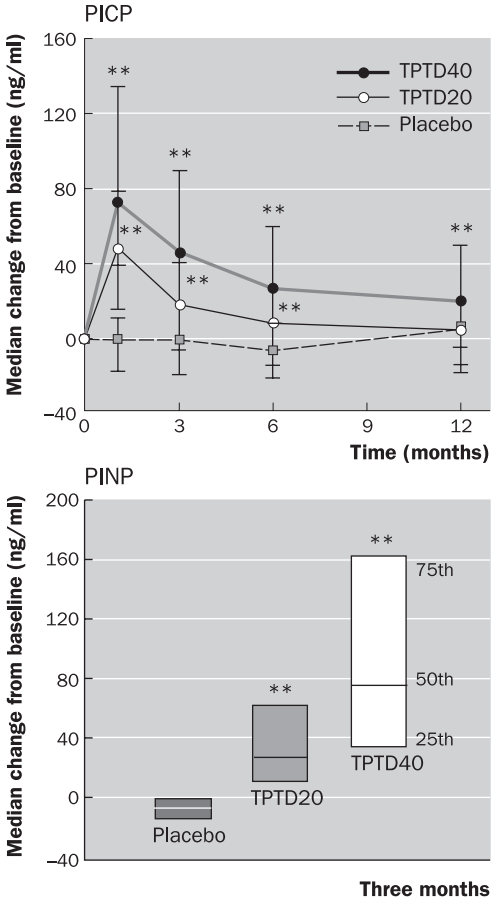

Fig. 8.5 Median absolute changes in serum PICP from baseline at 1, 3, 6 and 12 months. Bars represent the 25th and 75th percentiles. Absolute changes in serum PINP at 3 months are represented in the bar graph. The 75th percentile is represented by the top of the bar graph, the median by the *white line*, and the 25th percentile by the bottom of the bar graph. TPTD20, teriparatide 20 g/day; TPTD40, teriparatide 40 g/day. $*P<0.05$, $**P<0.01$ versus placebo. Source: Chen *et al.* (2005) with permission of ASBMR.

Comment

Early increases in two bone formation markers were the best predictors of the BMD response to teriparatide in this analysis. However, there were no correlations between changes in bone turnover markers and fracture risk during teriparatide therapy in the Fracture Prevention Trial because the power of the study was limited by the small number of fractures in the biochemical marker cohorts. Further

studies are therefore required to define the reduction in fracture risk on the basis of biochemical bone turnover marker responses to teriparatide therapy.

Conclusion

Previously, bone turnover could only be assessed by invasive and/or expensive bone histomorphometry or nuclear medicine methods. The elucidation of the underlying pathophysiological cellular processes of bone turnover in osteoporosis led to the development of biochemical markers of bone resorption and formation that can be measured in the serum and urine. The bone turnover markers reflect different cellular activities of osteoclasts and osteoblasts. This is an important consideration in the selection of a marker. Bone turnover levels tend to track over time; 70–80% of women classified as having high bone turnover at baseline are classified similarly 4 years later. The classification of bone turnover level in the individual may be improved by using both a marker of bone resorption and a marker of bone formation. It is also important to note that fracture-induced effects on bone turnover are significant and are thus potential confounders in the assessment of patients with osteoporosis and their response to anticatabolic therapy.

The recent publications in patients with osteoporosis summarized above indicate that biochemical markers of bone turnover, particularly bone resorption markers, may add an independent, predictive value in the assessment of bone loss and fracture risk. Changes in bone turnover markers during anti-osteoporotic therapy also predict changes in BMD and reductions in the risk of fracture. With anticatabolic agents, the decrease in bone turnover marker levels with treatment is strongly related to the reduction in vertebral fracture risk with raloxifene, or in vertebral and non-vertebral fracture risk with risedronate or alendronate. In fact, changes in bone turnover are better predictors than BMD of the reduction in the risk of vertebral fracture with raloxifene therapy. After anabolic therapy with teriparatide, early increases in bone formation markers are strong predictors of BMD responses, but as yet there are no data relating bone marker changes to reductions in fracture risk. In all studies, the use of within-treatment group analyses has the same limitation as observational studies, making it more difficult to generalize these findings to individual patients. However, there are clearly potential advantages of using bone turnover markers for monitoring anti-osteoporotic treatment in addition to bone mass measurements, to identify non-responders or non-compliance, particularly early during treatment before changes in BMD may become apparent.

Despite the rapid advances in the use of biochemical markers in the assessment of disorders of bone metabolism, including osteoporosis, bone markers are currently used mainly in the research arena. However, with the advent of reduced analytical variability and serum assays for bone turnover markers, their transition into everyday clinical practice is fast approaching. The use of more complex treatment regimens in the near future, requiring closer monitoring, will also increase their clinical utility.

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9

Bone quality

JULIET COMPSTON

Introduction

The recent interest in bone quality has been stimulated by the recognition that the traditional measure of bone strength in clinical practice, namely bone densitometry, does not always reliably predict fracture risk [1]. This has led to the search for other aspects of bone composition and structure that may contribute, independently of bone mineral density (BMD), to bone fragility and fracture risk. This review describes some disease states in which abnormalities of bone quality are associated with increased fracture risk, in some cases despite increased BMD. In addition, approaches to the assessment of bone quality will be discussed together with how these have advanced our understanding of the mechanisms by which pharmacological interventions improve bone strength.

Components of bone quality

Bone strength is determined by bone mass, geometry and quality. The latter comprises a number of aspects of bone structure and composition, including bone turnover, microarchitecture, the degree and distribution of mineralization, the extent of microdamage and its repair and, finally, the composition of bone matrix and mineral (Fig. 9.1). These components are largely interdependent, so that a

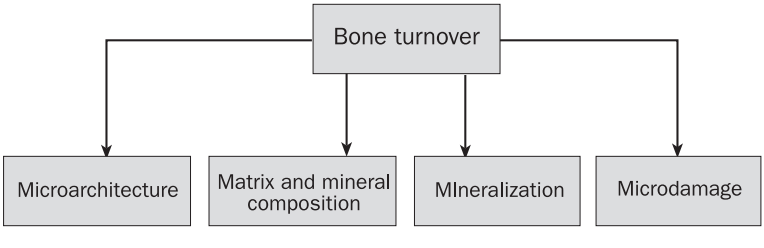

Fig. 9.1 Determinants of bone quality.

Table 9.1 Assessment of bone quality

Variable	Method
Bone turnover	Biochemical markers, histomorphometry
Bone microarchitecture	Histomorphometry, μCT, SR-μCT, HR-MRI, pQCT
Bone mineralization	Microradiography, qBSEI, SAXS, spectroscopy
Microdamage	Histology, confocal microscopy
Matrix/mineral composite	SAXS, TEM, FTIR, Raman spectroscopy, biochemistry

μCT, micro-computed tomography; SR, synchrotron radiation; HR-MRI, high-resolution magnetic resonance imaging; pQCT, high-resolution peripheral quantitative computed tomography; qBSEI, quantitative back-scattered electron imaging; FTIR, Fourier transform infrared; TEM, transmission electron microscopy; SAXS, small-angle X-ray scattering.

primary abnormality in one will lead to changes in others. In particular, bone turnover is a major determinant of other components of bone quality and hence its measurement in clinical practice is of key importance.

Assessment of bone quality

The assessment of bone quality *in vivo* is limited to measurement of bone turnover and of some aspects of bone geometry and architecture. Nevertheless, using biopsy or autopsy specimens, a number of approaches have been developed that have expanded our understanding of the contributions of bone quality to bone strength in untreated and treated disease (Table 9.1).

Bone turnover

Bone turnover is most commonly assessed in clinical practice by measurement of biochemical markers of resorption and formation (Table 9.2). The markers, which are mainly serum-based, reflect whole-body turnover and thus provide assessment predominantly of cortical bone, which constitutes 80–90% of the skeleton. They show considerable biovariability, both within and between individuals, and some are affected by dietary intake, so specimens should ideally be obtained in the fasting state and at a standard time of the day. It should be noted that biochemical markers reflect bone turnover, but do not provide information about remodelling balance in individual bone remodelling units.

Bone histomorphometry can also be used to assess bone turnover. Following the administration of two time-spaced doses of a tetracycline derivative prior to the biopsy, its uptake at actively forming surfaces can be visualized and quantified (Fig. 9.2) [2]. The surface extent of tetracycline-labelled surfaces provides an index of bone turnover, provided that bone remodelling is in a steady state and that bone resorption and formation are coupled. *In vivo*, biopsies are taken from the iliac crest and bone turnover at this site may not reflect turnover elsewhere; indeed, there is evidence for considerable intra-individual variation throughout the skeleton [3].

Table 9.2 Biochemical markers of bone turnover

Bone formation	
	Osteocalcin
	Bone-specific alkaline phosphatase
	Procollagen type 1 N propeptide (P1NP)
Bone resorption	
	Collagen type 1 telopeptides (CTX, NTX)
	Deoxypyridinoline
	Tartrate-resistant acid phosphatase type 5b

Thus it is not surprising that there may be discrepancies between biochemical markers and histomorphometry in their assessment of bone turnover; in particular, the magnitude of suppression of bone turnover by anticatabolic agents is generally greater when assessed by the latter technique. Methods such as ^{18}F-fluoride positron emission tomography and single photon emission computed tomography gamma-camera imaging using technetium-labelled bisphosphonate provide new approaches to the assessment of regional bone turnover at sites of clinical relevance, for example the spine.

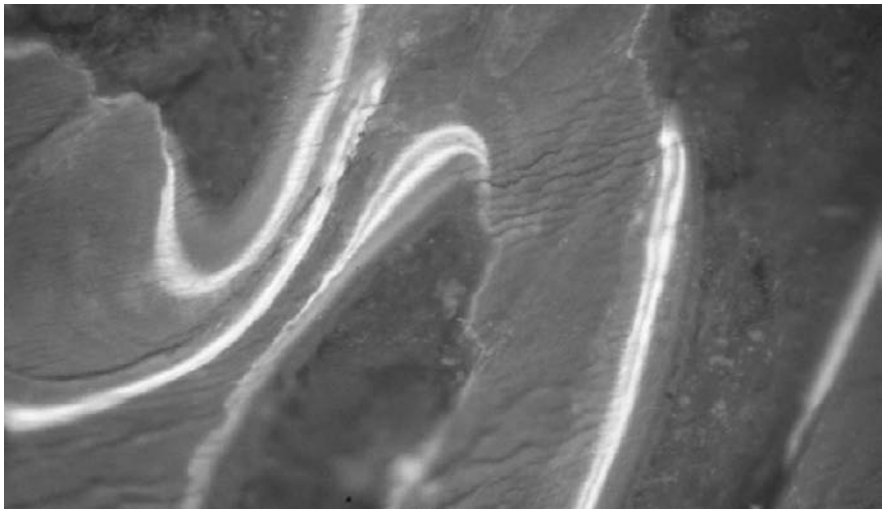

Fig. 9.2 Tetracycline labelling in bone following administration of two time-spaced oral doses of a tetracycline derivative prior to the biopsy. The tetracycline is taken up at actively forming surfaces of bone and fluoresces under blue light.

Assessment of bone microarchitecture

Changes in bone microarchitecture make an important contribution to bone strength and may not always be wholly captured by changes in BMD. Both cortical and cancellous architecture are important in this respect; in cancellous bone the size and shape of trabeculae and their connectivity and orientation (anisotropy) all contribute to bone strength, whilst in cortical bone the relevant measurements are cortical width, cortical porosity and bone size. Although some of these architectural features can be assessed in histological sections of bone biopsy specimens using two-dimensional approaches, such as measurement of trabecular thickness, separation and number, strut analysis, trabecular bone pattern factor and marrow and trabecular star volume [4], more sophisticated methods have now been developed that enable three-dimensional visualization and quantification. These include high-resolution magnetic resonance imaging (HR-MRI), high-resolution peripheral quantitative computed tomography (HR-pQCT), microcomputed tomography (μCT) and synchrotron radiation μCT [5]. These are currently research tools and, *in vivo*, can only be applied to the peripheral skeleton; however, technological advances may eventually extend their use to the central skeleton. In addition, these approaches have the potential to yield biomechanical information through the use of finite element analysis (FEA).

Changes in bone microarchitecture in untreated and treated disease states are determined by the underlying alterations in bone remodelling. Thus, high turnover states and increased osteoclast activity predispose to trabecular penetration, loss of connectivity, cortical thinning and increased cortical porosity, whilst low bone turnover states and reduced osteoblast activity are associated with trabecular thinning and relative preservation of bone microarchitecture (Fig. 9.3).

Assessment of bone mineralization

Mineralization of bone matrix in adult human bone occurs in two phases. Primary mineralization describes the deposition of bone mineral during the bone remodelling cycle, whereas secondary mineralization is the process of further mineralization subsequent to completion of the remodelling cycle. The degree of secondary mineralization is critically dependent on bone turnover: when this is low, there is more time for mineralization to proceed, whereas in high-turnover states recently formed bone is removed before there is time for prolonged secondary mineralization [6]. The amount of mineralization, and its distribution throughout bone, can be assessed *ex vivo* by several methods, including microradiography, quantitative back-scattered electron imaging and spectroscopic techniques. The degree of mineralization is captured by BMD measurements, but its contribution relative to other factors influencing BMD cannot be deduced directly.

Assessment of microdamage

Microdamage in bone consists of microcracks and microfractures. The relationship between these, if any, is unknown and although both forms of microdamage

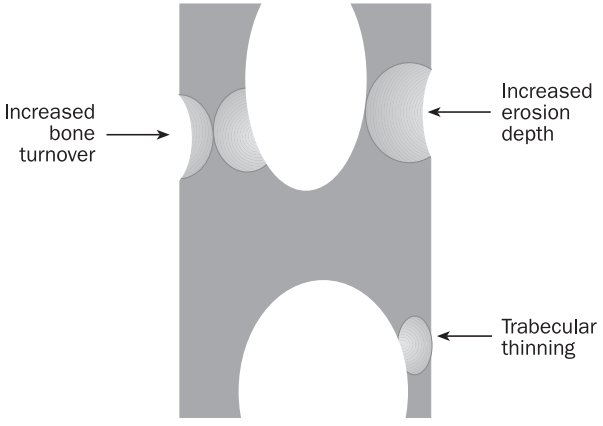

Fig. 9.3 Mechanisms of trabecular penetration. Both increased resorption depth and increased bone turnover favour trabecular penetration. However, trabecular thinning will also eventually lead to trabecular penetration, as a result of erosion by a resorption cavity of normal depth.

accumulate with age their biomechanical consequences remain unclear [7]. Assessment of microdamage relies on histological techniques and confocal microscopy and quantitative data are mainly restricted to animal studies.

Assessment of bone matrix and mineral composition

The importance of bone matrix and mineral composition as determinants of bone strength has until recently received little attention. Changes in the cross-linking of type 1 collagen [8] and post-translational modifications, such as lysyl-hydroxylation, glycosylation and β-isomerization of aspartate residues in carboxyterminal telopeptides, may have significant biomechanical implications [9,10], as may alterations in the size and structure of bone mineral. The extent to which such changes are driven by bone turnover is currently unknown, but since collagen structure and mineralization are so closely associated it is likely that, when changes do occur, both are affected [11].

Recently, new approaches to studying bone matrix and composition have been developed. These include Raman and Fourier transform infrared spectroscopy, small-angle X-ray scattering (SAXS) and transmission electron microscopy. These techniques can only be applied *ex vivo* to bone specimens; however, assays for the measurement of β-isomerization of cross-linked C-terminal telopeptide of type 1 collagen (CTX) have recently been developed. This approach, together with the development of other serum- or urine-based biochemical measurements of changes in collagen composition, is an important area for future research.

Disease states: what they teach us about bone quality

Increased bone fragility and fracture risk may be caused by diverse abnormalities in bone quality and sometimes occur despite increased BMD. Examination of these disease states illustrates the interdependence of the different components of bone quality and the importance of normal bone quality in the maintenance of skeletal integrity. Some examples are given below.

Changes in bone mineralization

Quantitative abnormalities of mineralization provide an example of how both extremes may be associated with increased bone fragility. Osteomalacia is associated with defective mineralization of bone, resulting in accumulation of osteoid (Fig. 9.4). Osteomalacic bones are soft and bend easily, resulting in the characteristic skeletal deformities that are seen in rickets and in severe cases of adult osteomalacia; in addition, pseudofractures and pathological fractures may occur. In contrast, osteopetrosis is characterized by increased mineralization of bone as a result of absent or greatly reduced osteoclastic activity (Fig. 9.5). Bones affected by this condition are stiff and brittle and thus can absorb little energy before breaking; despite greatly increased BMD, fracture risk is increased in this condition.

An example of a qualitative abnormality of bone mineral that is associated with increased fracture risk is seen in bone that has been exposed to fluoride. The size and composition of hydroxyapatite crystals is changed as a result of replacement of the hydroxyl group of hydroxyapatite by fluoride; in addition, there may be accumulation of osteoid and the formation of woven bone [**12**].

Abnormalities of type 1 collagen

The primary defect in osteogenesis imperfecta is the production of abnormal type 1 collagen. Depending on the mutation involved and its phenotypic expression, there may be alterations in the bone matrix/mineral composite, reduced mineralization of bone and abnormalities in bone modelling and architecture. These changes are associated with increased fracture risk [**13**].

Even subtle abnormalities in the structure of type 1 collagen may have adverse effects on bone strength and fracture risk. A polymorphism affecting a binding site of the transcription factor Sp1 in the promoter region of the collagen type 1A1 gene has been described that is associated with reduced spine BMD and increased fracture risk [**14**]. The latter cannot be explained solely on the basis of the reduction in BMD, indicating that the abnormal collagen structure contributes independently to increased fracture risk. In individuals with the unfavourable genotype the ratio of $\alpha 1/\alpha 2$ chains is increased, resulting in reduced bone strength [**15**]. The abnormal collagen structure is also associated with reduced mineralization of bone.

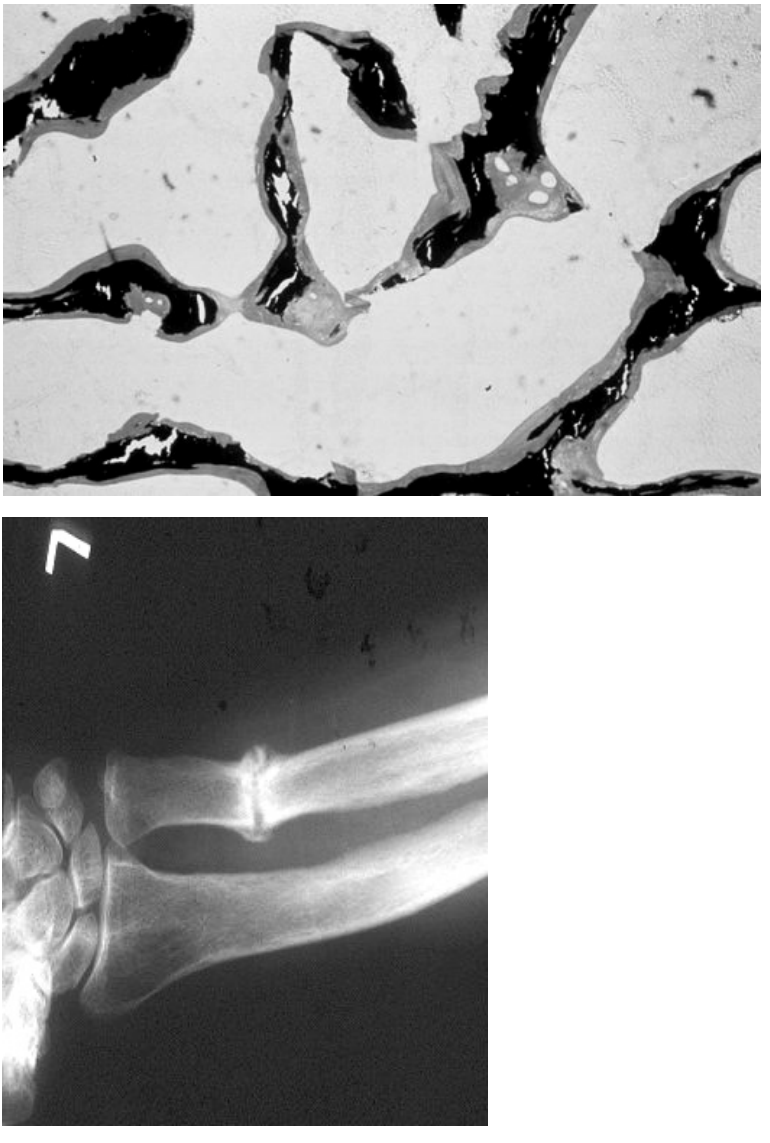

Fig. 9.4 (a) Histological section of osteomalacic bone showing increased amounts of osteoid (grey staining). (b) Pathological fracture of ulna due to osteomalacia.

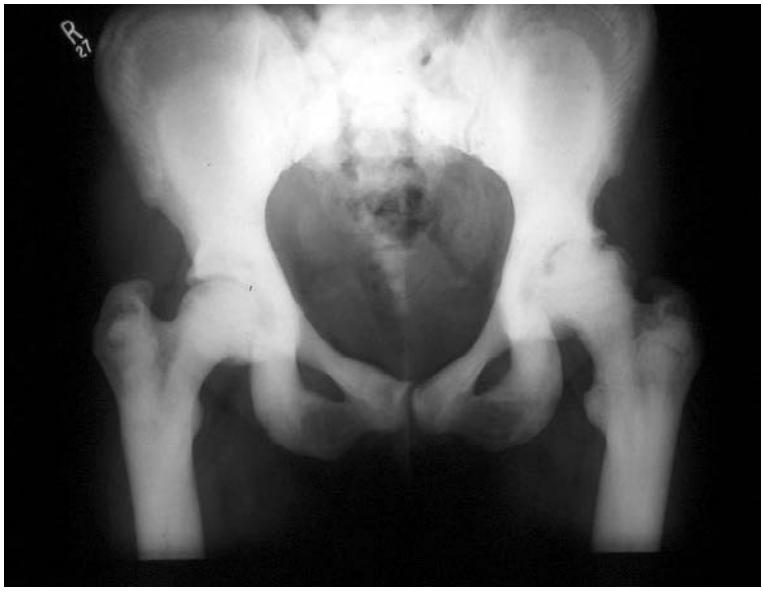

Fig. 9.5 X-ray of pelvis in a patient with osteopetrosis. Note the increased radiodensity of bone and disordered microarchitecture of cortical and cancellous bone.

High bone turnover

A number of high turnover states are associated with increased fracture risk; these include post-menopausal osteoporosis, Paget's disease of bone, post-transplantation bone disease and secondary hyperparathyroidism. High bone turnover reduces bone strength not only through reduction in bone mass but also because it has adverse effects on bone microarchitecture, an effect that is largely independent of the changes in bone mass. In addition, the degree of mineralization of bone is reduced.

In bone loss induced by oestrogen deficiency, the increase in bone turnover is accompanied by a remodelling imbalance that results from increased erosion depth, particularly in the early stages of oestrogen deficiency, and reduced bone formation at the level of the individual remodelling unit. These changes in remodelling are associated with trabecular penetration and reduced connectivity of the cancellous bone. In addition, there is an increase in cortical porosity and endosteal resorption, the latter resulting in cortical thinning. Other changes in bone quality include a reduction in the degree of mineralization of bone and its homogeneity, and alterations in bone matrix composition that are as yet poorly characterized.

In Paget's disease of bone, the increases in bone turnover and osteoclastic activity are associated with multiple alterations in bone quality. Bone matrix may have

a mosaic structure due to the presence of both woven and lamellar bone, mineralization is abnormal and there are also abnormalities of bone architecture and geometry. These changes are associated with an increased risk of fracture.

The pathogenesis of post-transplantation bone loss has not been wholly defined but it is likely that glucocorticoid therapy plays a major role. Bone loss in this condition affects cortical and cancellous bone similarly [16]; this is in contrast to secondary hyperparathyroidism, in which bone loss is predominantly cortical. Whilst increased bone turnover is likely to contribute to bone loss in the early stages of glucocorticoid therapy, in the longer term reduced bone turnover and formation at the level of the bone remodelling unit are mainly seen. Evidence that the increase in fracture risk associated with glucocorticoid therapy is to some extent independent of BMD [17] would be consistent with alterations in bone quality, and this is an important area for future research.

Low bone turnover

In theory, low bone turnover might be expected to increase bone fragility as a result of hypermineralization, reduced osteocyte viability and the accumulation of microdamage with impairment of its repair [18]. In dogs, oversuppression of bone turnover results in significantly greater amounts of microdamage but does not appear to have significant effects on bone strength. In humans, the condition of adynamic renal bone disease [19,20] is associated with very low bone turnover, but robust evidence for an increased risk of fracture in this condition is lacking at present. Interestingly, biochemical markers of bone turnover do not always reflect the suppression of bone turnover seen histologically and, in some patients, BMD values are normal.

There has been considerable interest in whether long-term treatment with potent anticatabolic agents in humans might result in oversuppression of bone turnover and increased bone fragility. Clinical trials indicate that antifracture efficacy is maintained for up to 5 years of treatment; subsequently, the data are less robust but studies for up to 7 years of treatment with risedronate [21] and 10 years with alendronate [22] are consistent with continued efficacy and have not demonstrated an increase in fracture risk above that expected. Interestingly, although alendronate has a very long terminal half-life in bone, significant bone loss was observed in the proximal femur within 1–2 years of cessation of long-term therapy [23], suggesting that the alendronate present in bone was largely non-bioavailable. Similarly, resumption of bone loss within 1 year of withdrawal of therapy has been reported for risedronate.

Odvina *et al.* [24] recently reported the presence of spontaneous fractures, often with evidence of impaired healing, in nine individuals who had been treated with alendronate. Three of these patients were also receiving hormone replacement therapy and two were taking prednisolone. Bone biopsy in all cases showed complete absence of double tetracycline labelling, although biochemical markers of bone turnover were normal in many cases and only two patients had osteoporosis as defined by densitometric criteria. In the absence of controls, it is not possible to

conclude that the fractures in these patients were attributable to alendronate therapy. Nevertheless, these cases raise the possibility that very low bone turnover may be associated with increased bone fragility despite normal BMD values, and emphasize the need for further research into this important topic. They also illustrate the discrepancies that may be seen between histomorphometric and biochemical assessments of bone turnover.

A possible association between osteonecrosis of the jaw and bisphosphonate therapy has also been reported recently [25]. This condition, which often presents with a non-healing tooth extraction socket or painful exposed bone in the mandible or maxilla, is seen most commonly in individuals with malignant disease and has a multifactorial pathogenesis including infection, ischaemia, inflammation and impaired healing of affected bone. Although not exclusively associated with bisphosphonate therapy, the increased numbers of cases reported in such patients has raised the possibility that bisphosphonates may contribute to osteonecrosis by several mechanisms, including immunosuppression, inhibition of angiogenesis and suppression of bone turnover. It should be emphasized that in the majority of bisphosphonate-treated individuals with this condition, high doses of intravenous bisphosphonates have been used. However, a few cases have been reported in postmenopausal women without malignant disease who were receiving treatment with oral alendronate or risedronate for the treatment of osteoporosis.

Effects of pharmacological agents on bone quality

The relatively poor ability of therapeutically induced increases in BMD to predict fracture reduction has stimulated particular interest in the effects of pharmacological interventions on bone quality. Information about effects on bone turnover, microarchitecture and mineralization has been obtained for a variety of interventions and some data on the effects of drugs on the bone matrix/ mineral composite are also emerging.

Effects on bone turnover

The degree of suppression of bone turnover induced by anticatabolic drugs varies considerably, whether measured by biochemical markers or bone histomorphometry. The most potent interventions in this respect are alendronate, zoledronate and ibandronate, which reduce activation frequency in iliac crest bone biopsies by around 75–90% [26–28]. Risedronate and conventional hormone replacement therapy are of intermediate potency, with a reduction of around 50% [29,30] and the weakest effect is observed with raloxifene (approximately 20%) [31]. These differences in bone turnover suppression do not appear to be reflected by variations in antifracture efficacy, at least in the spine; thus, fracture reduction at this site appears to be similar amongst interventions, although the different studies cannot be compared directly because of differences in the patient populations, study design and definition of vertebral fracture. However, different degrees of suppression of bone

turnover may be relevant to antifracture efficacy at non-vertebral sites. Thus, for weaker anticatabolic agents such as raloxifene, whilst the modest reduction in bone turnover is sufficient to reduce fractures at cancellous bone sites, where high bone turnover has a marked effect on bone strength, this may not be the case at cortical bone sites, where the effects of bone turnover on bone microarchitecture are much less prominent, and where larger increases in BMD are required to provide protection against fracture [32].

There is now strong evidence that the reduction in bone turnover induced by anticatabolic agents is a major and independent determinant of fracture reduction, at least at vertebral sites [33,34]. This can be attributed to the important role of high bone turnover in the pathogenesis of vertebral fracture, which again is independent of BMD [35] and the consequent prevention of microarchitectural deterioration by anticatabolic agents. Thus, even modest reductions in bone turnover result in a substantial reduction in vertebral fractures, regardless of the magnitude of change in BMD.

In the case of teriparatide (recombinant human parathyroid hormone peptide 1–34), activation frequency is increased in cancellous bone, but because this is associated with a positive remodelling balance, bone mass increases.

Effects on microarchitecture

Effects on microarchitecture have been demonstrated both for anticatabolic and anabolic interventions and, as expected, largely reflect the associated changes in bone turnover. The main effect of anticatabolic agents is to preserve existing bone architecture, thus preventing the deterioration that occurs in post-menopausal women in the absence of treatment. This has been demonstrated in iliac crest biopsies using two-dimensional histological techniques in women treated with hormone replacement therapy [36], raloxifene [31] or ibandronate [28], and using μCT in women treated with risedronate [37,38]; in the latter population, preservation of bone microarchitecture could be demonstrated as early as 1 year after the initiation of therapy. Studies on cortical bone architecture in individuals treated with anticatabolic agents are sparse, but decreased cortical porosity [39] and unchanged cortical thickness [37] have been reported.

In contrast, the anabolic agent teriparatide improves bone microarchitecture, in both cancellous and cortical bone. Thus, increased connectivity density of cancellous bone and increased cortical thickness have been demonstrated using μCT of iliac crest biopsy specimens [40,41]. There is also some evidence for increased periosteal bone formation, resulting in increased bone size.

Effects on mineralization

The degree of mineralization of bone increases with anticatabolic therapy, due to the reduction in bone turnover, and may also contribute to increased bone strength. The potential importance of this mechanism first emerged when it was shown that 3 years of alendronate therapy in post-menopausal women with osteoporosis increased the mean degree of mineralization in iliac bone by around 11%; this

effect was seen in both cancellous and cortical bone [42]. Subsequently, similar changes, although of a lower magnitude, have been reported in bone obtained from women treated with risedronate [37], hormone replacement therapy [43] and raloxifene [44]. In addition to the increased degree of mineralization, there is also increased homogeneity of mineralization.

The extent to which these changes contribute to reduced fracture risk is unclear. The increases in the degree of mineralization observed in iliac crest bone are quantitatively similar to those observed in BMD in the lumbar spine; this has led some to propose that it is the increased mineralization that accounts for most of the fracture reduction. However, it is unknown whether changes in mineralization in the spine mirror those occurring in the iliac crest; furthermore, it seems unlikely that this mechanism could explain the early reduction in fractures seen with anticatabolic agents.

In post-menopausal women with osteoporosis who are treated with teriparatide, there is a small reduction in the degree of mineralization of bone, reflecting the increased bone turnover that results from this treatment [45].

Effect on bone matrix and mineral composition

As yet, relatively little is known about the effects of anticatabolic and anabolic interventions on the bone matrix/mineral composite. There is some evidence that age-related changes in the ratio of non-reducible to reducible collagen cross-links and in bone mineral crystallinity that occur with ageing are prevented with anticatabolic therapy. However, at present the biomechanical consequences of these effects, if any, are unclear.

The effects of strontium ranelate on bone mineral structure are of particular interest since strontium, like calcium, is a bone-seeking element that is taken up by bone mainly by adsorption onto bone mineral, exchanging with a maximum of one in ten calcium ions in hydroxyapatite [46]. These changes in mineral composition are not associated with any change in the degree of mineralization of bone, nor do they appear to have adverse effects on biomechanical properties.

Conclusion

Bone quality comprises a number of structural and compositional variables that are only partially captured by measurements of BMD and hence may contribute independently to bone strength and fracture risk. There have been important advances in the assessment of bone quality in recent years, which have provided new insights into bone fragility in both untreated and treated bone disease. The translation of these advances into clinical practice is an important priority for future research and may eventually lead to better prediction of the risk of fracture and an improved understanding of the mechanisms by which pharmacological interventions affect bone strength.

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Part III

Management and prevention

10

Falls: epidemiological aspects and prevention

PAUL GERDHEM

Introduction

The majority of non-spine fractures are caused by a fall. Besides fractures, falls may cause injuries of soft tissues, such as lacerations or concussions, influencing the well-being of the individual and requiring healthcare resources.

One third of the elderly aged 65 and older and up to one half of those aged 80 and over fall at least once a year. Up to 20% of all falls require medical attention and up to 10% of all falls result in fracture or other serious injury [**1**].

Risk factors for falls are often divided into extrinsic and intrinsic factors. Extrinsic factors are environmental factors such as obstacles and bad lighting. Intrinsic factors are those associated with neuromuscular function and visual capacity. Since neuromuscular function and visual capacity deteriorate with age, the risk of falls increases with age.

Several of the risk factors can be identified during the clinical consultation. Among these are previous falls, physical activity level, the use of medication, self-assessed visual and balance ability, cognitive ability, diseases and disabilities [**2**]. A quick assessment of balance can be done by simply observing the patient's ability to walk, dress or rise from a chair. Several more or less complicated tests exist for the assessment of balance or the risk of falling [**3,4**].

This review covers reports on falls published over the last year and a half. The aim is to present an updated review of the epidemiology and prevention of falls.

Assessment of fall risk

Clinical history and biological age predicted falls better than objective functional tests

Gerdhem P, Ringsberg KA, Akesson K, Obrant KJ. *J Clin Epidemiol* 2005; **58**: 226–32

BACKGROUND. Assessment of the risk of falling is of importance since the consequences, such as a fracture, may be devastating. The objective of this study was to find the test or tests that best predicted falls in a population-based sample of elderly women. The fall-predictive abilities of a questionnaire, a subjective estimate of biological age and objective functional tests (gait, balance [Romberg and computerized sway test], thigh muscle strength, visual acuity) were compared in 984 randomly selected women, all aged 75 years.

INTERPRETATION. A recalled fall was the most important predictor of future falls. Only recalled falls and intake of psychoactive drugs independently predicted future falls. Women with at least five of the most important fall predictors (previous falls, conditions affecting the balance, tendency to fall, intake of psychoactive medication, inability to stand on one leg, high biological age) had an odds ratio of 11.27 (95% confidence interval [CI] 4.61–27.60) for a fall (sensitivity 70%; specificity 79%). The more time-consuming objective functional tests were of limited importance for fall prediction. Instead, a simple clinical history, inability to stand on one leg and a subjective estimate of biological age were more important as part of the fall risk assessment.

Comment

This study compared different ways of assessing the risk of falling, such as the clinical history, a completely subjective estimate of biological age and objective functional tests of variables related to balance. The single most important predictor of falls was previous falls. Objective measures of muscle strength and sway tests did not add any information in the assessment of fall risk. That a subjective biological age estimate predicts falls has not been reported previously. Biological age was defined here as a subjective and fast estimate of the general appearance of the health of the individual and was scored from 1 to 100. The general visual impression is one of the first items in the clinical examination of all patients and the present data indicate that a quick subjective estimate of a person's general health appearance gives information about whether a person is prone to falling. The authors have previously reported the correlations between biological age and balance, fractures and survival [**5,6**].

Visual impairment, risk of falls and treatment of cataract

Several different visual screening tests have been examined as risk factors for falls. Lord and Dayhew found that adequate depth perception and distant edge-contrast sensitivity were especially important in avoiding falls [7]. Poor depth perception, poor contrast sensitivity and poor visual acuity have also been associated with falls and fractures [8,9].

Higher risk of multiple falls among elderly women who lose visual acuity

Coleman AL, Stone K, Ewing SK, *et al*. *Ophthalmology* 2004; **111**: 857–62

BACKGROUND. The association between changes in visual acuity and frequent falls during a mean follow-up of 5.6 years was investigated in 2002 independently living women, with a mean age of 76 years. Binocular visual acuity with habitual correction was measured using visual charts in which the number of letters read correctly was recorded. The change between the first and second examinations was stratified into five categories (no loss or improvement, loss of 1–5 letters, loss of 6–10 letters, loss of 11–15 letters, loss of more than 15 letters).

INTERPRETATION. In this cohort, 28% fell at least once and 11% fell at least twice during the 1-year period after the second eye examination. Women with declining visual acuity between the two eye examinations had a greater risk of frequent falls (two or more falls during the year after the second examination). In the different categories, the risk, described as the odds ratio (adjusted for confounders) and 95% CI, was 2.08 (1.39–3.12) for the group with loss of 1–5 letters, 1.85 (1.16–2.95) for the group with loss of 6–10 letters, 2.51 (1.39–4.52) for the group with loss of 11–15 letters and 2.08 (1.01–4.30) for the group with loss of more than 15 letters. In comparison, a history of frequent falling was associated with an odds ratio for frequent falls of 5.54 (3.88–7.92).

Comment

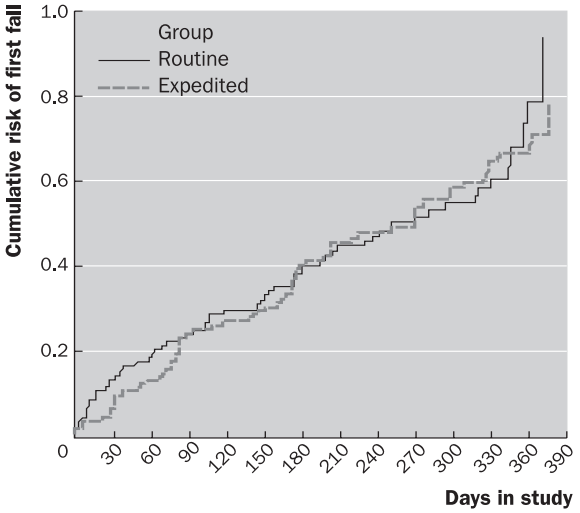
This study shows that decline in visual acuity is a risk factor for falls. Since visual acuity can be corrected with glasses, lenses or cataract surgery, it seems important to identify these individuals to minimize the risk of future falls. Even a small decline in visual acuity was associated with an increase in the risk of falling. This study further strengthens the association between visual disorders and falls and this should be kept in mind when seeing the elderly patient at the office. The study by Coleman *et al.* is an observational study and indicates that efforts to improve vision are effective in preventing falls, but does not give firm evidence for this. It is important to recognize that poor vision is a risk factor for falls and may also be a risk factor for fractures. Efforts should therefore be made to optimize visual capacity in the elderly individual.

Falls and health status in elderly women following first eye cataract surgery: a randomised controlled trial

Harwood RH, Foss AJ, Osborn F, Gregson RM, Zaman A, Masud T. *Br J Ophthalmol* 2005; **89**: 53–9

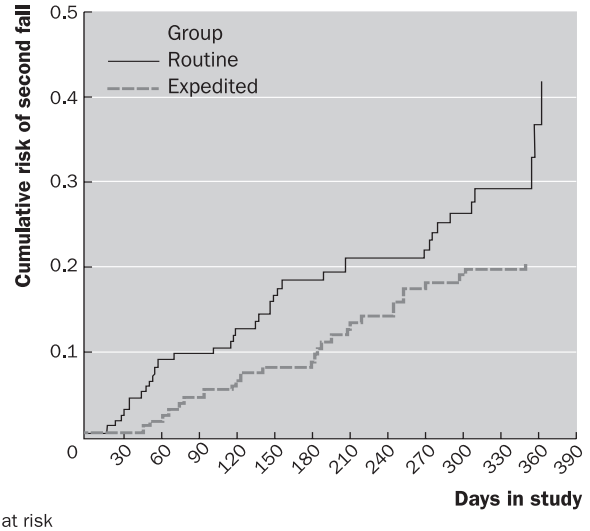
BACKGROUND. The authors wanted to determine whether first eye cataract surgery reduces the risk of falling. The study population consisted of 306 women (mean age 78 years) with cataract who were randomized to either expedited surgery (a wait of approximately 4 weeks) or routine (12 months' wait) surgery. Participants not randomized to early surgery received an up-to-date spectacle prescription. Falls were ascertained with a falls calendar, with follow-up every 3 months. The total follow-up time was 12 months.

INTERPRETATION. Visual functioning improved in the operated group. During the 12-month follow-up, 49% of the women in the operated group fell at least once and 25% at least twice. In the non-operated group 45% fell at least once and 25% fell at least twice. However, the rate of falling (total number of falls) was reduced by 34% in the operated group (rate ratio 0.66; 95% CI 0.45–0.96). Measures of health status improved in the operated group. Four participants in the operated group had fractures (3%) versus twelve (8%) in the control group ($P = 0.04$). The hazard ratio for any falls for women in the operated group was 0.95 (95% CI 0.69–1.35) and for recurrent falls (more than one fall) it was 0.60 (0.36–0.98) (Figs. 10.1 and 10.2).



Numbers at risk					
Operated	154	119	97	85	62
Control	152	117	95	79	15

Fig. 10.1 Cumulative risk of first falls. Source: Harwood *et al.* (2005).



Numbers at risk

Operated	154	144	135	123	102
Control	152	134	115	98	21

Fig. 10.2 Cumulative risk of second falls. Source: Harwood *et al.* (2005).

Comment

This study illustrates that women with cataract and therefore poor vision are at a high risk of falling, as illustrated by the fact that almost half of the women had a fall the year before the study start, but also after the study start. Still, three-quarters of the women had corrected vision better than the driving standard. In addition to the cataract, the women in this cohort were frail, with a median of eight comorbid diagnoses and five medications. Both recurrent falls and the rate of falling were significantly reduced, which further strengthens the idea that if you suspect an individual to have poor vision, the person should referred for an eye examination. This is also one of the few studies that also report the consequences of falls, such as fractures. Albeit fractures were limited in number, there were significantly fewer fractures in the intervention group.

Interventions to prevent falls

Several effective interventions for preventing falls in elderly people have been described [**1,2**]. Muscle strengthening and balance retraining, home hazard assessment and modification for older people with a falls history, withdrawal of psychotropic medication and multidisciplinary treatment are likely to be beneficial. There are still few data on the prevention of falls in hospital settings. The same is

true of the possibility of preventing falls with single interventions, such as vitamin D supplementation, Tai Chi exercise and the use of a cognitive, behavioural approach.

Effect of vitamin D on falls: a meta-analysis

Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, *et al. JAMA* 2004; **291**: 1999–2006

BACKGROUND. Previously the effect of vitamin D on fracture risk has primarily been attributed to bone mineral density (BMD) changes. Earlier studies have shown an effect of supplementation already after 8–12 weeks, a finding indicative of muscle strength benefits. The authors searched for clinical studies on vitamin D and falls in several databases. Included were double-blind, placebo-controlled studies of vitamin D in elderly populations that examined falls from low-energy trauma. The five best studies were included in the primary analysis. A second analysis, including another five studies, was also done.

INTERPRETATION. Based on five randomized controlled trials including 1237 participants (men and women), the authors found that vitamin D significantly reduced falls by 22% (corrected odds ratio of falling 0.78; 95% CI 0.64–0.92) compared with participants receiving calcium or placebo. Inclusion of another five studies (including a total of 10 001 participants) in a sensitivity analysis resulted in a smaller but still significant effect size (adjusted odds ratio 0.87; 0.80–0.96) (Fig. 10.3). In the primary analysis, the lowest dose of vitamin D was 400 IU/day but reported calcium intake from dairy products was high, at 800–1000 mg/day. In the other four trials, the participants were given either vitamin D 800 IU/day plus 1200 mg/day of calcium or an active vitamin D metabolite analogue alone.

Comment

A fracture-reductive effect of vitamin D (with or without calcium) has been shown in both community-living and institutionalized individuals [**10–12**]. A possible explanation for the effect of vitamin D on falls is that 1,25-hydroxy vitamin D binds to a highly specific nuclear receptor in muscle tissue, leading to improved muscle function and a reduced risk of falling. Vitamin D appears to reduce the risk of falling by 20% in individuals with stable health. Together with earlier data on fracture reduction and bone density gain with treatment with vitamin D and calcium [**12**], this study by Bischoff-Ferrari *et al.* strengthens the use of vitamin D and calcium in the elderly population. The type of vitamin D did not seem to influence the results. From a safety view it therefore seems clear that cholecalciferol and not active vitamin D analogues should be used, thereby minimizing the risk of the hypercalcaemia that is occasionally seen with treatment with active vitamin D analogues. At present, data suggest that vitamin D should be combined with calcium, unless calcium intake is sufficient. Vitamin D intake should probably be closer to 800 IU/day than 400 IU/day.

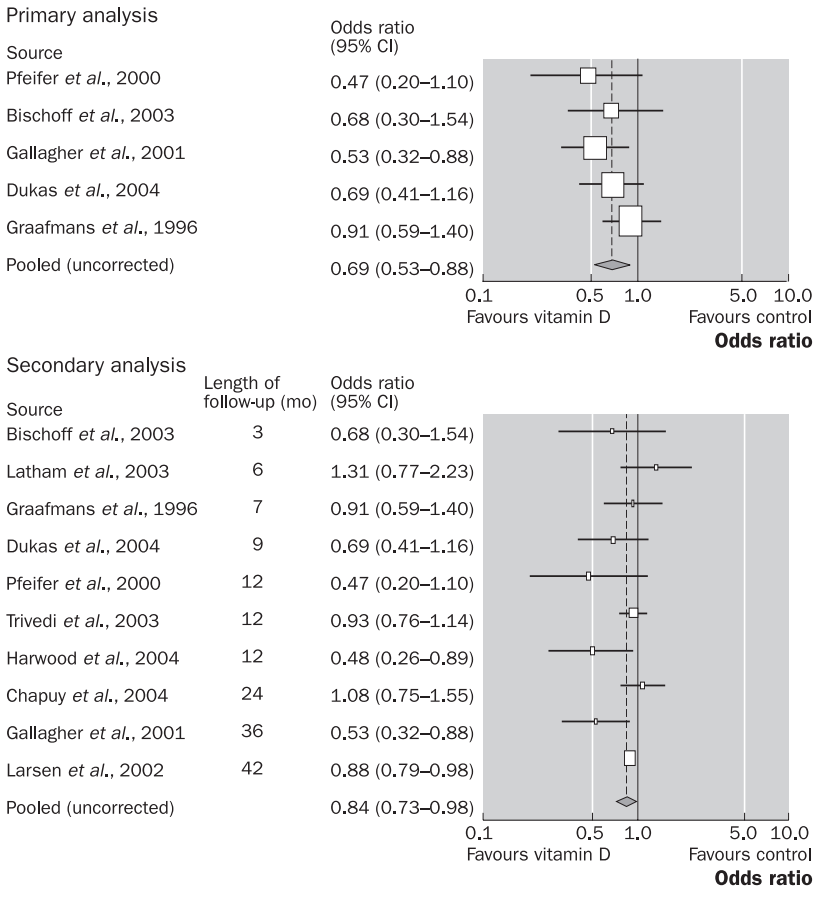


Fig. 10.3 Forest plots comparing the risk of falling between vitamin D-treated groups and control groups for the primary and sensitivity analyses. Source: Bischoff-Ferrari *et al.* (2004).

Tai Chi: improving functional balance and predicting subsequent falls in older persons

Li F, Harmer P, Fisher KJ, McAuley E. *Med Sci Sports Exerc* 2004; **36**: 2046–52

BACKGROUND. This study was done to determine whether improved functional balance through a Tai Chi intervention is related to subsequent reductions in falls among elderly persons during 6 months after the intervention. Two hundred and fifty-six healthy, physically inactive older adults (mean age 77.5 years) participated in

a 6-month randomized controlled trial with allocation to Tai Chi or an exercise stretching control group, followed by a 6-month post-intervention follow-up. Fall counts were recorded during this follow-up period.

INTERPRETATION. Tai Chi reduced the likelihood of falling during the 6-month post-intervention period (Table 10.1): there were 28 falls among the 125 individuals in the intervention group and 74 falls among the 131 individuals in the control group. Tai Chi participants showed improvements in measures of functional balance (Berg balance scale, dynamic gait index, functional reach) at the intervention end-point and significantly reduced their risk of falls during the 6-month post-intervention period, compared with those in the exercise stretching control group. An improvement in functional balance scores during the intervention period was associated with a reduction in the risk of falls.

Comment

Since the first randomized study on preventing falls by Tai Chi exercise [**13**], interest in this type of exercise has increased even more. Tai Chi consists of self-initiated slow but continuous movements and is associated with improved balance in older persons. However, the effect of an intervention such as Tai Chi may not be immediate. In fact, earlier studies have indicated that it may take some months before the propensity to falling is reduced, at least if the exercising individuals are frail [**14**]. This study is interesting because it examined the post-intervention period. It seems that the effect of Tai Chi is sustained, at least for the 6-month post-intervention period studied here. The reduced propensity to falling in this study can be attributed to improved balance in the Tai Chi group, which was not seen in the control group. The effect was also unaffected by the physical activity level in the post-intervention period. This study also showed that there were fewer fallers in the Tai Chi than in the control group (the relative risk of falls in the Tai Chi group was 0.40; 95% CI 0.25–0.61). The exercise involved three 1-hour sessions per week; despite this the dropout rate was acceptable (21%). The number needed to treat to avoid a fall in the intervention group was 4 (95% CI 3–7), which is a good figure. Tai Chi seems a promising way to achieve better balance and to prevent falls among community-living elderly people.

Table 10.1 Information on falls during the 6-month post-intervention follow-up

Falls	Tai Chi (n = 125)	Control (n = 131)
Reporting one fall, n (%)	22 (18)	64 (49)
Reporting two falls, n (%)	3 (2)	2 (2)
Reporting three falls, n (%)	0	2 (2)
Total falls reported	28	74

256 subjects were included based on intention-to-treat analysis. Fall data were available for 188 participants (n = 95 in Tai Chi group, n = 93 in exercise control) during the 6-month post-intervention follow-up. For dropouts, fall status was determined using the last available fall information.
Source: Li *et al.* (2004).

The effectiveness of a community-based program for reducing the incidence of falls in the elderly: a randomized trial

Clemson LRG, Cumming RG, Kendig H, Swann M, Heard R, Taylor K. *J Am Geriatr Soc* 2004; **52**: 1487–94

BACKGROUND. This is a randomized trial which reports the effect of a behavioural programme using a small-group learning environment, with emphasis on improving falls self-efficacy and encouraging behavioural change. The primary goal of the intervention was to reduce the number of falls. Community residents (*n* = 310) with a previous history of falls or who were concerned about falling were randomized into the programme or control group. The programme took place over 7 weeks and included group learning and practice of the exercises that were taught. The programme ended with a home visit within 6 weeks of the final programme session. At the home visit an occupational therapist listed self-initiated actions taken by the participants and gave recommendations for further actions that arose during the home visit. A booster session was conducted 3 months after the initial 7-week programme. The total intervention time was 17 h. The control group received up to two social calls in which no discussions of falls or falls prevention took place.

INTERPRETATION. Falls during a 14-month follow-up (post-intervention) were recorded. Eighty-nine out of 153 controls (58%) and 82 out of 157 programme subjects (52%) reported one or more falls during the follow-up. The corresponding figures for two or more falls were 53 (35%) in the control group and 40 (26%) subjects in the programme group. The number of falls was significantly reduced (by 31%) in the programme group (255 vs 179 falls) in an analysis model that accounted for follow-up time (relative risk 0.69; 95% confidence interval 0.50–0.96; negative binomial regression model). The number of falls per month is shown in Fig. 10.4. At the end of the 14-month follow-up, 59% of programme participants were still doing their exercise routinely. Seventy per cent of programme participants had adhered to at least 50% of the home visit recommendations at the end of the 14-month follow-up.

Comment

This study renews the idea that cognitive-behavioural learning in a small-group environment can reduce falls. The intervention included several aspects of the risk of falling. The part of the programme that was responsible for the positive effect is not possible to elucidate. The significant differences between the groups that were seen at the end of the study were less use of psychotropic drugs in the intervention group and a higher proportion of vision assessments in the intervention group. Results of previous studies on behavioural change indicate that the behavioural programme alone may not be sufficient for a significant reduction of falls, but, combined with intervention components in which exercise is specifically encouraged or trained, this multiple intervention may reduce falls. On the other hand, individually delivered exercise interventions have been effective in reducing falls,

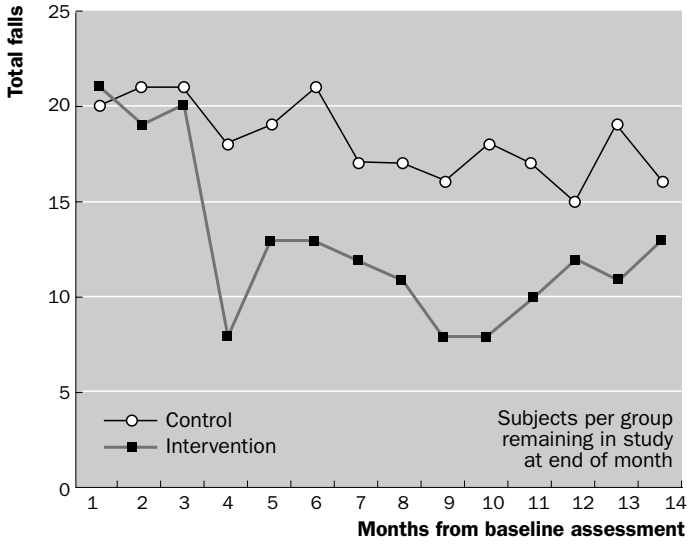


Fig. 10.4 Falls per month for control and intervention groups. Source: Clemson *et al.* (2004).

while group-delivered exercise has not [1]. Therefore, in this study, the behavioural part may be responsible for some of the positive effects of the intervention, but the study also included an individual consultation with an occupational therapist.

Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials

Chang JT, Morton SC, Rubenstein LZ, *et al. BMJ* 2004; **328**: 680

BACKGROUND. This report assessed the relative effectiveness of interventions to prevent falls in older adults. This was a systematic review and meta-analyses of data were sought in several health-related databases and reference lists from review articles and systematic reviews. Studies that reported a multifactorial assessment of the risk of falls with a management programme, exercise, environmental modifications or education were sought. Studies in which adequate control groups were available were included. Forty trials met the inclusion criteria.

INTERPRETATION. Data for the analysis of participants who fell at least once came from 22 studies (26 interventions). Data for the meta-analysis on the monthly rate of

falling came from 27 studies (30 intervention groups). A multifactorial falls risk assessment and management programme was the most effective component for reducing the risk of falling at least once (adjusted risk ratio 0.82) and the monthly fall rate (adjusted incidence rate ratio 0.63) (Table 10.2). Exercise interventions also had a beneficial effect on the risk of falling (Table 10.2). Interventions to prevent falls in older adults are effective in reducing both the risk of falling and the monthly rate of falling.

Comment

Multifactorial risk assessment and management programmes were effective in reducing the risk of falling, supporting the result of a recently updated Cochrane review [**1**]. Exercise was the second best method to reduce the risk of falling. Environmental modifications and education were part of some programmes but were not associated with a lower risk of falling. The primary end-point for statistical interpretation in most studies on falls is the number of falls; the authors of this study used both the number of fallers and the number of falls. One has to realize that, when studying the number of fallers (i.e. persons who fall) in different groups, it is more difficult to reach statistical significance than when the rate of falls or the total number of falls in each group is compared. Meta-analyses including several studies may compensate for this. A significant result with respect to the number of individuals with falls is a stronger and less doubtful statistical outcome, since an individual with a history of a fall tends to fall again. Nevertheless, frequent falls are also associated with a higher risk of injury. As in most meta-analysis, the authors did not have access to individual data, which may obscure the present findings. The confirmative nature of the present data strengthens the efficiency of multifactorial programmes in the prevention of falls. In addition, it gives some evidence that exercise may be effective in preventing falls.

Falls in inpatients

Effectiveness of targeted falls prevention programme in sub-acute hospital setting: randomised controlled trial

Haines TP, Bennell KL, Osborne RH, Hill KD. *BMJ* 2004; **328**: 676

BACKGROUND. Falls have been reported to occur in between 13 and 32% of patients admitted to hospitals. This study was done to assess the effectiveness of a targeted, multiple-intervention falls prevention programme in reducing falls and injuries in a subacute hospital. The study included 626 men and women with a mean age of 80 years. The participants were randomly assigned on an individual basis to the intervention or control group. The intervention consisted of a fall risk alert card with an information brochure, an exercise programme, an education programme and hip protectors. The outcome was the incidence rate of falls, injuries related to falls and

Table 10.2 Meta-regression estimates of effects of individual intervention components, controlling for other intervention components

	Participants who fell at least once*			Monthly rate of falling†		
Treatment component	**No. of studies (comparison pairs)**	**Adjusted risk ratio (95% CI)**	**Number needed to treat**	**No. of studies (comparison pairs)**	**Adjusted incidence rate ratio (95% CI)**	**Fewer falls in treatment group‡**
Multifactorial falls risk assessment and management programme	10 (10)	0.82 (0.72–0.94)	11	7 (7)	0.63 (0.49–0.83)	11.8
Exercise	13 (15)	0.86 (0.75–0.99)	16	19 (21)	0.86 (0.73–1.01)	2.7
Environmental modifications	5 (4)	0.90 (0.77–1.05)	NA	5 (6)	0.85 (0.65–1.11)	NA
Education	2 (3)	1.28 (0.95–1.72)	NA	1 (1)	0.33 (0.09–1.30)	NA

NA, not applicable.
* $r^2 = 0.29$.
† $r^2 = 0.16$.
‡ per 100 patients per month.
Source: Chang *et al*. (2004).

the proportion of participants who experienced one or more falls during their hospital stay.

INTERPRETATION. Participants in the intervention group ($n = 310$) experienced 30% fewer falls than those in the control group ($n = 316$) (Peto log-rank test, $P = 0.045$). There was a trend to fewer fallers in the intervention group (relative risk 0.76; 95% CI 0.56–1.06) and there were 28% fewer injurious falls in the intervention group ($P = 0.20$). The mean length of stay was approximately 30 days in each group. The beneficial effect of the programme was seen after a length of stay of 45 days (Fig. 10.5).

Comment

The study results are applicable to subacute hospital settings. The programme identified fall-risk behaviours in individual patients by means of an assessment tool aimed at the medical, nursing, physiotherapy and occupational therapy areas. Patients with gait and transfer problems were referred to balance exercises and patients with problems with activities of daily living were referred to an educational programme on falls prevention. Patients started the use of hip protectors if falls occurred without a diagnosed cause. The control group received the assessment but the measures were not instituted. The programme led to a 30% reduction in falls in a hospital setting, which may be considered a good result. The study was powered to detect a difference in falls but not to detect a difference in injurious falls, but these showed a trend in the same direction as the prevention of falls. The study design was unique since it also recruited cognitively impaired patients. Multifactorial programmes seem to be effective in a hospital setting. Which part of or parts of the intervention are most efficient is still an open question. These interventions, which

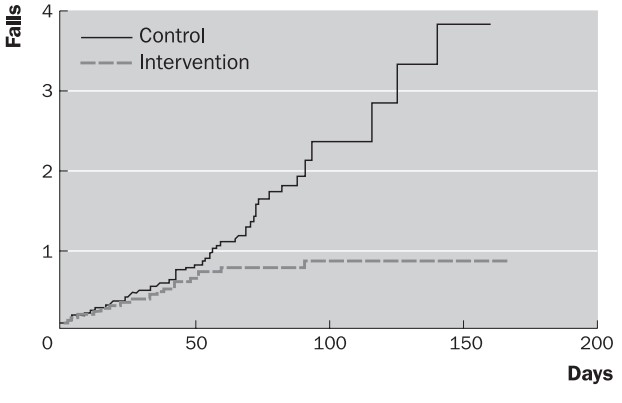


Fig. 10.5 Nelson-Aalen cumulative hazard estimates (Peto log-rank test: $P = 0.045$) for the control and intervention groups with a similar fall rate until about day 45 when there is a drop in fall rate in the intervention group. Source: Haines *et al.* (2004).

show an effect after 45 days, are not likely to be effective in an acute hospital with a high turnover and where patients stay for a short time.

Using targeted risk factor reduction to prevent falls in older in-patients: a randomised controlled trial

Healey F, Monro A, Cockram A, Adams V, Heseltine D. *Age Ageing* 2004; **33**: 390–5

BACKGROUND. In this study eight elderly care wards or units of a district general hospital were randomized to either usual care or the use of a pre-printed core care plan for patients identified at high risk of falling, to whom appropriate remedial measures were introduced. The plan was targeted to the reduction of risk factors (Table 10.3). The number of falls in each group was compared both during a 6-month period before the intervention and during the 6-month period in which the intervention took place.

INTERPRETATION. The number of falls in the wards was studied during 1 year (more than 66 000 bed days and 3386 patients). The mean age of the patients was 81 years and the mean length of stay in the hospital was 19 days. After introduction of the care

Table 10.3 Components of the core care plan and guidelines

Health screening checklist	**Targeted intervention**
Eyesight—able to recognize pen/key/watch from 2 m distance	If unable to recognize, optician visit if lost glasses, ophthalmology referral if no known reason for poor eyesight
Medication—check for sedatives, antidepressants, diuretics, polypharmacy, etc.	Medical review of prescription benefit related to falls risk
Lying and standing blood pressure	Refer any deficit to medical staff. Advise patient on changing position slowly
Ward test of urine	Send midstream urine sample if positive for nitrites, blood or protein
Difficulty with mobility	Refer to physiotherapist
Environmental check	
Review risk/benefit of bedrails for individual	Documentation of risk/benefit in nursing notes and removal or addition of bedrails as appropriate
Footwear safety	Advise relatives on replacement
Bed height	Keep at lowest height
Position in ward	Nurse patient with history of falls as close to nurses' station as possible (considering other patients' needs)
Simple environmental cause of falls (e.g. loose cable, wet floor)	Act to correct it
Nurse call bell	Explained and within reach

Source: Healey *et al.* (2004).

plan there was a significant reduction in the relative risk (RR) of recorded falls on intervention wards (RR 0.79; 95% CI 0.65–0.95) but not on control wards (RR 1.12; 95% CI 0.96–1.31). The difference in change between the intervention wards and control wards was significant (RR 0.71; 95% CI 0.55–0.90; $P = 0.006$). There was no significant reduction in the incidence of falls-related injuries.

Comment

The data in this study were analysed at the group level, not the individual level, by using an existing reporting system for falls. The randomization took place at the ward level, not on an individual basis. However, it is difficult to implement a care plan, which affects the staff, in any other way. There were some differences between the two groups, which to some extent could be attributed to the study design. Randomization took place in matched pairs, but the wards may have had slightly different speciality profiles. The intervention group had a slightly longer hospital stay, but this was similar both before and after the start of the intervention. The care plan was aimed at risk factor reduction rather than the application of generic interventions. The care plan was implemented within the ordinary care on the wards. Bias, such as staff spreading knowledge about falls prevention to control wards, cannot be excluded, but if it had happened it would probably have diminished the difference between the intervention and control wards. The guidelines of the care plan offer a simple way of reducing falls in wards. There was no reduction in the number of injurious falls, but the study was not powered to find such a difference.

Epidemiology of falls

The studies reviewed in this chapter represent various settings and disease backgrounds and confirm earlier epidemiological data on falls [**1,15–17**]. In the population-based samples of women (mean age 75 and 76 years) reported by Gerdhem *et al.* and Coleman *et al.*, 24 and 27.8% respectively fell during a 1-year follow-up. About half of the individuals fell each year in high-risk groups of women (mean age 78) with cataract, scheduled for surgery (Harwood *et al.*), individuals with a history of falling or a concern about falling (mean age 78) (Clemson *et al.*) and physically inactive individuals (mean age 77.5) (Li *et al.*).

Another high-risk group is inpatients. Healey *et al.* and Haines *et al.* had similar figures on falls, with between 16 and 18 falls per 1000 bed-days in the control groups in elderly care wards and a subacute hospital setting. In the study by Haines *et al.*, 22% of the patients fell during a mean hospital stay of 30 days, and 22% of the falls led to an injury.

Fall-induced deaths among elderly people

Kannus P, Parkkari J, Niemi S, Palvanen M. *Am J Public Health* 2005; **95**: 422–4

BACKGROUND. Falls and fall-induced injuries in older people are a major public concern in modern societies with a growing elderly population. Injury is the fifth leading cause of death in older adults. Most of these fatal injuries are related to falls. The authors used the national statistics of Finland and compared the data on fall-induced deaths in the whole Finnish population aged 50 or above between the years 1971 and 2002.

INTERPRETATION. The results showed that the number of fall-induced deaths among elderly Finns is clearly increasing among men and women. The fall-induced death rates for the population aged 50 or above were compared for different time periods, and age-adjusted incidences were calculated. In men, the age-adjusted incidence of fall-induced deaths increased during the study period; it was 41.8 (per 100 000 persons) in 1971 and 55.4 in 2002 (Fig. 10.6a). The finding was similar for age-specific incidence rates in men: for the period from 1971 to 1974 the mean incidence rates were 12.6, 21.8, 64.9 and 268.7 in the age groups of 50–59, 60–69, 70–79 and 80 years or older, compared with 25.4, 36.0, 83.9 and 377.6 for the period from 1998 to 2002. The age-adjusted incidence of fall-induced deaths among women decreased between 1971 and 1975, since when it has remained at the same level (Fig. 10.6a). Based on these data and the growing elderly population, the authors foresee a huge increase in the number of fall-induced deaths in future years (Fig. 10.6b).

Comment

The burden of fall-related injuries is clearly likely to increase steeply because of the growing elderly population. The reason for increasing age-specific incidence is a matter of speculation. It seems that an increasing number of frail, fall-prone, elderly men are included in the older age groups. The data were based on the Finnish Official Cause-of-deaths Statistics, which are considered to be 100% correct concerning the cause of death; autopsies were performed in a high proportion of cases, and there is no mention of any difference in the method used to gather the data during the period studied. An increasing lifespan could be part of the explanation. A prolonged life is also achieved among frail individuals who are prone to falling. It is important to gain further epidemiological knowledge about this phenomenon and also to institute measures to prevent falls.

Conclusion

Today, there are several studies that give information on risk factors for falling. Increasing age is associated with a higher rate of falls. A high number of comorbidities

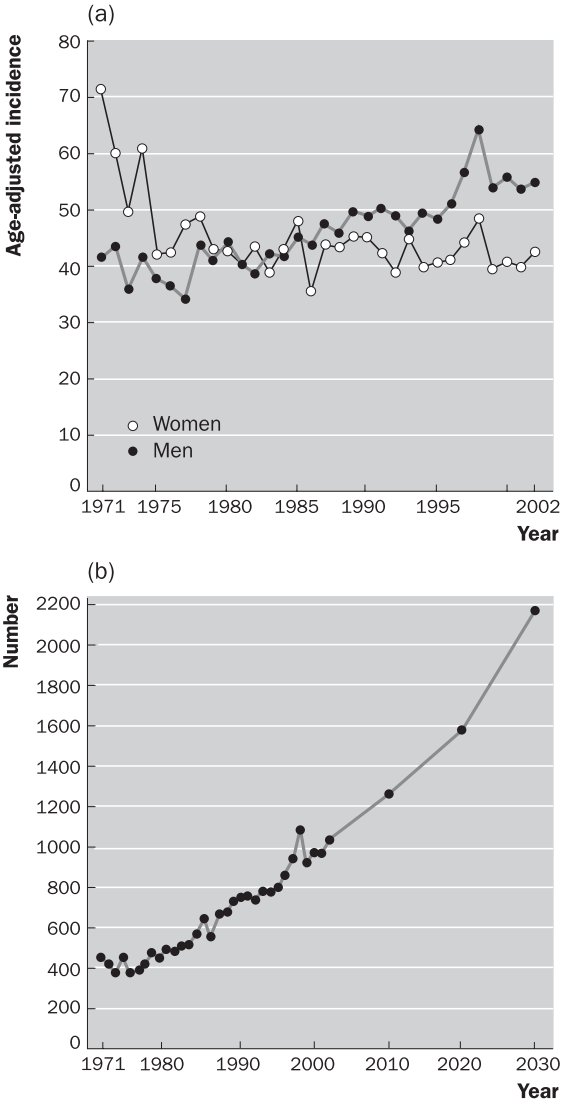


Fig. 10.6 Secular trends in fall-induced deaths among elderly Finns aged 50 or older: (a) age-adjusted incidence (per 100 000 persons) between 1971 and 2002; (b) number of deaths between 1971 and 2002 and prediction of the development until the year 2030. Source: Kannus *et al.* (2005).

is associated with an increased rate of falls. The rate of falls among individuals in institutions is higher than that among individuals in the community.

Falls can be prevented by a multidisciplinary approach and all elderly people can benefit from balance training [1]. The studies reviewed here show that it is possible to reduce the number of people falling by up to 34%.

In risk assessment for falls, a few simple questions and the assessment of biological age may be as effective as objective tests. There is now evidence for an effect of vitamin D supplementation on falls in the elderly. Falls prevention programmes in subacute hospital settings may be effective, but the data reviewed here have to be confirmed by others in other hospital settings. Li *et al.* has confirmed and strengthened evidence that Tai Chi can be used to prevent falls, and also that the effect can continue after the end of the study intervention. The study by Harwood *et al.* indicates that cataract surgery might be beneficial in the prevention of falls and fractures. A cognitive behavioural approach, at least when combined with exercise interventions, may be effective in preventing falls, as suggested by Clemson *et al.*

Studies on the effectiveness of interventions in the reduction of injurious falls are still lacking. The need for such studies is stressed by the data on fall-induced deaths by Kannus *et al.* Supplementation with vitamin D in the elderly reduces fall rates and increases bone mass; together, these have a fracture-reducing effect [10–12]. For other fall-preventive interventions, data on injurious falls are missing or scarce. Meanwhile, we have to assume that the interventions effective in reducing falls are also effective in reducing injuries.

Several barriers for successful implementation of fall reduction programmes exist. Initially decreased fall rates after the start of a fall prevention programme may increase a few years after the start of the programme [18]. This highlights that implementation of a programme on falls prevention has to be revitalized frequently. Low-intensity fall prevention programmes may in some instances even be harmful and increase fall rates [19]. Compliance may be a barrier to successful implementation of programmes in patients [20]. These issues may have a serious impact on the effectiveness of programmes introduced in all settings, and they need to be considered if we are to achieve long-term success. These issues also need to be addressed in further studies.

Assessment schemes to identify individuals who need interventions for falls prevention have been suggested by Tinetti [21] and Oliver *et al.* [22]. An assessment of the risk of falling should be made when in contact with the elderly patient. Several effective methods to reduce the risk of falling exist. Targeted interventions to reduce falls and injurious falls should be offered to those at highest risk, who are most likely to benefit from an intervention. This strategy is presumably also the most cost-effective way to prevent falls, and injuries from a fall, in a society facing an increase in the proportion of elderly people who are at risk of falling.

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11

Diet and osteoporosis with specific reference to calcium and vitamin D

SUSAN LANHAM-NEW

Introduction

There is an urgent requirement for public health strategies to improve bone health at both the individual and the population level, especially given that: (i) the World Health Organization predict that by 2050 there are likely to be 6.26 million hip fractures worldwide (compared with 1.66 million in 1990) [1]; (ii) estimates indicate that by 2030 one in three of the adult population will be aged 65 years and over. We know that skeletal integrity is regulated by a combination of endogenous and exogenous factors. Whilst the non-modifiable factors account for approximately 75% of bone variation, this still leaves ample space for nutrition and physical activity (the key modifiable factors) to exert an influence (Fig. 11.1). Consideration needs to be given to the application of dietary advice to different population groups. For effective strategies, emphasis needs to be given at three levels in combination, as shown in Fig. 11.2: (i) universal primary prevention; (ii) selective prevention in high-risk groups; and (iii) prevention targeted at individuals [2].

This chapter reviews a number of key recent papers focusing on the effect of nutrition on bone health across the age ranges. First, the effects of calcium and vitamin D supplementation on the prevention of osteoporotic fractures in the elderly will be reviewed, with extensive introductions and discussions on this topic; several key UK studies published this year will be highlighted. Secondly, the effects of tanning on vitamin D status and bone density will be discussed with specific reference to effects on skeletal integrity and implications for public health. Thirdly, long-term calcium supplementation studies on the attainment of peak bone mass will be reviewed. Other key areas which will be addressed include the effects of dietary acidity/alkalinity on bone health; the influence of phyto-oestrogen supplementation on bone mass; the effect of vitamin K nutrition in the younger population; and the link between the vitamin B complex and bone.

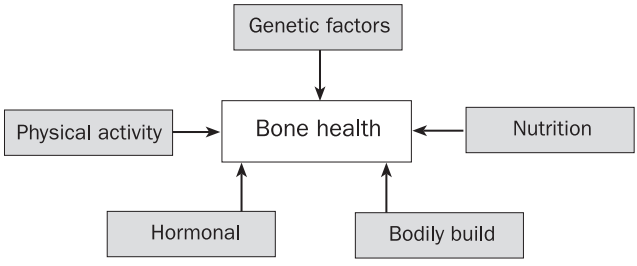

Fig. 11.1 Endogenous vs exogenous factors influencing bone health.

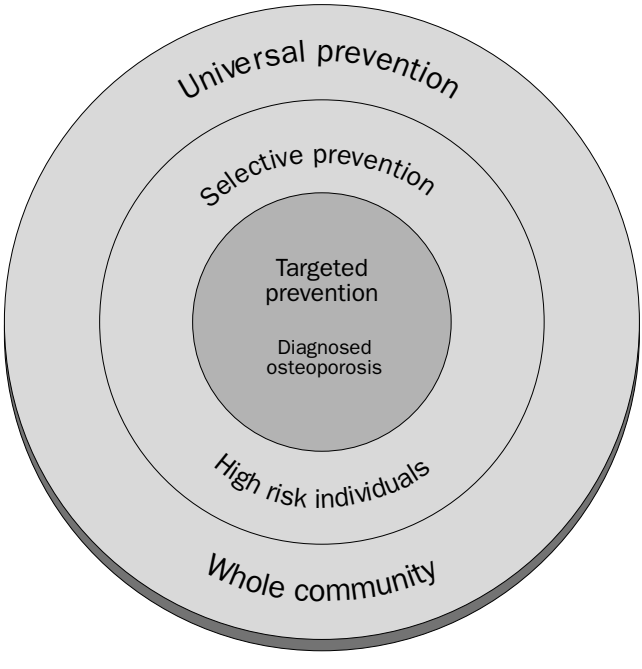

Fig. 11.2 Approaches to preventing disease. Source: Goulding (2003) [2].

Effects of calcium and vitamin D on prevention of osteoporotic fracture

It is well established that both calcium and vitamin D are critical to health. Calcium is the most abundant mineral element in the body and has two key roles: structural

and regulatory. As regards its structural role, bone consists of a protein matrix encased in a crystalline mineral. Approximately 1 kg of calcium is contained within the skeleton (99% of the calcium is contained in the bones and teeth) and it is this mineral part which contributes to the strength of bone. Bone mineral provides a huge reserve of calcium, behaving as a large ion exchanger that allows interaction between ions in the body fluids and bone. Calcium is the most abundant mineral element in the body. As regards its regulatory role, plasma concentrations of calcium are maintained within very narrow limits (90–110 mg/l). Although only 1% of calcium is found in soft tissues and body fluids, this calcium is required for a number of key functions, including the maintenance of cellular structure; inter- and intracellular metabolic function and signal transmission; muscle contraction, including contraction of the heart muscle; nerve function; the activities of enzymes; and the normal clotting of blood. The regulation of serum calcium levels is carefully maintained by the calciotrophic hormones (parathyroid hormone [PTH], calcitonin [CT] and calcitriol (the hormonally active metabolite of vitamin D, $1,25(OH)_2D_3$)) [3].

Vitamin D is required for the maintenance of bone health in older individuals and also for bone growth and development in children. The active vitamin D metabolite 1,25 di-hydroxyvitamin D regulates calcium absorption as well as mediating the mineralization of osteoid tissue within bone [4].

Whilst it is well documented that vitamin D synthesis mediated by sunlight is affected by the ageing process, there is a remarkable lack of awareness of this public health nutrition message. Findings of the recent National Diet and Nutrition Survey (NDNS) of people aged 65 years and over [5] showed that 97% of free-living elderly women and 99% of those living in nursing homes had intakes of vitamin D below the Reference Nutrient Intake (RNI) and over one-third of the institutionalized elderly were vitamin D-deficient, with the likelihood of a much higher prevalence of vitamin D insufficiency amongst this group. Furthermore, results of the recent NDNS survey of young people aged 4–18 years found that significant proportions of those in the older age groups had poor vitamin D status, a finding that has been mirrored in studies of other adolescent groups [6]. These data (on both the younger and older populations) clearly have important implications for skeletal health.

Oral vitamin D_3 and calcium for the secondary prevention of low-trauma fractures in elderly people (Randomized Evaluation of Calcium or Vitamin D, RECORD): a randomised placebo-controlled trial

Grant AM, Avenell A, Campbell MK, *et al*. *Lancet* 2005; **365**: 1621–8

Background. Vitamin D and calcium supplementation has been shown to significantly reduce fracture rates in the institutionalized elderly [7]. Participants in this trial of 3270 women received 1.2 g of calcium and 800 IU of vitamin D daily or a

placebo for a period of 18 months. The supplementation trial was found to increase serum 25-hydroxyvitamin D ($25OH_2D_3$) from 40 to 100 nmol/l, with a concomitant decrease in serum PTH also from 54 to 30 pg/ml in the group supplemented with calcium and vitamin D. In a further calcium and vitamin D study, men and women living at home were supplemented with 500 mg of calcium and 700 IU of vitamin D [8]. Bone mineral density (BMD) at the lumbar spine and the neck of the femur increased and there was a reported reduction in the incidence of non-vertebral fractures by a total of 54% over the 3-year period in the group receiving calcium and vitamin D when compared with those receiving the placebo. It is important to note, however, that the study was not specifically powered to examine fracture reduction.

It is intriguing that vitamin D supplementation alone is not effective [9]. In a Norwegian supplementation trial, the use of cod liver oil containing 10 μg (400 IU) of vitamin D did not prevent fracture in 1144 nursing home residents [10]. A point of note is the difference between vitamin D supplementation levels. In the studies by Chapuy [7] and Dawson-Hughes [8], the amounts of supplementary vitamin used were 20 and 17.5 μg/day respectively, whereas in the studies by Lips [9] and Meyer [10], only 10 μg/day was used, without additional calcium.

Two recent UK trials are conflicting. In a study by Trivedi *et al.* (2004), 100 000 IU of vitamin D_3 given orally every 4 months to men and women aged 65–85 years significantly reduced the overall fracture risk by 22%, although there were no significant reductions in fractures at any specific site or in either sex alone [11]. A total of 2037 men and 649 women were studied; they were living in the community.

In a more recent randomized controlled trial undertaken in Wessex, UK, a total of 9440 subjects were studied (5086 women and 4354 men). Subjects were living in the community, were aged 75 years and over, and were randomized to receive an injection of 300 000 IU of vitamin D or a placebo every autumn for a period of 36 months. The results of the study showed no reduction in falls and no reduction in the risk of any first fracture or first forearm fracture with vitamin D. A point of concern was the finding that the risk of the first hip fracture was actually increased (hazard ratio 1.48; 95% confidence interval [CI] 1.01–2.17) with the vitamin D treatment [12].

INTERPRETATION. This study by Grant *et al.* was a pragmatic, randomized, controlled trial examining the effects of calcium and vitamin D supplementation in the secondary prevention of osteoporotic fractures in men and women aged 70 years and over. The study design was such that the independent effects of calcium supplementation alone and vitamin D supplementation alone could also be investigated. A total of 4481 women and 811 men were studied over a 24-month period. Subjects were recruited if they had a low-trauma fracture and most of the subjects were community dwellers. Results showed no difference in fracture reduction in any of the groups, whether receiving calcium and vitamin D in combination or alone (Table 11.1). Serum $25OH_2D_3$ levels were found to be significantly increased (from 35 to 60 nmol/l) in the groups receiving vitamin D alone and calcium plus vitamin D supplementation.

Comment

The findings of this UK-funded calcium and vitamin fracture prevention trial indicate that calcium and vitamin D are ineffective in the secondary prevention of

Table 11.1 Specific outcomes in supplement and placebo groups

	Vitamin D_3 and calcium (n = 1306)	Vitamin D_3 (n = 1343)	Calcium (n = 1311)	Placebo (n = 1332)
New fractures	184	212	189	196
Confirmed fractures	179	208	185	192
Low-trauma fractures	165	188	166	179
Proximal femur	46	47	49	41
Other leg and pelvic	37	48	41	54
Distal forearm	33	33	33	28
Clinical vertebral	0	4	3	1
Reported falls	161	219	185	196

Source: Grant *et al.* (2005).

osteoporotic fractures in older men and women living in the community. As noted in the accompanying *Lancet* editorial by Sambrook [13], it is important to note that the overall compliance with the study medication was relatively poor (65% over 2 years), and it is especially important to note that it was 8% lower in subjects taking calcium. Furthermore, it is a pity that vitamin D levels were measured in such a small number of subjects. From the data available it would appear that the increase in vitamin D was much less than that achieved in the Chapuy study [7], and that the groups were probably much more replete in vitamin D.

A further trial with calcium and vitamin D published this year from the UK, the Northern and Yorkshire study, was a randomized, controlled trial which examined the effect of daily supplementation with 1000 mg of calcium and 800 IU of vitamin D in a total of 3315 women [14]. Subjects were aged 70 years and over and had a specific clinical risk factor for hip fracture. The clinical risk factors included previous fracture, weight below 58 kg, being a smoker, a family history of hip fracture, and fair or poor health. Questionnaires were sent to the subjects through the primary care setting and subjects were then randomized to either the control group or to a nurse-focused clinic where they were given calcium and vitamin D supplements. No significant reductions in fracture with the calcium and vitamin D treatments were identified after a period of 18–42 months (median follow-up period, 25 months) and there was no reduction in falls or improvement in the quality of life.

These data do not support the findings of a factorial, cluster-randomized, pragmatic, intervention study of 9605 community-dwelling residents living in a northern European region (Denmark) [15]. A daily supplement of calcium carbonate (1000 mg) and vitamin D (400 IU) over a period of 3 years resulted in a 16% reduction in the incidence rate of fracture (relative risk 0.84; 95% CI 0.72–0.98) compared with subjects who were offered no supplement but an environmental and health programme [15].

Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density

Tangpricha V, Turner A, Spina C, Decastro S, Chen TC, Holick MF. *Am J Clin Nutr* 2004; **80**: 1645–9

Background. **Vitamin D is the generic term for two molecules, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). The former is derived by ultraviolet irradiation of the ergosterol that is widely distributed in plants and other fungi, whereas the latter is formed from the action of ultraviolet irradiation on the skin. The action of sunlight on the skin converts 7-dehydrocholesterol to previtamin D, which is then metabolized to vitamin D by temperature-dependent isomerization. Vitamin D is then transported via the general circulation to the liver, where the enzyme 25-hydroxylase converts it to 25OHD. Further conversion to $1,25(OH)_2D_3$ occurs in the kidney. 25OHD is the main circulating vitamin D metabolite and is the best indicator of clinical status, whereas $1,25(OH)_2D_3$ is the active form of the vitamin which is involved in calcium homeostasis [4].**

Sources of vitamin D

It is now well established that there are two sources of this vitamin: (i) endogenous (skin); and (ii) exogenous (diet). It is generally believed that the major source of vitamin D is the exposure of skin to the ultraviolet B-rays contained in sunlight. However, the relative contributions of these two sources are thought to vary widely among individuals and among geographical areas, but as yet there are few good data available. Many of the published studies were carried out almost 20 years ago, since when there have been improvements in both vitamin D assays and a vast expansion in food composition tables of vitamin D intake.

Effects of climate on vitamin D status

Much of the ultraviolet in sunlight is absorbed by clouds, ozone and other forms of atmospheric pollution. Thus, because of the reduced zenith angle of the sun and increased path length of sunlight through the atmosphere, the effective level of ultraviolet energy decreases with north–south distance from the seasonally varying latitude at which the sun is directly overhead. In the UK, there is no ultraviolet radiation of the appropriate wavelength (280–310 mm) from the end of October to the end of March, and for the remaining months of the year 60% of the effective ultraviolet radiation occurs between 11.00 a.m. and 3.00 p.m. [16].

Dietary effects on vitamin D status

There are relatively few dietary sources of vitamin D, the major providers being fat spreads, fish, eggs, fortified cereals and pastry products. Until fairly recently, information on vitamin D intake from meat was not available, but new analytical data for the composition of meat now includes the contribution from the metabolite 25-hydroxycholecalciferol ($25(OH)D_3$) rather than just cholecalciferol itself. Recently

published work in this area has shown that meat is a much more significant contributor to vitamin D intake than was previously thought [17].

Importance of vitamin D to a key health outcome: bone health

Vitamin D status is known to be affected by the ageing process and there is now some good evidence to show that vitamin D levels (i) fall with age; (ii) are inversely related to PTH (which is also known to have seasonal variation); (iii) menopausal bone loss is partially regulated by dietary intake of vitamin D; and (iv) elderly people are susceptible to vitamin D deficiency or vitamin D 'insufficiency'. The effect of vitamin D and its metabolites on bone is very complex. It is known to stimulate matrix formation and bone maturation and increase osteoclastic activity, and may influence the differentiation of bone cell precursors. Together with PTH and calcium, it regulates calcium and phosphorus metabolism and promotes calcium absorption from the gut and kidney tubules. Deficiency of vitamin D has been shown to reduce calcium absorption and increase PTH excretion, thereby stimulating osteoclastic activity and thus increasing bone loss [18].

INTERPRETATION. Healthy adults ($n = 156$) aged 18–70 years participated in this study. Subjects were classified as tanners if they had regularly been using a tanning bed (more than once a week) for longer than 6 months ($n = 50$). Non-tanners were those subjects who did not use a tanning bed ($n = 106$). A blood sample (for measurement of 25OHD) was taken between March and June and BMD was assessed at the lumbar spine, hip and total body sites. Results showed that subjects who regularly used a tanning bed had serum 25OHD concentrations 90% higher than the control subjects (115.5 [SD 8.0] vs 60.3 [3.0] nmol/l), and concomitantly tanners had PTH concentrations 18% lower than those of the control subjects (21.4 [SD 1.0] vs 25.3 [0.8] pg/ml). Furthermore, as shown in Table 11.2, tanners had significantly higher BMD at the total hip site.

Comment

There is a great deal of controversy concerning the balance between adequate sunlight exposure for optimizing vitamin D status and the increasing concern about skin cancer [4]. It is well established that the use of sunscreens which have a moderate to high sun-protective factor (>8) significantly reduce the

Table 11.2 Bone mineral content (BMC) and bone mineral density (BMD) at the hip in tanners and non-tanners

	Tanners ($n = 50$)	**Non-tanners ($n = 102$)**
BMD (g/cm^2)	0.975 ± 0.03	0.920 ± 0.01
BMC (g)	33.2 ± 1.0	31.1 ± 0.8
Z-score	0.20 ± 0.2	–0.18 ± 0.01

Source: Tangpricha *et al*. (2004).

amount of vitamin D_3 produced in the skin by up to 95%. It is also well established that subjects who have no or little exposure to sunlight have vitamin D deficiency |**17**|.

This study set out to examine whether subjects who used a tanning bed regularly (and hence were exposed regularly to ultraviolet B radiation) had significantly higher 25OHD levels and higher BMD.

The results showed that the prevalence of vitamin D deficiency was significantly lower in tanners than non-tanners (8 and 41% respectively), and the tanners had significantly higher vitamin D levels and significantly lower levels of PTH.

Low vitamin D status has been implicated in an increased risk of falling and recent meta-analysis has shown that vitamin D supplementation reduces the risk of falls amongst institutionalized and free-living elderly people |**19**|. Mechanisms of action need further definition but certainly muscle weakness, which can affect balance and mobility, has been implicated |**20**|. Hence, these findings have important public health implications since they suggest that the moderate use of tanning beds may also provide some medical benefit. Further trials are required which examine the effect of chronic use of tanning beds on vitamin D and bone health.

Influence of additional calcium on peak bone mass development

Calcium supplementation and bone mineral density in females from childhood to young adulthood: a randomised controlled trial

Matkovic V, Goel PK, Badenhop-Stevens NE, *et al*. *Am J Clin Nutr* 2005; **81**: 175–88

BACKGROUND. Calcium supplementation studies in children and adolescents tend to suggest a difference in BMD at the end of the intervention period of the order of 1–5% (depending on skeletal site). However, some studies have failed to show a difference in bone mass longitudinally after withdrawal of the supplement, which may suggest evidence of the bone remodelling transient effect. More data are clearly required urgently, since clinical trials investigating the effect of increased calcium intake (either through foods or supplements) on peak bone mass development have been of relatively short duration |20|.

INTERPRETATION. Matkovic *et al*. report the results of a 4-year randomized clinical trial which involved 354 females at stage 2 of puberty. The study was optionally extended for a further 3 years. Mean intake of calcium over the 7-year period was 830 mg/day, calcium-supplemented individuals receiving an additional 670 mg/day of calcium. Results indicated that calcium supplementation significantly influenced bone

Table 11.3 Bone outcome measures and stature in supplemented and placebo groups at baseline, 4 years and 7 years

	Baseline		Year 4		Year 7	
	Supplemented group	**Placebo group**	**Supplemented group**	**Placebo group**	**Supplemented group**	**Placebo group**
Height (cm)	145.7 ± 7.3	144.7 ± 7.0	163.2 ± 5.6	163.5 ± 6.1	165.2 ± 5.6	164.9 ± 6.1
Total body BMD (g/cm^2)	0.892 ± 0.055	0.888 ± 0.057	1.105 ± 0.067	1.094 ± 0.070*	1.160 ± 0.071	1.152 ± 0.066
Proximal radius BMD (g/cm^2)	0.502 ± 0.046	0.496 ± 0.049	0.654 ± 0.048	0.641 ± 0.053*	0.664 ± 0.049	0.652 ± 0.049*
Distal radius BMD (g/cm^2)	2.071 ± 0.197	2.079 ± 0.197	0.387 ± 0.054	0.366 ± 0.058*	0.450 ± 0.053	0.438 ± 0.050
Metacarpal cortical area (CA) (cm^2)	0.137 ± 0.020	0.132 ± 0.017	0.186 ± 0.024	0.178 ± 0.021*	0.196 ± 0.024	0.186 ± 0.020*
Metacarpal total area (TA) (cm^2)	0.392 ± 0.053	0.392 ± 0.049	0.436 ± 0.053	0.434 ± 0.049	0.443 ± 0.052	0.440 ± 0.047
Ratio of CA:TA	0.349 ± 0.036	0.339 ± 0.035	0.429 ± 0.040	0.412 ± 0.047*	0.445 ± 0.043	0.425 ± 0.048*

*Groups significantly different at $P<0.05$
Source: Matkovic *et al.* (2005).

accretion in young females during the pubertal growth spurt, and although the effect diminished in young adulthood, the significant effects remained at the metacarpals and at the forearm of all tall persons (Table 11.3). The authors conclude that calcium requirements for maximum skeletal development are associated with bone size.

Comment

This is a vital study in the field of calcium and peak bone mass by Matkovic and colleagues, which demonstrates the longer-term effects of calcium on bone mass. Further support for increased calcium intake during the early years can be found in the study by Dodiuk-Gad *et al.* [**21**], who report the results of a follow-up study to a 3.5-year calcium supplementation study in 96 adolescent girls. Multivariate analysis revealed that total body BMD accretion from the beginning of the intervention study to the follow-up study in the active treatment cohort was attributed to calcium supplementation and to the time since inclusion in the initial study. These results confirm the findings of Bonjour *et al.* [**22**], which showed that a statistically significant increase in mean BMD at the six skeletal sites in calcium-supplemented subjects compared with control subjects was maintained 3.5 years after the end of supplementation.

Effects of dietary alkali on indices of bone health

The health-related benefit of a high consumption of dietary alkali (hence high consumption of fruit and vegetables) has been gaining much interest and prominence in the literature over a considerable time. Of interest to the field of osteoporosis is the role that bone plays in acid–base balance. Natural, pathological and experimental states of acid loading/acidosis have been associated with hypercalcuria and negative calcium balance, and more recently the detrimental effects of 'acid' from the diet on bone mineral have been demonstrated [**23**]. Further support for a positive link between fruit and vegetable intake and bone health can be found in the results of the DASH (Dietary Approaches to Stopping Hypertension) intervention trial [**24**]. In addition, a number of population-based studies published in the last decade have demonstrated a beneficial effect of fruit and vegetable/potassium intake on axial and peripheral bone mass and bone metabolism in men and women across the age ranges.

Low dietary potassium intakes and high dietary estimates of net endogenous acid production are associated with low bone mineral density in pre-menopausal women and increased markers of bone resorption in post-menopausal women

Macdonald HM, New SA, Fraser WD, Campbell MK, Reid DM. *Am J Clin Nutr* 2005; **81**: 923–33

BACKGROUND. It is now possible to estimate net endogenous non-carbonic acid production (NEAP) from knowledge of the dietary protein and potassium contents of a diet. This in turn enables exploration of the effects of dietary 'acidity' and 'alkalinity' on bone. Hence, the aim of this study was to determine whether lower dietary 'acidity' (a lower dietary protein intake but a high potassium intake; that is, a low estimate of NEAP) was associated with higher axial and peripheral bone mass and lower bone turnover, independently of key confounding factors.

INTERPRETATION. The relationship between dietary potassium/protein, estimates of NEAP and estimates of Potential Renal Acid Load (PRAL) with markers of bone health were examined in the subjects participating in the Aberdeen Prospective Osteoporosis Screening Study (APOSS). A total of 3326 subjects were studied for measurement of BMD, 2929 subjects having also had their bone resorption measured. As shown in Fig. 11.3, comparison of the highest with the lowest quartile of potassium intake or the

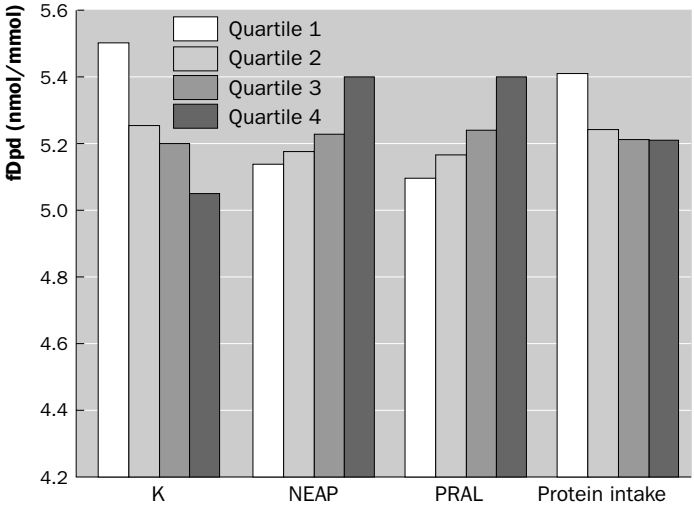

Fig. 11.3 Concentrations of fDpd excretion with quartiles of K, NEAP, PRAL and protein intake. fDpd, free deoxy-pyridinoline excretion. Source: Macdonald *et al.* (2005).

lowest with the highest NEAP showed that there was a difference of 6–8% in bone resorption. Furthermore, a difference of 8% was seen in BMD between the lowest and highest quartiles of potassium intake in pre-menopausal women.

Comment

These are interesting, novel findings with respect to the effect of dietary 'acid' on skeletal integrity. The results indicate that diets characteristic of a lower protein but higher potassium content (i.e. lower 'acidity' or higher 'alkalinity') are associated with lower bone resorption. From a clinical point of view, the key messages are as follows: quantifying the acid–base content of diets generally consumed by populations is critical (especially for the determination of their effects on bone status). Since it is considered that normal adult humans eating typical Western diets have chronic, low-grade metabolic acidosis (producing in excess of 1 mEq of acid per kg per day) and since the net rate of NEAP is difficult to measure directly, this study shows that it is useful to examine dietary data for the ratio of protein to potassium intake and then apply a simple algorithm that has been shown by Frassetto *et al.* (1998) [**25**] to determine the net renal acid excretion (a predictor of calcium excretion).

Hence, whilst further studies in other populations are required, it may well be useful to the clinician to examine the 'acid' content of their patient's diet and, if it is found to be 'acidic', direct them towards a shift in the alkali intake, i.e. a higher intake of fruit and vegetables. Whilst fruits and vegetables cannot yet be claimed to be a proven therapy for osteoporosis, the data certainly suggest a positive link between these food groups and optimum bone health [**26**].

Phyto-oestrogens and bone health

The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial

Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. *Am J Clin Nutr* 2004; **79**: 326–33

BACKGROUND. Soy protein consumption may also help to explain why it is so difficult to find a clearcut answer to whether there are bone health differences between populations who follow a vegetarian-based diet compared with those following a non-vegetarian diet [27]. Soy isoflavones have a chemical structure similar to that of oestradiol and have been shown to possess a certain degree of weak oestrogenic activity. In the animal model, comparable favourable bone effects have been shown between 17β-oestradiol and soy protein isolate, genistein or daidzein [28]. Whilst there are studies which support a beneficial effect of soy protein isolates on bone mass in both pre- and peri-menopausal women, more data are urgently required.

The available epidemiological studies looking at the association between soy product consumption and hip fracture rates are conflicting.

INTERPRETATION. Atkinson *et al*. report the findings of a 12-month intervention study looking at the effect of a red clover-derived isoflavone supplement on bone density and bone turnover in a group of women aged 49–65 years ($n = 177$). As shown in Fig. 11.4, lumbar spine bone loss was significantly lower in the isoflavone-supplemented group but no differences were seen at the hip site. Bone formation markers increased significantly in the supplemented group. Further intervention studies are urgently required.

Comment

These are intriguing data. There is a great deal of controversy about whether isoflavones are beneficial to bone in the longer term. Animal studies suggest an effect but there are all too few human intervention trials currently published. Concern over hormone replacement therapy has heightened the search for alternative therapies [**29**]. These data would support the view that phyto-oestrogens are of benefit to trabecular bone, but further research is urgently required to determine the bioactivity of compounds, dose-effectiveness, the contribution of soy protein versus isoflavones, and the mode of action.

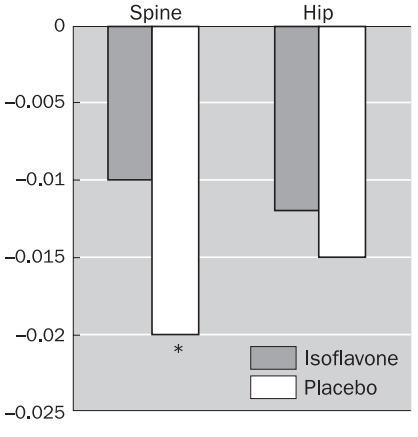

Fig. 11.4 Changes in spine and hip BMD at 12 months by treatment group. Source: Atkinson *et al*. (2004).

Vitamin K and bone health

Vitamin K, bone turnover and bone mass in girls

Kalkwarf HJ, Khoury JC, Bean J, Elliot JG. *Am J Clin Nutr* 2004; **80**: 1075–80

BACKGROUND. Vitamin K has an important function for the skeleton: it acts as a cofactor in the post-translational carboxylation of several bone proteins, osteocalcin being the most abundant. Deficiency of vitamin K results in the synthesis of under-carboxylated osteocalcin (ucOC) [30]. There are observational data to show that low serum concentrations of both vitamin K_1 and ucOC are associated with an increased risk of osteoporotic fractures. However, studies examining the association between vitamin K and bone density have been inconsistent, suggesting that the effect of vitamin K on skeletal integrity may not act only through a mechanism of reduced BMD [31]. Recently, low plasma phylloquinone concentrations have been associated with low spine BMD (with a similar non-significant trend of an elevated percentage of ucOC with low spine BMD; $P<0.08$) in post-menopausal women not using hormone replacement therapy, but not in pre-menopausal women or post-menopausal women using hormone replacement therapy) [32].

INTERPRETATION. Kalkwarf *et al.* examined the effect of vitamin K status on bone turnover in healthy girls aged 3–16 years ($n=245$). Better vitamin K status (high plasma phylloquinone and low ucOC percentage) was associated with lower bone resorption and bone formation. Furthermore, plasma phylloquinone was inversely associated with cross-linked N-telopeptide of type I collagen (NTX) breakdown and osteocalcin concentrations. Trials on the effect of vitamin K supplementation on bone health in our younger population are needed, but these data suggest that better vitamin K status is associated with decreased bone turnover in girls who regularly eat a typical US-style diet.

Comment

Little is known about vitamin K status and bone metabolism in children. This is an area that requires urgent attention, given that exogenous strategies for improving the accretion of bone during growth may help reduce the risk of osteoporosis in later years. These data by Kalkwarf and colleagues clearly suggest that better vitamin K status is associated with bone turnover in young healthy girls consuming a diet that is representative of the American diet. In general, further vitamin K/bone health supplementation studies are required to determine their effect in maximizing peak bone mass attainment, reducing post-menopausal bone loss and preventing osteoporotic fracture.

Link between folate/vitamin B complex, homocysteine and bone

Homocysteine levels and the risk of osteoporotic fracture
Van Meurs JBJ, Dhonukshe-Rutten RAM, Pluijm SM, *et al*. *N Engl J Med* 2004; **350**: 2033–41

Homocysteine as a predictive factor for hip fracture in older persons
McLean RR, Jacques PF, Selhub J, *et al*. *N Engl J Med* 2004; **350**: 2042–9

BACKGROUND. The link between homocysteine and the risk of fracture suggests the potential for a positive effect of vitamin B complex on the skeleton. There is increasing evidence at the experimental, clinical and epidemiological levels that raised homocysteine levels are associated with increased fracture risk [33]. These levels can be reduced simply and cheaply by folic acid supplementation (although care must be taken that pernicious anaemia is not missed with folate supplementation rather than supplementation with a vitamin B complex containing vitamin B_{12}). In the absence of specific trials on folic acid and fracture reduction, we cannot yet say whether this is an effective strategy for osteoporosis prevention, but it is certainly an area for urgent research.

INTERPRETATION. Van Meurs *et al*. and McLean *et al*. report data showing that raised homocysteine levels are associated with increasing risk of fracture in Dutch (Rotterdam study) and USA (Framingham study) populations, respectively. Van Meurs and colleagues report that a homocysteine level in the highest age-specific quartile was associated with an increase in the risk of fracture by a factor of 1.9. The associations between homocysteine and the risk of fracture appeared to be independent of BMD and other potential risk factors for fracture. McLean and colleagues show that men and women in the highest quartile of plasma homocysteine level had a greater risk of hip fracture than those in the lowest plasma homocysteine quartile, the risk being 4 times as high for men and 1.9 times as high for women.

Comment

Mechanisms of action are not entirely clear but there are some suggestions that high levels of homocysteine in the serum may weaken bone by interfering with collagen cross-linking, thus increasing the risk of osteoporotic fracture [**34**]. There appears to be little evidence for a direct effect of homocysteine on bone, which may explain why results looking at homocysteine, vitamin B complex and bone density yield inconsistent results. Further research is urgently required.

Conclusion

The effects of nutrition on the skeleton are powerful and wide-ranging. There is evidence to suggest that such effects begin *in utero* and remain in place throughout the entire life-span. This provides us with clear target audiences upon whom we can focus our nutrition and bone health messages. On the dietary front, calcium and vitamin D are clearly key nutrients for optimum bone health. The most convincing evidence for the benefit of calcium and vitamin D supplementation in fracture prevention is in institutionalized elderly women. Recent UK trials suggest that treatment with calcium and vitamin D is of no benefit in the prevention of fractures in older community-dwelling women. At all costs, we must protect our population groups from the potential of suboptimum intakes and look to dietary strategies of fortification for particularly vulnerable groups such as the elderly, post-menopausal women and adolescent females. Since the decline in bone mass is seen as a natural phenomenon of ageing, we must encourage sufficient protein/energy nutrition in our ageing population and again look to the development of protein- and energy-dense foods for our frail elderly men and women. Newer nutritional ideas with sound evidence for a positive effect are appearing, including vitamin K, phyto-oestrogens and dietary alkali. Whilst plausible mechanisms have been proposed for the effect of other micronutrients on bone health, such as magnesium, trace elements and vitamin C, more research is required on the specific effects of these nutrients as supplements on markers of bone health.

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12

Physical activity and osteoporosis

MAGNUS KARLSSON, HENRIK AHLBORG

Introduction

About 30–50% of women and 15–30% of men will suffer a fracture related to osteoporosis in their lifetime [1]. This high incidence forces us to initiate prevention strategies, as fractures are associated with increased morbidity and mortality and impose a financial burden on the community [2]. During the last few years, a number of double-blind, randomized controlled trials have shown that several different drugs can reduce the risk of fracture by about 50% in individuals with osteoporosis, a bone mineral density (BMD) 2.5 standard deviations (SD) below the young normal mean according to the definition of osteoporosis advocated by the World Health Organization [3]. This risk reduction is confined to the most vulnerable high-risk group, whereas most fractures are derived from the much larger population of individuals at a more modest risk [4], individuals with osteopenia (BMD between –1 and –2.5 SD below the young normal mean) [3]. Patients with osteopenia who have previously sustained a vertebral fracture might also benefit from therapy, whereas those with osteopenia alone and no other risk factors should not be considered for prophylactic pharmacological therapy. Thus, the problem of fractures in the community cannot be solved with drugs alone. Instead, interventions are needed that are safe, widely accessible, inexpensive to implement and that increase bone strength. Exercise has the first three features and could thus be an attractive approach to reducing the burden of fractures. A variety of questions remain to be answered, however. Does exercise not only increase BMD but also affect bone size or skeletal architecture, all traits contributing to the resistance of bone to fracture? Does exercise influence the skeleton irrespective of the age of the individual? Does an exercise intervention programme in a defined population, that also includes individuals uninterested in sports, increase bone strength? Does exercise reduce the BMD loss and influence the bone structure in the peri- and post-menopausal period? Do exercise-induced skeletal benefits remain after a reduction in activity level? Finally, as not only bone strength but also balance, coordination, muscle strength and the tendency to fall influence the fracture risk, is exercise during young years associated with a reduced fracture risk in old age?

Can exercise enhance the accrual of bone mineral density during growth?

The skeletal effects of exercise may differ between young and old individuals. The mechanical threshold for old rats was shown to be higher than that of young rats but, once activated, their osteoblasts had the same capacity as those of younger rats to enhance bone formation [5]. The relative bone formation rate in elderly rats is 16 times less and the relative bone-forming surface five times less than in younger rats under similar loads [5,6]. Data also suggest that the exercise-induced skeletal response in humans is dependent on age. BMD was up to four times higher in the playing than in the non-playing arm in female players who began their tennis training 5 years before menarche compared with those starting 15 years after menarche [7]. An intervention programme with similar design for 7–10 months has been reported to increase the accrual of BMD in pre-pubertal but not in post-pubertal girls [8–12]. But there remain unanswered questions. Only one of the published intervention studies has included the exercise intervention within the school curriculum [11]. The rest included the exercise activity on a voluntary basis. This increases the risk of selection bias, making it compulsory to evaluate whether the described benefits could also be achieved in a population-based cohort. Furthermore, prospective intervention studies must show that the exercise-induced benefits remain beyond 1 year before exercise can be recommended as a strategy to increase peak bone mass. The studies cited below add another brick to the wall of our current knowledge.

Bone mass and structure are enhanced following a 2-year randomised controlled trial of exercise in pre-pubertal boys

MacKelvie KJ, Petit MA, Khan KM, Beck TJ, McKay HA. *Bone* 2004; **34**: 755–64

BACKGROUND. Exercise during growth increases bone mineral accrual but less is known about bone geometry and bone strength. This study compared the skeletal changes in 31 pre-pubertal boys aged 10.2 ± 0.5 years who participated in a 12-minute school-based, high-impact circuit intervention three times a week for 20 months, and in 33 controls. Changes in total body, proximal femur, and lumbar spine bone mineral content (BMC) and bone area were assessed, as were geometric variables and bone strength at the narrow neck, intertrochanteric region and femoral shaft regions by a hip structure analysis (HSA) program with proximal femur dual energy X-ray absorptiometry scans (DXA; Hologic QDR 4500).

INTERPRETATION. At baseline there was no difference between the groups in height or weight and during the study there was no difference in physical activity score, calcium intake, weight or height gain. At the narrow neck region, boys receiving the intervention had greater bone expansion on both the periosteal (+2.6%; $P = 0.1$) and endosteal

(+2.7%; $P = 0.2$) surfaces, resulting in greater changes in section modulus (bone bending strength) (+7.5%; $P = 0.02$, analysis of covariance, adjusting for height change, final Tanner stage and baseline bone values). Also, changes in the BMC of the femoral neck were significantly greater in boys receiving the intervention (+4.3%; $P < 0.01$), whereas there were no differences in changes in bone area.

Comment

A school-based, high-impact exercise intervention implemented three times a week for 12 min in pre-pubertal boys is an effective strategy for site-specific gains in bone strength at the narrow neck region of the proximal femur. The implications of these findings are discussed after the second study cited in this section.

A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomised controlled trial in girls

MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA. *Pediatrics* 2004; **114**: 509–11

BACKGROUND. This paper includes the girls in the previously cited study, where the 32 girls receiving the intervention, aged 9.9 ± 0.6 years, had a high-impact, circuit-based, jumping intervention for 10 min three times a week for 20 months. The changes in BMC for the total body, lumbar spine, proximal femur and lean and fat mass, estimated by dual energy radiograph absorptiometry (Hologic QDR 4500) and the changes in weight, height, Tanner stage, general physical activity and calcium intake were compared with those of 43 age-matched controls.

INTERPRETATION. Girls were at Tanner stage 1–3 at baseline. There were no significant differences in baseline or 20-month change in body size or body composition, average physical activity or calcium intake between groups. There were substantially greater gains in lumbar spine (42 vs 38%) and femoral neck (25 vs 20%) BMC in girls receiving the intervention than in control girls ($P < 0.05$, analysis of covariance; covariates were baseline BMC and height, change in height, physical activity, and final Tanner stage).

Comment

Three brief sessions of high-impact exercise per week implemented over two consecutive school years within the elementary school curriculum elicited a substantial advantage in bone mineral accrual in pubertal girls. The two studies cited indicate that an exercise intervention programme could enhance the accrual of BMD during growth. Long-term prospective studies are needed to find out whether these effects can be found in the long-term perspective and whether they remain into adulthood, so that physical activity can be recommended as one approach to increase peak bone mass. It is extremely important to answer this question if we are going to

introduce increased physical activity into society so as to increase peak bone mass and, in a longer perspective, to use physical activity as a fracture-reductive tool.

Can exercise reduce bone loss in post-menopausal women?

Bone strength depends on material properties, such as BMD, and on skeletal geometry, such as bone size. Both traits can be influenced during adolescence by mechanical load [8,10–12]. In contrast, exercise is consistently reported to influence the skeleton to a lesser extent in adulthood than during growth [4–6,13]. Thus, it has been questioned whether the gain in BMD in absolute values in elderly people is meaningful in terms of reducing the fracture risk. However, as all individuals experience BMD loss with ageing, a decrease in this loss must be regarded as favourable even if exercise does not confer an absolute gain in BMD. A similar decrease in BMD loss could lead to benefits of biological significance if additive effects persist over decades. Any similar long-term benefits may have been missed in the randomized controlled trials published so far, none of which have exceeded 2 years [14]. Furthermore, as data support the view that physical activity predominately influences the skeleton during periods with high bone turnover and fast growth, as in the pre- and peripubertal period [7–12], it is of specific interest to evaluate exercise-induced skeletal effects during the 5–10 years following menopause, as this is a period with significantly increased BMD loss [15]. However, the testing of this hypothesis raises methodological problems as the women must be identified and have their baseline measurement done at menopause, not at a specific chronological age. So far, all published exercise intervention studies in this age group have evaluated women with the baseline defined by chronological age. Some studies have included women both before and after menopause in the same cohort, others only post-menopausal women but with different durations of post-menopausal period. Today there is only one published abstract that prospectively reports the effect of physical activity with menopause as the baseline measurement, and this is therefore also the first study that may be used to test the hypothesis described above [16]. This is probably of great relevance, as bone loss is highest during the first 5–10 years following menopause [15]—it is hypothesized that the greatest influence of exercise on the skeleton is found during periods when rapid changes occur in the skeleton [7]. The hypothesis is supported by the fact that, despite a higher level of physical activity at baseline, BMD was not higher in the active women, whereas a similar post-menopausal level of activity was associated with a lower loss of forearm BMD. There are also long-term benefits: at age 72 the BMD of moderately physically active women was 0.6 SD higher than that of the inactive women. However, as this was not a randomized study, it cannot prove causality [16]. With all these restrictions in mind, the data imply that moderate physical activity in the post-menopausal period is associated with an increase in BMD of 0.6 SD in a cortical,

non-weight-loaded bone, similar to the BMD increases in the femoral neck obtained with bisphosphonates, a benefit known to halve the risk of fracture.

Can exercise influence bone size and geometry so that bone strength increases?

The most compelling evidence that exercise influences the skeletal architecture is derived from unilateral loading studies that control for genetic determinants of BMD. The earliest studies were comparisons of bone structure in tennis players, showing that long-term tennis players had 10–35% greater cortical thickness and greater bone mass in the playing versus the non-playing arm [**17,18**]. Several researchers [**7,19–21**] have supported this notion, reporting that, after adjustment for differences in training history, there is a difference not only in BMD but also in geometrical structure when the dominant and non-dominant arms are compared. Studies in competitive athletes also provide compelling evidence supporting the biologically important changes in bone size and architecture that can be achieved during growth [**8,20**]. For instance, pre-pubertal gymnasts had greater areal BMD (10–30%), with the greatest differences reported in the arms, a weight-bearing site in gymnasts [**8**]. At the mid-femoral shaft, the gymnasts increased their volumetric BMD because of endocortical contraction, not periosteal expansion [**8**], and Bradney *et al.* reported that pre-pubertal boys increased BMD after 10 months of exercise by endocortical, not periosteal, apposition [**10**]. Studies using computed tomography or magnetic resonance imaging have confirmed that bone geometry can be affected by exercise, as when Bass *et al.*, in a cross-sectional study, suggested that exercise in pre- and peripubertal tennis players produces a periosteal response, while endocortical contraction is the dominant response in post-pubertal players [**20**]. With the introduction of HSA, it is now also possible to include mechanical parameters in the evaluation of exercise-induced benefits in the hip when estimated by DXA. The three studies cited below help us to understand the three-dimensional response of the skeleton to physical activity.

Hip section modulus, a measure of bending resistance, is more strongly related to reported physical activity than BMD

Kaptoge S, Dalzell N, Jakes RW, *et al. Osteoporos Int* 2003; **14**: 941–9

BACKGROUND. This study evaluated whether physical activity has a closer relationship with section modulus, an indicator of bending resistance, than with BMD, because physical activity might expand the bony envelope, which tends to reduce BMD for a constant BMC. Four hundred and twenty-three men and 436 women aged 72 ± 3 years (mean ± SD) in a prospective population-based cohort had their hip BMD measured on two occasions 2–5 years apart by DXA (Hologic, 1000 W). HSA was used to calculate the section modulus and BMD in the hip at the narrow neck,

intertrochanter and shaft (Fig. 12.1). Physical activity and lifestyle were evaluated using a questionnaire. Multivariate repeated-measures analysis of variance was used to model the associations between weight, height, age, physical activity and lifestyle variables with section modulus, cross-sectional area (CSA), periosteal diameter and BMD.

INTERPRETATION. In all regions, female gender was associated with lower values of all outcomes, and body weight was positively associated with all outcomes, i.e. section modulus, CSA, periosteal diameter and BMD ($P<0.0001$). Periosteal diameter was positively associated with reported lifetime physical activity (intertrochanter and shaft, $P<0.0001$). There was a significant decline in BMD with age at the narrow neck and shaft regions ($P<0.03$), and the periosteal diameter increased with age (narrow neck and shaft, $P<0.02$). Both section modulus and CSA were positively associated with heavy physical activity after age 50 years in all regions ($P<0.02$), whereas narrow neck BMD was the only BMD associate of heavy physical activity after 50 ($P<0.04$**).**

Comment

Proximal femur width is positively associated with reported lifelong physical activity. If this is mediated through a loading-related effect on subperiosteal expansion, BMD would be an unsatisfactory outcome measure in physical activity studies since

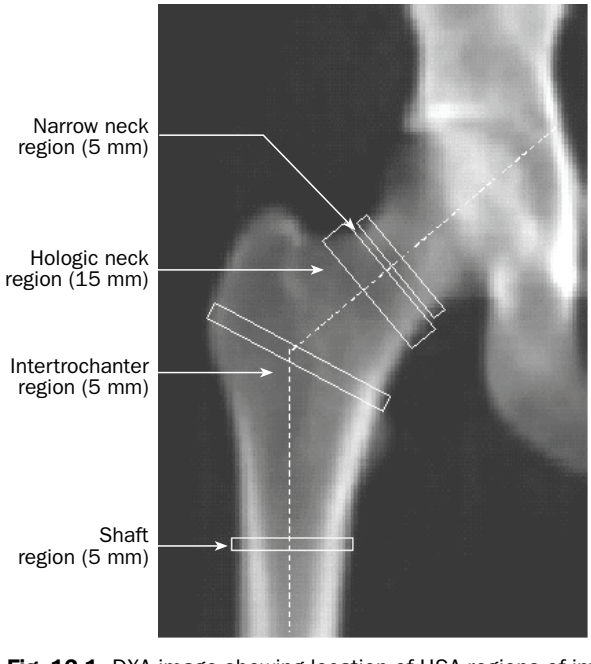

Fig. 12.1 DXA image showing location of HSA regions of interest. Source: Kaptoge *et al*. (2003).

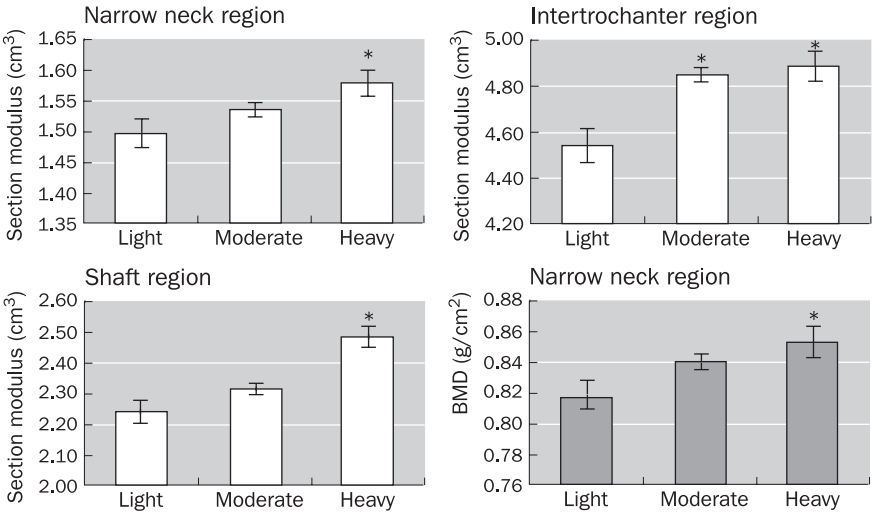

Fig. 12.2 Time spent per week on recreational activities classified as no-impact activity was positively associated with BMD, CSA and section modulus (multivariate $P<0.02$). Source: Kaptoge *et al*. (2003).

it is inversely related to projected bone area. Section modulus, in contrast, was associated with several measures of recent physical activity and relates more directly to the bending experienced by the proximal femur in response to a given load. These data are consistent with an effect of mechanical loading in regulating bone strength through an anabolic effect that is maximal in the subperiosteal cortex, where the highest loading-related strains are experienced.

Femoral bone structural geometry adapts to mechanical loading and is influenced by sex steroids: the Penn State Young Women's Health Study

Petit MA, Beck TJ, Lin HM, Bentley C, Legro RS, Lloyd T. *Bone* 2004; **35**: 750–9

BACKGROUND. One hundred and twelve participants were enrolled in the Penn State Young Women's Health Study at age 12, of whom 76 were re-measured after 10 years. Measurements were recorded twice per year for the first 4 years and annually thereafter. Proximal femur DXA scans (Hologic QDR 2000) were taken from 17 to 22 years and analysed using an HSA program to assess a real BMD, subperiosteal width, cortical thickness, bone CSA and section modulus at the narrow neck and femoral shaft. Total body lean mass (g) was measured with DXA total body scans. Nutrition, anthropometry and sex steroids were measured from 12 to 22

years of age. Multiple regression models were used to assess predictors of change in bone variables (17–22 years) and absolute bone values (average at age 21 and 22 years, *n* = 79).

INTERPRETATION. Neck section modulus (+3.1%) and width (+1.3%), but not BMD (–0.8%), increased significantly from age 17 to 22 years. At the shaft, all variables increased (+1.0–4.0%; $P<0.01$). After controlling for baseline (age 17) height, weight and bone measurement, the primary predictors of change in bone strength were weight change (neck) or lean mass (shaft), and age of menarche. After controlling for height and weight, only lean mass predicted absolute young adult section modulus at both the neck ($r^2=0.48$; $P<0.01$) and the shaft ($r^2=0.67$; $P<0.01$). When lean mass was removed from the model, sports exercise score replaced lean mass as a predictor of section modulus at both neck ($r^2=0.40$; $P<0.01$) and shaft ($r^2=0.60$; $P<0.01$). For neck and shaft cortical thickness and BMD, both oestradiol and sports score/lean mass were positive predictors ($r^2=0.15$–0.40; $P<0.01$). For neck bone width, testosterone level (negative) and lean mass (positive) were significant ($r^2=0.48$). Results were similar for each geometric variable at the shaft site.

Comment

These data suggest that bone adapts its bending strength primarily to mechanical loading, represented by lean mass and sports exercise score, and that sex steroids are associated with the geometric structure of bone.

Femoral neck structure in adult female athletes subjected to different loading modalities

Nikander R, Sievanen H, Heinonen A, Kannus P. *J Bone Miner Res* 2005; **20**: 520–8

BACKGROUND. This study tested the hypothesis that the type of loading partly determines the femoral neck structure. A total of 255 pre-menopausal female athletes representing high-impact loading (volleyball, hurdling), odd-impact loading (squash-playing, soccer, speed-skating, step aerobics), high-magnitude loading (weightlifting), low-impact loading (orienteering, cross-country skiing) and non-impact loading (swimming, cycling) and their 30 non-athletic counterparts were measured with DXA. Besides the conventional areal BMD of the femoral neck, HSA was used to estimate the CSA, subperiosteal width (W) and section modulus at the narrowest section of the femoral neck.

INTERPRETATION. High-impact and odd-impact loading sports were associated with the highest age-, weight-, and height-adjusted areal BMD (23 and 29% higher values compared with non-athletic referents), CSA (22 and 27%) and section modulus (22 and 26%) (Fig. 12.3). In contrast, repetitive, non-impact loading sports were not associated with any clear benefit in any bone value compared with the referents. The subperiosteal width at the narrowest femoral neck section was similar in all groups. The type of loading predicted 13% of the total variation in section modulus. Both high-impact and odd-impact loading modalities were associated with a large benefit in section modulus,

corresponding to more than 1 SD in the reference group, whereas repetitive, low-impact loading showed a benefit that was only one-half of this (Fig. 12.3).

Comment

We conclude that mechanical loading and its modality are strong external determinants of structure and the concomitant strength of the femoral neck. Particularly effective seems to be loading that arises from high impacts or impacts

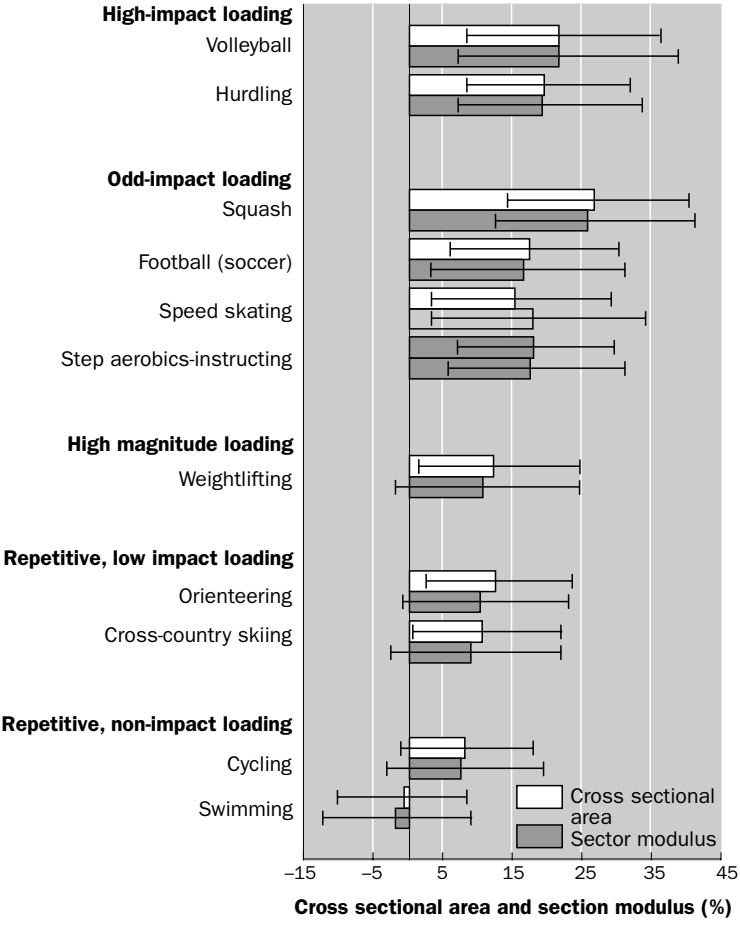

Fig. 12.3 Adjusted percentage differences in the cross-sectional area and section modulus between different athlete groups and the non-athletic reference group. The bars represent 95% confidence intervals. The classification of the loading modality is also indicated (*boxes on left*). Source: Nikander *et al.* (2005).

from atypical loading directions. The study cited here highlights how important it is not only to evaluate exercise-induced effects on BMD but also the mechanical parameters of the skeleton. The next few years will probably see the publication not only of studies using hip strength analyses, estimated from two-dimensional imaging techniques (as with DXA scans), but also of studies with computed tomography and magnetic resonance imaging using three-dimensional techniques. These studies will further increase our knowledge of the effect of exercise on the skeleton, separated into the contributions of material properties such as BMD, and on aspects of skeletal geometry such as bone size, in relation to final bone strength. This is probably of clinical importance as these traits contribute independently to bone strength.

Are exercise-induced benefits eroded by retirement from exercise?

The last question to be discussed in this review is what happens to exercise-induced benefits on reduction or cessation of exercise. Many individuals exercise during adolescence and young adulthood, but reduce their activity in middle age, when family demands and workload leave less time for leisure activities. Are exercise-induced benefits retained in the period of retirement from exercise? This is a clinically relevant question if exercise during growth and adolescence is to be regarded as a means of preventing the clinical problem of osteoporosis fractures, as fragility fractures occur predominantly in old age. Currently there exist short-term prospective data following former athletes after retirement from exercise. Kontulainen *et al.* reported that the differences observed in BMC between the playing and non-playing arms in racket players remained after detraining, suggesting that bone mass benefits are maintained after retirement from exercise [**22**]. Exercise may also affect the structural characteristics of the skeleton. Haapasalo *et al.* reported that exercise caused an increase in bone size in the dominant humerus, radius shafts and distal humerus in racket players, without a change in volumetric bone density [**19**]. The observations fit the notion that exercise produces increases in bone size that are permanent after retirement, but any endocortical thickening due to endocortical apposition may be lost or partly lost with retirement. However, a few years of detraining may be too short for the detection of greater bone loss in the formerly loaded arm in comparison with the less loaded arm. Instead, we have to rely on cross-sectional data in old former athletes. Retired male soccer players had a higher residual BMD, compared to non-exercising controls, during the first two decades after retirement, but when four to five decades of retirement were considered, no BMD benefits were observed in the former soccer players [**23**]. Similar data were found in female soccer players, with a BMD benefit observed after a decade of retirement, although less than in active soccer players [**24**]. Similar data have also been described in former male weightlifters [**25–28**] and former professional male

and female ballet dancers [29]. All these studies suggest that most exercise-induced skeletal benefits are lost three to five decades after cessation of an active career [23–29]. However, these inferences must be confirmed in prospective studies. The two prospective trials cited below, following retired athletes over a longer period, help us to increase our understanding of the skeletal response to detraining.

Bone loss and fracture risk after reduced physical activity

Nordstrom A, Karlsson C, Nyquist F, Olsson T, Nordstrom P, Karlsson M. *J Bone Miner Res* 2005; **20**: 202–7

BACKGROUND. Physical activity increases peak bone mass and may prevent osteoporosis if a residual high BMD is retained into old age. This study evaluated BMD by DXA in 97 young male athletes aged 21.0 ± 4.5 (mean ± SD) and 48 age-matched controls. The measurements were repeated 5 years later, when 55 of the athletes had retired from sports. In a second, older cohort, the incidence of fracture was recorded in 400 former older athletes and 800 controls aged 60 or above.

INTERPRETATION. At baseline, the young athletes had higher BMD (g/cm^2) than controls in total body, spine and femoral neck, with a mean difference of 0.08–0.13 (all $P<0.001$). During the follow-up period, the athletes who retired lost more BMD than the still active athletes in the total body and femoral neck, with a mean difference of 0.03–0.07 (both $P<0.01$) (Fig. 12.4). Nevertheless, BMD was still higher in the retired young athletes than in the controls in the total body and femoral neck, with a mean difference of 0.06–0.08 (both $P<0.05$). In the older cohort, there were fewer former

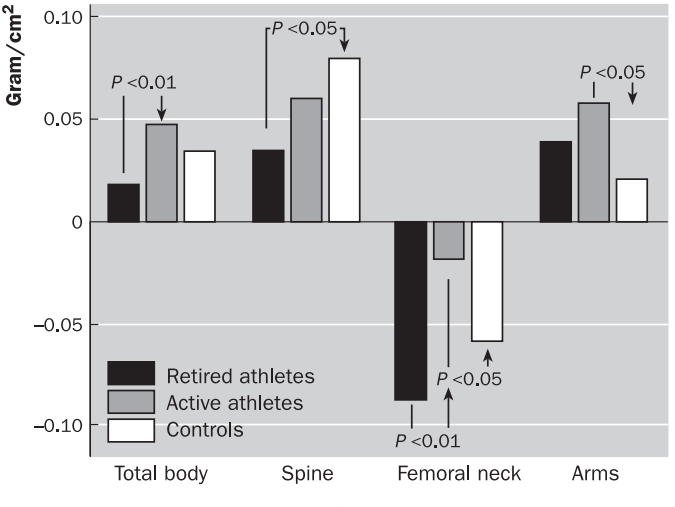

Fig. 12.4 Changes in BMD (g/cm^2) in a young cohort of athletes and controls during the 5 years of follow-up. Source: Nordstrom *et al*. (2005).

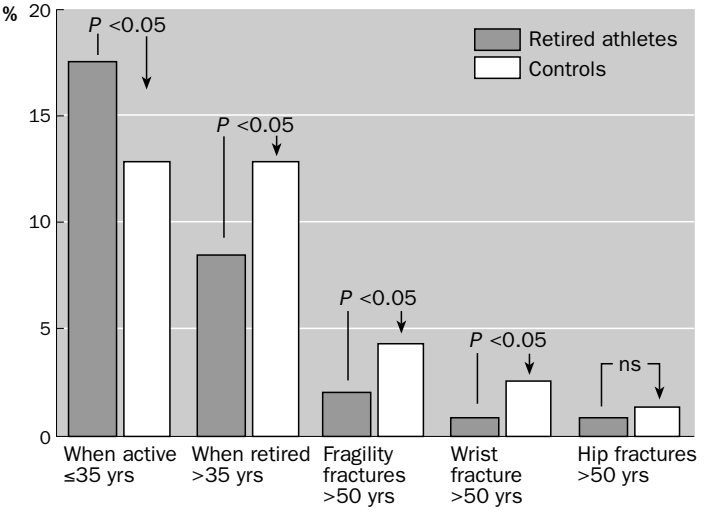

Fig. 12.5 Proportion of former older athletes and controls 60 years of age with fractures. Source: Nordstrom *et al.* (2005).

athletes aged 60 or above than controls with fragility fractures (2.0 vs 4.2%; $P<0.05$) and distal radius fractures (0.75 vs 2.5%; $P<0.05$) (Fig. 12.5).

Comment

This study suggests that in men there is an association between retirement from exercise and loss of the exercise-induced benefits in BMD, but that in spite of this former athletes have a lower risk of fracture than controls. The implications are discussed after the next study to be cited.

Reduced training is associated with increased loss of bone mineral density

Valdimarsson Ö, Alborg HG, Düppe H, Nyquist F, Karlsson KM. *J Bone Miner Res* 2005; **20**: 906–12

BACKGROUND. Physical activity during adolescence increases BMD (g/cm^2), but whether the benefits are retained with reduced activity is controversial. At baseline, DXA was used to evaluated BMD in 48 active female soccer players aged 18 ± 4 years (mean ± SD), in 18 former female soccer players aged 43 ± 6 years and retired for 9 ± 5 years, and in 64 age- and gender-matched controls. The soccer players were re-measured after a mean of 8 ± 0.3 years, when 35 of the players who had been active at baseline had been retired for a mean of 5 ± 1 years.

Interpretation. The players still active at the follow-up had a higher BMD at baseline than the matched controls in the femoral neck (1.13 ± 0.19 vs 1.00 ± 0.13 g/cm^2; $P = 0.02$). The yearly gain in BMD during the follow-up was higher in the active players than in the controls (leg, 0.015 ± 0.006 vs 0.007 ± 0.012 g/cm^2; $P = 0.04$). The soccer players who retired during the follow-up had a higher BMD at baseline than the matched controls (femoral neck, 1.13 ± 0.13 vs 1.04 ± 0.13 g/cm^2; $P < 0.01$). The players who retired during the follow-up lost BMD whereas the controls gained BMD during the study period (yearly change in the femoral neck, –0.007 ± 0.01 vs 0.003 ± 0.02 g/cm^2; $P < 0.01$). The soccer players who were already retired at baseline had higher BMD at the start of the study than the matched controls (legs, 1.26 ± 0.09 vs 1.18 ± 0.10 g/cm^2; $P = 0.01$). The former players who were retired already at the start of the study lost BMD, whereas the controls gained BMD during the study period (yearly change in the trochanter, –0.006 ± 0.01 vs 0.002 ± 0.01 g/cm^2; $P = 0.03$).

Comment

This study demonstrates that decreased physical activity in both the short term and the medium-long term is associated with greater BMD loss in former female soccer players than in controls. However, it cannot be concluded from the two studies cited here that all benefits will be lost in the long term, as there were still residual BMD benefits after two decades of retirement. In addition, we cannot state whether residual benefits in bone size or bone quality remain in the former athletes, benefits that could possibly lead to a reduced fracture incidence. In the second of these two studies, the long-term retired female athletes still had a BMD that was higher by 5.1% in the legs at follow-up after close to two decades of retirement in comparison with the controls. Possible explanations for this finding, as well as the findings of the study evaluating male former athletes, may be that the athletes in the present studies had reached a much higher BMD during the period of high physical activity, that they had been active longer, that they had started exercising at an earlier age, and that they had exercised at a high level in comparison with the previously published cross-sectional studies in retired athletes. The present studies could not establish whether retired athletes continue to lose the exercise-induced benefits of an even longer period of retirement, so that there would be no residual higher BMD at the ages when the fragility fractures rise exponentially. The obvious decrease in the BMD benefits found in active athletes with increased duration of retirement leads us to speculate that no benefits will remain in old age.

One weakness of the studies is that they do not evaluate bone quality or skeletal architecture, so we should exercise great caution in drawing conclusions about residual benefits in bone strength in former athletes. Another weakness, even though these were prospective studies, is that these were not randomized controlled trials. Thus, no conclusions regarding causality could be drawn. The fact that the authors found fewer former athletes than controls with fractures did not contradict the hypothesis that there could be residual benefits in skeletal architecture in old former athletes not captured by the DXA measurement. However, genetic, inherited stronger bones or a better-functioning neuromuscular system, present already

before the start of the exercise and making the individuals more likely to take exercise, as well as differences in lifestyle factors after retirement, may also have led to fewer fractures in the former athletes.

Conclusion

The most compelling evidence for the beneficial effect of exercise on BMD is found during growth [7–12]. It is unclear whether physical activity in general could prevent age-related bone loss or restore already lost BMD in adults, and specifically in individuals above age 65 years over a longer period. However, the study by Ahlborg *et al.* [16] supports the hypothesis that if exercise is provided in the early post-menopausal period, a period with high bone turnover, skeletal benefits of biological significance can be obtained by physical activity. The prospective data obtained by following athletes with several years of retirement indicate greater bone loss in retired athletes in comparison with both athletes who continue with exercise and controls. This notion supports previously published cross-sectional data [23–28]. In contrast, there is some support in the literature for the possibility that benefits in bone size or shape may be permanent [19,30]. When one looks at the clinically relevant end-point, fractures, it seems as if there are fewer former athletes with fragility fractures than among individuals who have never been subjected to exercise. Future studies must evaluate whether this is the result of remaining exercise-induced benefits in bone architecture. Finally, we must realize that studies that evaluate the incidence of fracture in formerly active individuals rank low in the evidence-based hierarchy. At present no randomized controlled trial has been published which evaluates the effect of exercise with fractures as the end-point. There has never been, and will never be, a randomized, double-blind, placebo-controlled trial demonstrating that exercise in youth, adulthood or old age reduces fragility or osteoporosis-related fractures in old age. The kind of trial that would provide the next level of evidence, a randomized, controlled but unblinded study with fractures as an end-point, is possible but has never been done. The basis for the belief that exercise reduces fractures is derived from lower levels of 'evidence', namely, retrospective and prospective observation cohort studies and case–control and prospective studies that evaluate surrogate end-points for fractures. These studies are at best hypothesis-generating, never hypothesis-testing, as they are all subject to many systematic biases and should therefore be interpreted with scepticism. Absence of evidence is not evidence of absence of effect, and today when we provide recommendations we must lean on the highest published level of evidence, even if there is no randomized controlled trial. Following this strategy, we can today recommend exercise during growth as a strategy to increase peak bone mass and perhaps also reduce the future risk of fractures, and we can also recommend physical activity in the peri- and early post-menopausal period to possibly diminish the age-related bone loss.

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13

Management of osteoporosis: HRT; SERMs

CECILIA BOTTOMLEY, JANICE RYMER

Introduction

The 30–60% reduction in post-menopausal bone loss with selective oestrogen receptor modulators (SERMs) and hormone replacement therapy (HRT) is well established [1–5]. HRT, in the form of conjugated equine oestrogen or oestradiol, is given as a subcutaneous implant, orally, transdermally or, recently, intranasally. For women who have an intact uterus, a progestin must be added to protect against endometrial hyperplasia and malignancy from unopposed oestrogen. The only licensed SERM at present is raloxifene, a once-daily 60-mg oral preparation.

Hormone replacement therapy

Since the publication of findings from the Women's Health Initiative (WHI) [6] and the Million Women Study (MWS) [7], regulatory bodies (including the European Medical Evaluation Agency [EMEA], United States' Food and Drug Administration [FDA], the National Institute for Clinical Excellence [NICE] and the UK Committee on the Safety of Medicines [CSM]) have issued guidance recommending that HRT should not be prescribed as first-line treatment for the prevention or treatment of post-menopausal osteoporosis. The WHI confirmed a reduction in total fracture risk of 24%, but also showed an increased risk of cardiovascular disease (relative risk [RR] 1.29), stroke (RR 1.41) and breast cancer (RR 1.26). The MWS confirmed the increased risk of breast cancer especially in women using combined oestrogen/progestin HRT (RR 2.0).

Criticisms of the studies have been made and questions include whether the WHI findings are specific to the type of HRT used (0.625 mg conjugated oestrogens and 2.5 mg medroxyprogesterone acetate) and whether different types of HRT would give a different result, especially with regard to cardiovascular events. The WHI also included a relatively high-risk population of women at entry (high lipids, hypertension and raised body mass index) and outcomes were worse in older women, not in early menopausal women in whom HRT is normally prescribed. The

MWS relied on self-reporting through questionnaires and had a response rate of only 71%, both of which factors may have introduced significant reporting bias.

However, as a result of these two publications, many women have discontinued HRT and three of the papers in this chapter look at the long-term effect on fracture risk of stopping HRT after a short duration of use, with conflicting results (Banks, Bagger and Yates). The first of these papers also reports the effect on osteoporosis in relation to the type and dose of oestrogen and progestin, presented in a follow-on analysis from the MWS investigators.

The results of the oestrogen-only arm of the WHI trial are reviewed in this chapter (Women's Health Initiative Steering Committee).

In spite of the WHI and MWS results, HRT is still indicated as a first-line treatment for osteoporosis prevention in women with premature menopause [8], at least until the age of 50. It also remains the only effective treatment for the management of severe post-menopausal (hypo-oestrogenic) symptoms in whom the fracture reduction benefit may also be important. In addition, some older women still choose to continue to take HRT because of intolerance to other osteoporosis treatments or the perceived improved quality of life associated with it.

A new mode of administration of HRT examined in this chapter is pulsed intranasal oestrogen (Nielsen). A further study reviewed looks at how the response to HRT treatment may be affected by individual baseline risk factors (Rejnmark).

SERMs

The Multiple Outcomes of Raloxifene Evaluation (MORE) study, published in 1999, confirmed the effectiveness of raloxifene in reducing bone loss and vertebral fracture risk (RR 0.7; 95% confidence interval [CI] 0.5–0.8) with an associated reduction in breast cancer risk (RR 0.38; 95% CI 0.24–0.58) at 4 years [5]. The relative risk of venous thromboembolism, however, was found to be 2.35 (95% CI 1.20–4.02). Three papers discussed in this chapter are follow-on studies related to the MORE trial, looking at breast cancer risk reduction with longer-term use (Martino) and adverse events (Grady), and an attempt to apply the global index method from the WHI to the MORE data (Barrett-Connor).

Finally, a direct comparison trial of alendronate and raloxifene (Sambrook) and a study of combination treatment with alendronate and HRT compared with either treatment alone (Evio) are reviewed.

Fracture incidence in relation to the pattern of use of hormone therapy in post-menopausal women

Banks E, Beral V, Reeves G, Balkwill A, Barnes I; Million Women Study Collaborators. *JAMA* 2004; **291**: 2212–20

BACKGROUND. The MWS study (designed primarily to look at the health effects of HRT) was a prospective observational questionnaire study of 1 084 110 post-menopausal women aged 50–69 years, recruited from the UK general population, followed up for 1.9–3.9 (average 2.8) years for fracture incidence [7]. The objective of this paper from the same group was to look at the data collected from the MWS to investigate the effect of different patterns of use of post-menopausal hormone therapy on fracture incidence. The main outcome measure was the adjusted RR of incident fracture in hormone therapy users compared with never users at baseline.

INTERPRETATION. Some 5197 women (3.7%) reported one or more fractures, 79% resulting from falls. Current users of HRT had a significantly reduced incidence of fracture (RR 0.62; 95% CI 0.58–0.66; $P<0.001$). The protection was apparent soon after HRT began and the RR decreased with increasing duration of use ($P=0.001$) (Fig. 13.1). Among current users at baseline, the fracture reduction did not vary significantly according to whether oestrogen, oestrogen and progestin or other hormones were used. Nor did it vary significantly according to oestrogen dose or type of oestrogen or progestin used (Fig. 13.2). Tibolone users also had a significantly lower risk of fracture than never users (RR 0.67; 95% CI 0.54–0.83). Interestingly, past users of HRT at baseline experienced no significant protection against fracture (RR 1.07; 95% CI 0.99–1.15) and fracture rates returned to those of never users within about a year of ceasing use. The authors conclude that all types of HRT studied confer protection against fracture risk while used but that protection is lost soon after use ceases.

Comment

This study confirms no significant difference in fracture risk between oestradiol and equine oestrogen, or between norethisterone, medroxyprogesterone acetate, norgestrel or levonorgestrel. It also observes no difference for the different doses of oestrogen used. There was a suggestion that oral preparations and implants may have been associated with a lower risk of fracture than transdermal preparations. There was no apparent difference between the use of continuous combined as opposed to sequential combined regimes.

These results are therefore consistent with previous studies showing broadly equivalent effects on bone mineral density (BMD) of different HRT formulations.

The major strength of the study is the size of the study population. With the inclusion of 5000 incident fractures in almost 140 000 post-menopausal women, the results are valuable. The reliance on self-reporting may be considered a limitation of this study, as discussed in the introduction to the present chapter. However, the authors suggest self-reporting is reliable, 90% of such fractures being confirmed on radiography in other studies.

Duration of hormone therapy use at baseline	Total duration of hormone therapy use at baseline in cases, mean (SD), y	Cases/population	RR*	RR (95% CI)†
Never users		3010/70297	1.00	1.00
Past users				
Total duration of use, y				
<1	0.5 (0)	363/8076	1.08	1.08 (0.97–1.21)
1–4	2.0 (1.0)	373/8186	1.09	1.09 (0.98–1.21)
5–9	6.3 (1.4)	171/3941	1.02	1.00 (0.86–1.17)
≥10	12.4 (3.1)	55/1334	0.94	0.90 (0.69–1.18)
Current users				
Total duration of use, y				
<1	0.5 (0)	81/2801	0.73	0.75 (0.60–0.93)
1–4	2.7 (1.0)	405/15 707	0.65	0.66 (0.60–0.74)
5–9	6.8 (1.4)	458/18 604	0.59	0.58 (0.53–0.65)
≥10	12.8 (3.4)	206/7956	0.60	0.57 (0.50–0.66)

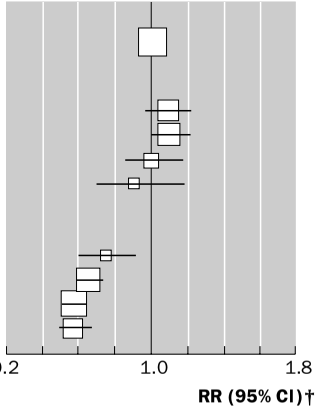


Fig. 13.1 Relative risk (RR) of incident fracture in relation to recency and duration of hormone therapy use. * Adjusted for age and region; † Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity. Source: Banks *et al*. (2004).

Hormone therapy used at baseline	Total duration of hormone therapy use at baseline in cases, mean (SD), y	Current users, cases/ population	RR*	RR (95% CI)†
All oestrogen only	6.8 (4.6)	513/19 189	0.65	0.64 (0.58–0.71)
All equine oestrogen	7.5 (5.0)	219/8460	0.63	0.62 (0.54–0.71)
≤0.625 mg	7.4 (5.1)	158/6025	0.63	0.62 (0.53–0.73)
>0.625 mg	7.9 (4.7)	61/2412	0.62	0.61 (0.47–0.78)
All oestradiol	6.0 (3.8)	244/8706	0.68	0.68 (0.59–0.77)
≤1 mg oral	5.9 (4.8)	23/1037	0.54	0.54 (0.36–0.81)
>1 mg oral	6.4 (5.0)	16/844	0.47	0.47 (0.29–0.77)
≤50 μg transdermal	5.8 (3.6)	151/4921	0.74	0.74 (0.62–0.87)
>50 μg transdermal	6.7 (4.0)	36/1072	0.84	0.83 (0.60–1.15)
By formulation				
Oral	7.3 (5.0)	290/11 546	0.61	0.60 (0.53–0.68)
Transdermal	6.0 (3.7)	197/6360	0.76	0.75 (0.65–0.86)
Implanted	7.9 (5.3)	21/976	0.53	0.52 (0.34–0.80)
All oestrogen-progestin combinations	5.4 (4.0)	539/22 472	0.58	0.58 (0.53–0.64)
By progestin constituent				
Medroxyprogesterone acetate	4.4 (3.8)	73/3027	0.58	0.59 (0.47–0.74)
Norethisterone	4.7 (3.5)	198/8094	0.59	0.60 (0.52–0.69)
Norgestrel/levonogestrel	6.3 (4.0)	256/10 890	0.57	0.57 (0.50–0.65)
By type of regimen	5.9 (3.9)	364/15 192	0.58	0.58 (0.52–0.65)
Sequential	4.4 (3.9)	149/6411	0.56	0.56 (0.48–0.67)
Continuous				
All other	4.5 (3.4)	127/4461	0.68	0.67 (0.56–0.80)
Tibolone	4.8 (3.3)	86/3037	0.67	0.67 (0.54–0.83)
Vaginal	1.0 (1.2)	6/221	0.62	0.62 (0.26–1.39)
Other/not known	4.3 (3.6)	35/1203	0.71	0.70 (0.50–0.97)
All current homone therapy	5.9 (4.3)	1179/46 122	0.62	0.62 (0.58–0.66)

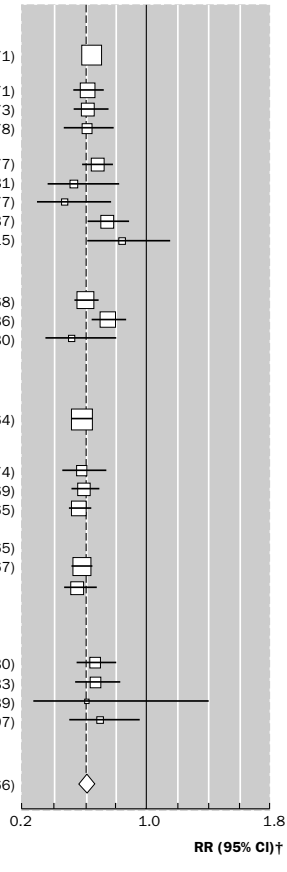


Fig. 13.2 Relative risk (RR) of incident fracture for current versus never users by type of hormone therapy at baseline. The RR is for current hormone therapy users vs never users (3010 cases/70 297 population). The *dashed line* represents the overall RR (0.62) for all current users of hormone therapy vs never users at baseline. * Adjusted for age and region; † Adjusted for age, region, socioeconomic status, time since menopause, body mass index, and physical activity. Source: Banks *et al.* (2004).

The suggestion that there was no significant reduction in fracture risk with previous use of HRT is at variance with other studies (Bagger) [9]. It is not clear in the MWS why women had taken HRT and whether they were at increased baseline fracture risk, for example because of family history of osteoporosis or low body mass index. It is also surprising that the fracture risk appeared to be similar to that of never users even within a year of ceasing HRT.

Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study

Bagger YZ, Tanko LB, Alexandersen P, *et al*. *Bone* 2004; **34**: 728–35

BACKGROUND. This study aimed to clarify whether 2–3 years of HRT in early menopausal women provides long-term benefit in terms of preventing bone loss and osteoporotic fractures. Study participants were 347 healthy post-menopausal women with normal bone mass who had previously completed one of four placebo-controlled trials of HRT or placebo for 2–3 years [10–13]. A total of 263 had not used any further bone-sparing treatment in the meantime. They were examined 5, 11 or 15 years after cessation of treatment.

INTERPRETATION. Bone mineral density at the spine (L1–L4) and bone mineral content in the forearm were measured at baseline, the end of trials and at follow-up. At follow-up, radiological appearance of vertebral fracture and new evidence of non-vertebral fracture were assessed. After stopping treatment the overall rate of bone loss returned to normal post-menopausal rates (Fig. 13.3) and HRT-treated women continued

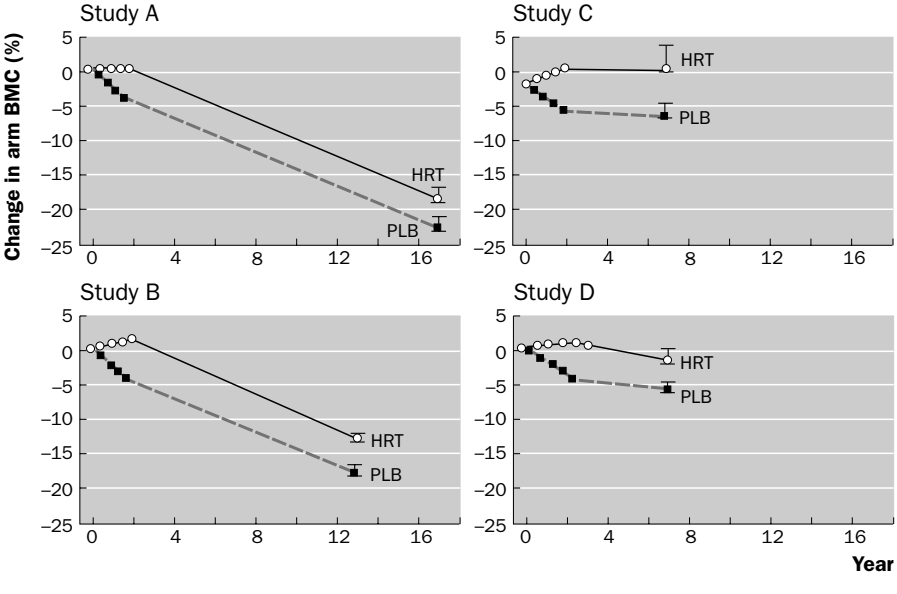


Fig. 13.3 Longitudinal changes in forearm bone mineral content (BMC) during 2–3 years of hormone replacement therapy (HRT) and certain years after stopping treatment. PLB denotes placebo. Data are mean *F* and SEM. Dashed lines indicate the period of HRT withdrawal. Source: Bagger *et al*. (2004).

Table 13.1 Number of women who had a fracture and odds ratio (OR) of osteoporotic fractures between HRT and placebo groups at the time of follow-up

Type of fracture		Placebo (n = 108)	HRT (n = 155)	OR (95% CI)	
				Unadjusted	Adjusted*
Vertebral fracture	Yes	26	18	0.41 (0.21–0.80)	0.47 (0.24–0.93)
	No	82	137	P = 0.008	P = 0.03
Non-vertebral fracture	Yes	13	12	0.61 (0.28–1.40)	0.68 (0.30–1.60)
	No	95	143	P = 0.24	P = 0.38
All fractures	Yes	36	27	0.42 (0.24–0.75)	0.48 (0.26–0.88)
	No	72	128	P = 0.003	P = 0.02

*Adjusted for age, baseline forearm bone mineral content and spine BMD.
Source: Bagger *et al*. (2004).

to show significantly higher values (>5%) of BMD and bone mineral content when compared with placebo women, even many years after stopping HRT. The HRT group had a significantly reduced risk of all osteoporotic fractures compared with the placebo group (OR 0.48; 95% CI 0.26–0.88) and of vertebral fractures (OR 0.47; 95% CI 0.24–0.93), though the reduction in non-vertebral fractures was not significant when analysed alone (Table 13.1). The authors calculate that the number needed to treat to prevent one fracture is 7.

Comment

Of the original 727 women studied, 479 were available for follow-up. Of these only the 263 who had not used further bone-sparing treatment were included, but baseline characteristics of original trial participants and those studied were shown to be similar by one-way analysis of variance. Thus, selection bias is likely to be small.

Due to the long-term nature of the follow-up, the authors note the differences in bone densitometers over time but refer to the standardization of quality control procedures, which allows fair comparability of measurements.

The original four trials used 1 or 2 mg oestradiol or 0.75 or 1.5 mg piperazine oestrone with various progestin regimes. This variation may be a strength of the study, as the results can be better related to HRT prescribing in general and do not limit the findings to one particular regime.

As HRT is now recommended for primary use over a shorter term, for the relief of perimenopausal symptoms, it is important to clarify whether the beneficial effect of HRT on bone density persists after cessation of therapy. BMD is known to decrease after cessation of HRT but results so far have been contradictory; early reports suggested that bone loss is actually accelerated after cessation [**14,15**] and the later Post-menopausal Oestrogen/Progestin Interventions (PEPI) study [**16**] suggested that there is a persisting benefit.

This study suggests that the rate of bone loss was similar in HRT and placebo groups at follow-up and that the rate of bone loss is not accelerated after cessation

of limited HRT. This study therefore adds weight to the PEPI trial in supporting the evidence of long-term benefit of limited HRT (2–3 years) in the reduction of bone loss and fracture.

Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment

Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES. *Obstet Gynecol* 2004; **103**: 440–6

BACKGROUND. This study also aimed to evaluate the association between cessation of hormone therapy and the risk of hip fracture. The study comprised a questionnaire at baseline and a 12-month follow-up assessing the use of HRT and the incidence of fractures. A total of 140 584 women who participated in the National Osteoporosis Risk Assessment (NORA) [17] were included. They were aged over 50 years, post-menopausal and had no previous diagnosis of osteoporosis.

INTERPRETATION. A total of 269 of the 140 584 women reported an incident hip fracture. Logistic regression was used to assess the association between HRT use and fracture. Women who were currently on HRT had a 40% lower incidence of hip fracture than never users. Women who had stopped HRT more than 5 years previously had similar fracture incidence to never users. Those who had discontinued HRT within the previous 5 years had an increased incidence of hip fracture (OR 1.65; 95% CI 1.05–2.59) relative to never users.

Comment

The National Osteoporosis Risk Assessment is a longitudinal observational study of osteoporosis among healthy post-menopausal women commenced in the US in 1997.

The finding of a higher hip fracture risk for women who had discontinued HRT within the previous 5 years, compared with never users, is surprising and concerning. However, no information is provided as to why these women had been commenced on HRT, why they had ceased to take it, or whether these factors may have some bearing on their baseline fracture risks. However, if confirmed, this higher risk of fracture may relate to a rapid rate of bone turnover occurring after cessation of HRT, though bone density has previously been shown to approach pre-treatment levels by around 2 years after discontinuing HRT [16].

The results also suggest a lower incidence of fractures for current users of up to 5 years than for those who have taken HRT for 6–10 or more than 10 years, which again is surprising, and it is difficult to know why this may be the case. If these findings were validated in other studies it would suggest that alternative osteoporosis protection should be considered for women discontinuing HRT. However, the results are at variance with the Bagger study, which shows a benefit of 2–3 years of HRT use in the long-term prevention of fracture.

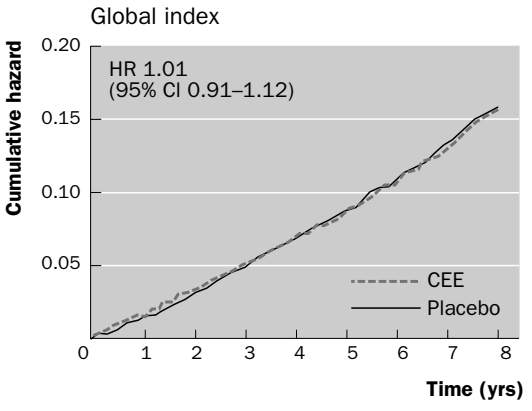
Many of the 200 160 women recruited initially were excluded from the follow-up of this survey on the basis of non-response (36 181) and missing responses (23 395). On telephone follow-up of the 140 584 women included in the analyses, only 78% (260) had the fracture diagnosis confirmed. Those who responded tended to be younger, better educated and more health-conscious than non-responders. Thus, despite the advantage of the large size and broad geographic and ethnic participation in this study, the reliability of the study is limited by the high number excluded and the reliability of hip fracture diagnoses.

Effects of conjugated equine estrogen in post-menopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial

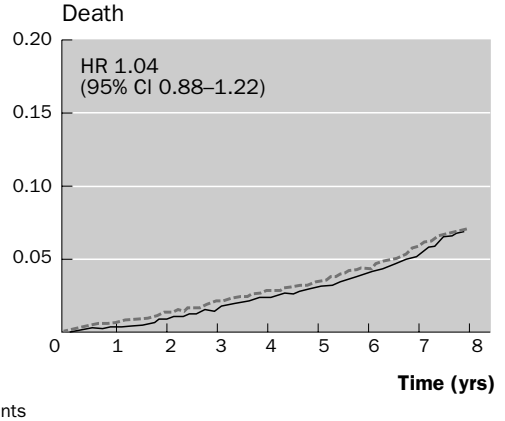
Anderson GL, Limacher M, Assaf AR, *et al.*; Women's Health Initiative Steering Committee. *JAMA* 2004; **291**: 1701–12

BACKGROUND. The randomized, double-blind, placebo-controlled WHI trial was designed to determine whether conjugated equine oestrogen alone (for women with prior hysterectomy) or in combination with progestin (medroxyprogesterone acetate) would reduce cardiovascular events in healthy post-menopausal women. The combined arm was terminated early, in July 2002, because health risks exceeded benefits [6]. The oestrogen-alone arm was then also halted early, in February 2004, after an interim analysis suggested a definite increased risk of stroke and no likelihood of the finding of evidence of prevention of coronary heart disease or increased breast cancer incidence by continuation of the trial. In the oestrogen-alone arm 10 739 women aged 50–79 years, with prior hysterectomy, were randomized to receive 0.625 mg/day conjugated equine oestrogen or placebo. The primary outcome was coronary heart disease incidence and the primary safety outcome was invasive breast cancer incidence. A global index of risks and benefits, including these benefits plus stroke, pulmonary embolism, colorectal cancer, hip fracture, and deaths from other causes, was used to summarize overall effects.

INTERPRETATION. The estimated hazard ratios (95% CIs) for oestrogen versus placebo after an average 6.8 years of follow-up were as follows: coronary heart disease, 0.91 (0.75–1.12); breast cancer, 0.77 (0.59–1.01); stroke, 1.39 (1.10–1.77); pulmonary embolism, 1.34 (0.87–2.06); colorectal cancer, 1.08 (0.75–1.55); and hip fracture, 0.61 (0.41–0.91). For the significant outcomes there was an absolute excess risk of twelve extra strokes per 10 000 person-years and an absolute reduction of six fewer hip fractures per 10 000 person-years. The estimated risk for all monitored events in the global index is shown in Fig. 13.4. There was a non-significant excess of two events per 10 000 person-years. The authors conclude that there was no overall difference in incident disease events between the oestrogen and placebo groups and that conjugated equine oestrogen should therefore not be recommended for chronic disease prevention in healthy post-menopausal women.



Events									
CEE	82	87	86	89	94	113	69	51	21
Placebo	69	86	94	103	98	98	89	48	20
Number at risk									
CEE	5310	5176	5064	4948	4824	4681	3744	2130	931
Placebo	5429	5300	5174	5048	4902	4750	3803	2184	1032



Events									
CEE	24	28	39	38	32	51	42	26	11
Placebo	14	25	34	42	36	43	42	36	17
Number at risk									
CEE	5310	5234	5180	5110	5036	4954	4020	2303	1029
Placebo	5429	5355	5290	5223	5138	5040	4092	2392	1141

Fig. 13.4 Kaplan–Meier estimates of cumulative hazards for global index and death. CEE, conjugated equine oestrogen; HR, hazard ratio; CI, confidence interval. Events shown are occuring during 1-year intervals through year 8 and beyond year 8. Source: Anderson *et al.* (2004).

Comment

Importantly, the reduction in hip fracture incidence is of a similar magnitude to that in the oestrogen and progestin arm of the WHI trial.

Both arms of the WHI look at healthy post-menopausal women without a previous diagnosis of osteoporosis. Women with cardiovascular risk factors were not excluded from the trial (4.1% had actually had previous myocardial infarction or coronary revascularization and nearly 50% were hypertensive or on hypertension treatment), and consequently a common criticism of the WHI trial has been that the women may have been a high-risk group for all adverse cardiovascular outcomes. In practice, many women taking HRT are in the perimenopausal age group and have much lower risk factors for cardiovascular disease overall than those in this trial, who had a mean age of 63.6 years. Figure 13.5 shows the clinical outcomes by age and randomization assignment and Fig. 13.6 demonstrates the differences in cumulative hazards for clinical outcomes. The results also show a trend from a reduced hazard ratio in the younger women to an increased hazard ratio in the older women.

In terms of coronary heart disease, this study differs from the combined arm of the WHI study and from the Heart and Estrogen/Progestin Replacement Study (HERS) [**18**] as it shows a non-significant decrease in coronary heart disease with long-term use of oestrogen alone. This may relate to the role of progestins in the previous trials, differences in study baseline characteristics for the study populations, the duration of intervention, and the role of chance.

The non-significant reduction in breast cancer incidence in the study group was also unexpected, and contrary to the increased incidence in the combined arm and also to other observational studies showing an increased risk with oestrogen alone (MWS).

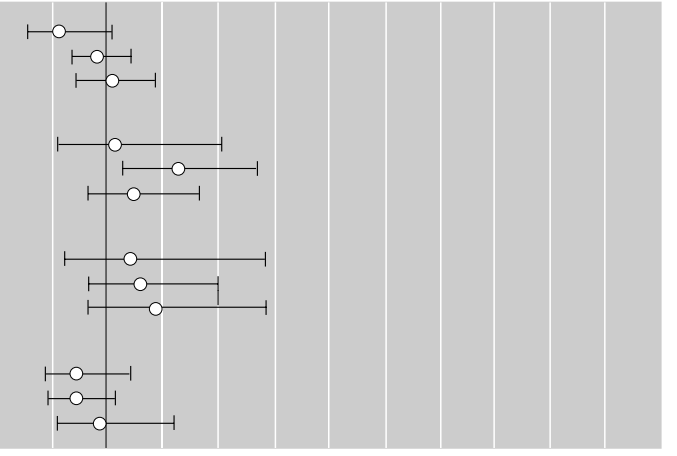
The decision to end the trial early is interesting in view of the fact that none of the predefined stopping boundaries had been crossed. The widespread publicity of the combined arm of the WHI may have influenced this decision.

Pulsed estrogen therapy in prevention of post-menopausal osteoporosis: a 2-year randomized, double-blind, placebo-controlled study

Nielsen TF, Ravn P, Bagger YZ, Warming L, Christiansen C. *Osteoporos Int* 2004; **15**: 168–74

BACKGROUND. Intranasal oestrogen has already been shown to be at least as effective as oral oestradiol and the oestradiol patch in reducing climacteric symptoms, with better tolerance. This study aimed to demonstrate the efficacy of 150 or 300 μg per day for 2 years in the prevention of early post-menopausal bone loss. Primary end-points were changes in BMD at the lumbar spine and femoral neck. Secondary end-points were changes in the bone markers serum osteocalcin (for bone formation) and urinary degradation products of the C-terminal telopeptides of type I collagen

Outcome by age (yr)	No. of cases (annualized %)		Hazard ratio (95% CI)	*P*-value for interaction
	CEE	Placebo		
Coronary heart disease				
50–59	16 (0.14)	29 (0.24)	0.56 (0.30–1.03)	
60–69	87 (0.54)	96 (0.59)	0.92 (0.69–1.23)	0.14
70–79	74 (0.88)	72 (0.84)	1.04 (0.75–1.44)	
Stroke				
50–59	19 (0.16)	19 (0.16)	1.08 (0.57–2.04)	
60–69	79 (0.49)	50 (0.30)	1.65 (1.16–2.36)	0.59
70–79	60 (0.71)	49 (0.57)	1.25 (0.85–1.82)	
Venous thromboembolism				
50–59	18 (0.15)	15 (0.13)	1.22 (0.62–2.42)	
60–69	49 (0.31)	39 (0.23)	1.31 (0.86–2.00)	0.39
70–79	34 (0.40)	24 (0.28)	1.44 (0.86–2.44)	
Invasive breast cancer				
50–59	25 (0.21)	35 (0.29)	0.72 (0.43–1.21)	
60–69	42 (0.26)	60 (0.36)	0.72 (0.49–1.07)	0.51
70–79	27 (0.32)	29 (0.34)	0.94 (0.56–1.60)	



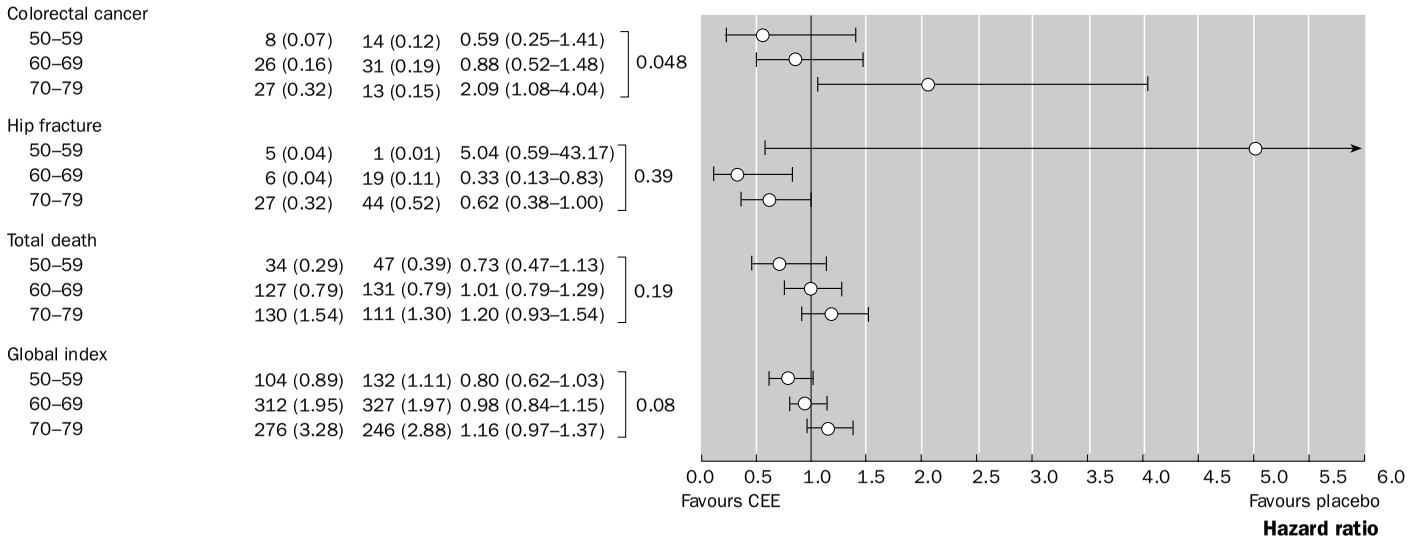


Fig. 13.5 Selected clinical outcomes by participant age and randomization assignment. CEE, conjugated equine oestrogen; CI, confidence interval. Data are plotted as hazard ratios with error bars showing 95% CIs. Source: Anderson *et al.* (2004).

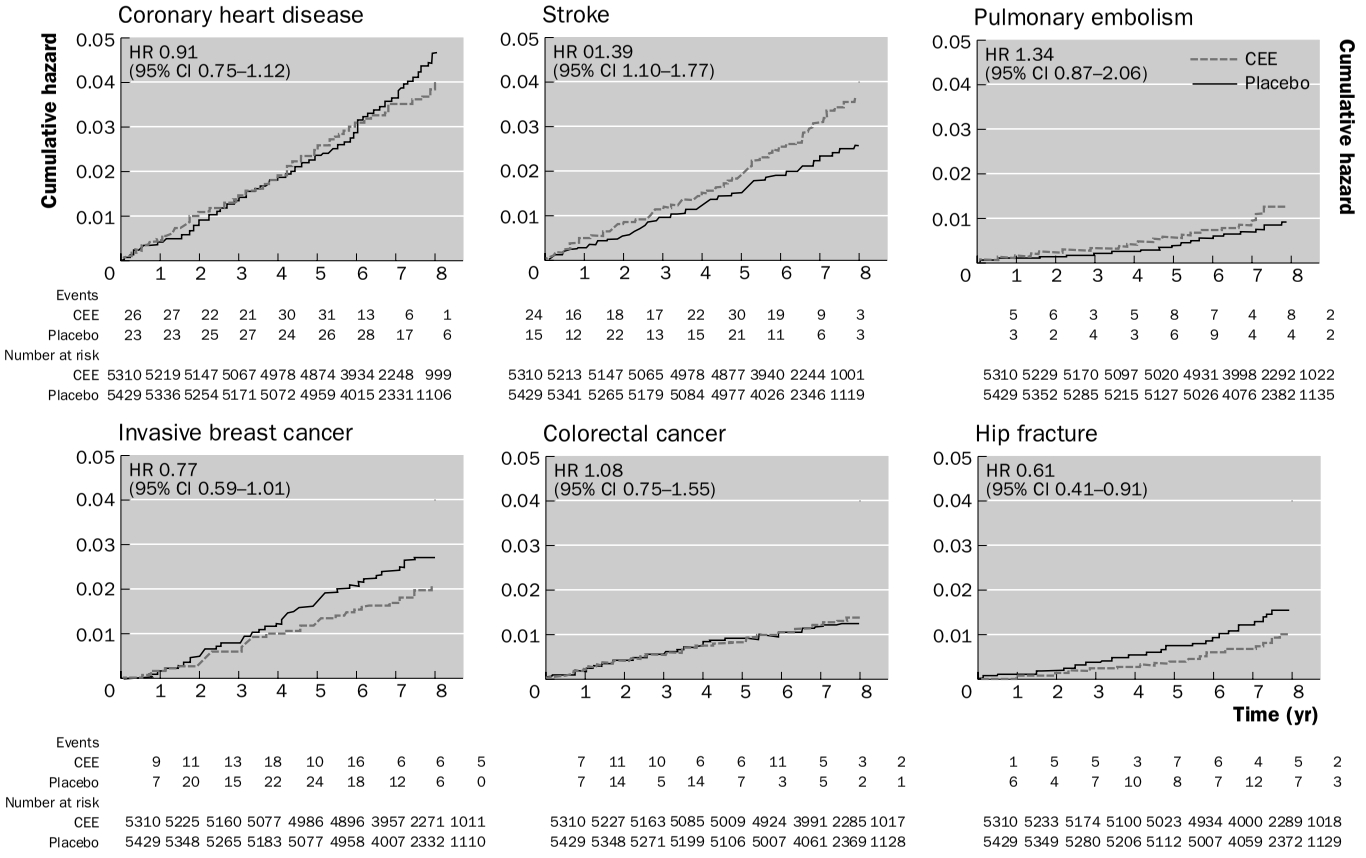


Fig. 13.6 Kaplan–Meier estimates of cumulative hazards for selected clinical outcomes. CEE, conjugated equine oestrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8. Source: Anderson *et al.* (2004).

(bone resorption). Three hundred and eighty-six women with clinically and biochemically confirmed menopause and without established osteoporosis were randomized to intranasal placebo, 17β-oestradiol 150 or 300 μg daily for 2 years. Women with an intact uterus were given a micronized progestin (or placebo) for 14 days per 28-day cycle.

INTERPRETATION. Bone mineral density increased at both the spine and hip in women receiving active treatment. The difference compared with placebo was 5.2 and 6.7% at the spine and 3.2 and 4.7% at the hip for the 150 and 300 μg doses, respectively ($P<0.001$). In the placebo groups a reduction in BMD below baseline was shown, of –3.2% at the spine and –3.3% at the hip ($P<0.001$). Correspondingly, markers of bone turnover decreased to normal pre-menopausal levels in the treated groups. The difference in BMD between placebo and 150 and 300 μg groups was more marked in the presence of at least one risk factor for osteoporosis (5.4 and 7.4% respectively at the spine and 4.0 and 5.2% respectively at the femoral neck). The authors suggest that the rates of adverse effects and discontinuation were similar to those for conventional HRT trials and conclude that intranasal oestrogen therapy is a promising alternative to conventional post-menopausal HRT.

Comment

Intranasal oestrogen offers the potential to relieve oestrogen deficiency symptoms with brief (pulsed) exposure of target tissues to oestrogen without the continuously elevated plasma levels associated with the oral route (serum concentration returns to 10% of the peak level 2 h after administration).

This study included women less than 5 years after the menopause, and aged from 40–65, a group who are likely to be prescribed HRT for symptomatic relief of climacteric symptoms. The findings of the beneficial effect on BMD are therefore relevant to current clinical practice, in which women experiencing natural or surgical menopause under the age of 50 are more likely to be recommended HRT.

In the study, 10.2% of women in the placebo group, 4.7% in the 150 μg group and 4.7% in the 300 μg group had used HRT previously. The inclusion of these women in this study (after a washout period of at least 6 months before randomization) is not discussed as a possible confounder for an increase in bone density.

Ninety-four per cent of the women treated reported at least one adverse event (most commonly rhinitis, sneezing and application site reaction) and 80 women withdrew from the study because of adverse events. Breakthrough bleeding was reported in 16% of the placebo group, 20% of the 150 μg group and 27% of the 300 μg group. Four breast neoplasms were reported but in three of these suspicious areas on the baseline mammogram were noted retrospectively.

Overall, the well-conducted, double-blind, randomized design adds strength to the results of this study and this paper is significant in being the first to show that pulsed intranasal oestrogen therapy significantly increases bone density compared with placebo, and that the increase is comparable to that with oral or transdermal oestrogens.

Larger studies are needed to demonstrate any safety benefit of this type of preparation for HRT adverse events before indicating preferential use over other forms of HRT.

Response rates to oestrogen treatment in perimenopausal women: 5-year data from the Danish Osteoporosis Prevention Study (DOPS)

Rejnmark L, Vestergaard P, Tofteng CL, *et al*. *Maturitas* 2004; **48**: 307–20

BACKGROUND. The Danish Osteoporosis Prevention Study (DOPS) is a prospective, 20-year, open-label, multicentre intervention trial on the effect of HRT on BMD and fracture risk in 2016 perimenopausal women. It includes a randomized arm and a self-selection arm, and attempts to mimic the normal clinical situation. Women are aged 45–58 years and are 3–24 months past the last menstrual bleeding or are experiencing hypo-oestrogenic symptoms with an elevated serum level of FSH (follicle-stimulating hormone). Women with osteoporosis are excluded. This study aimed to characterize women in the DOPS with no response or with a good response to HRT, evaluated by change in BMD. It included 466 women who had been treated with HRT for 5 years and 466 untreated women from the same cohort, all in the DOPS study. Non-responders were defined as those in whom BMD decreased more than the mean decrease in the untreated group. Good responders were those with a larger increase in BMD than the upper 95th percentile of untreated women. Baseline characteristics were then evaluated as predictors of a good response.

INTERPRETATION. Some 8.4 and 5.6% of women were classified as non-responders and 25 and 57% were good responders according to changes in BMD of the femoral neck and lumbar spine respectively. Combining measuring sites, 2.6% were non-responders and 20% were good responders. At the femoral neck, non-responders were significantly more often smokers and had a lower BMD at the spine (Fig. 13.7). A good response was significantly associated with increased age, a higher body weight and moderate (as opposed to low) alcohol consumption (Fig. 13.8). Low initial hip BMD was

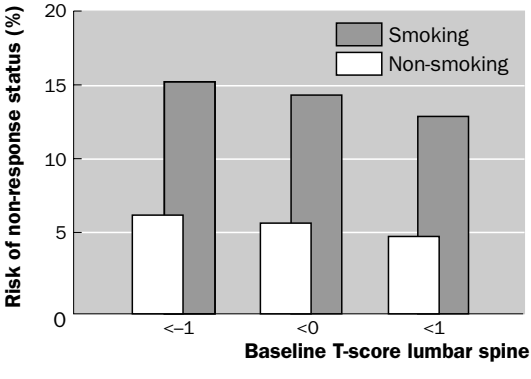
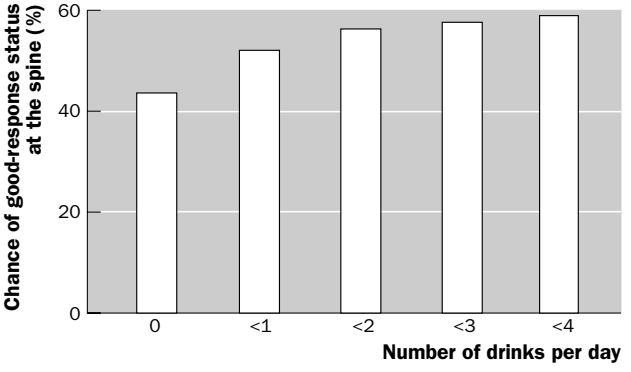
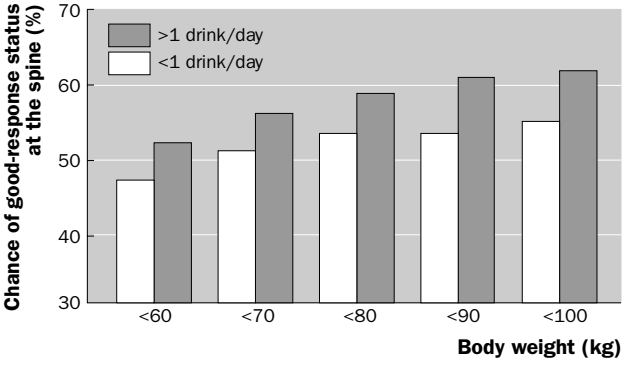


Fig. 13.7 Risk of being a non-responder according to baseline BMD at the lumbar spine for smokers and non-smokers. Source: Rejnmark *et al*. (2004).





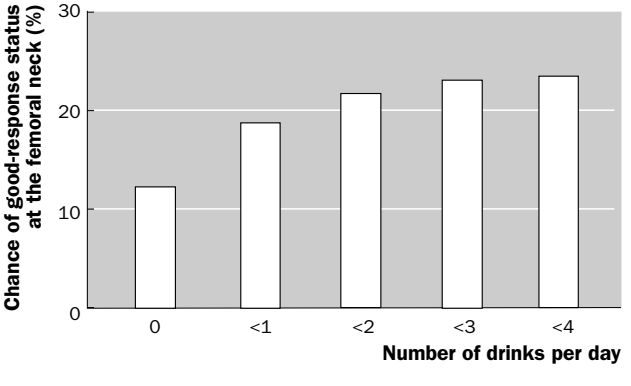


Fig. 13.8 Chance of a good response at the lumbar spine or femoral neck according to average alcohol intake and body weight. One drink is equivalent to 12 g of alcohol. Source: Rejnmark *et al*. (2004).

also favourable for a good response. The authors discuss possible mechanisms whereby the response may vary. For example, moderate alcohol intake has been shown to increase plasma oestradiol levels in women taking HRT, probably through altered clearance of oestradiol in these women. Obesity is associated with low levels of sex-hormone-binding globulin and therefore higher levels of bioavailable oestrogen. A direct toxic effect of tobacco on bone tissue and increased hepatic catabolism of oestrogen are proposed as mechanisms by which smoking affects the response.

Comment

A strength of the study is its subjects, who are taken from within a large, well-designed, prospective, randomized trial of HRT use. However, characteristics of women were taken at baseline (5 years prior to the analysis of response) and may not reflect ongoing characteristics. In particular, women's smoking habits, alcohol consumption and body weight may all alter significantly over time, especially as the subjects are around the menopause.

The study confirms that only 3% of women taking HRT do not respond in terms of bone density, emphasizing the role of HRT in the prevention of osteoporosis, when it is also indicated for climacteric symptoms.

In view of the potential serious complications of HRT, clinical practice has moved to a much more patient-specific assessment of the overall risk-to-benefit ratio of HRT. This paper is therefore helpful in attempting to identify women in whom a good response or non-response to HRT on BMD might be expected, thus allowing the individualization of treatment options.

Continuing outcomes relevant to Evista: breast cancer incidence in post-menopausal osteoporotic women in a randomized trial of raloxifene

Martino S, Cauley JA, Barrett-Connor E, *et al.*; CORE Investigators. *J Natl Cancer Inst* 2004; **96**: 1751–61

BACKGROUND. The MORE trial found a 72% reduction in invasive breast cancer for post-menopausal osteoporotic women during 4 years of raloxifene use. This study (the Continuing Outcomes Relevant to Evista [CORE] trial) aimed to examine the effect of raloxifene on invasive breast cancer after 4 further years of raloxifene use in women willing to continue. Women who had been assigned to either the 120 mg or 60 mg dose of raloxifene were assigned to continue taking 60 mg (n = 3510). Women previously assigned to placebo were assigned to continue with placebo (n = 1703). The study remained double-blinded. Breast cancer incidence was analysed with a log-rank test, and a Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% CIs.

INTERPRETATION. The 4-year incidences of invasive cancer and oestrogen receptor-positive invasive breast cancer were reduced by 59% (HR 0.41; 95% CI 0.24–0.71) and 66% (HR 0.34; 95% CI 0.18–0.66) respectively compared with placebo.

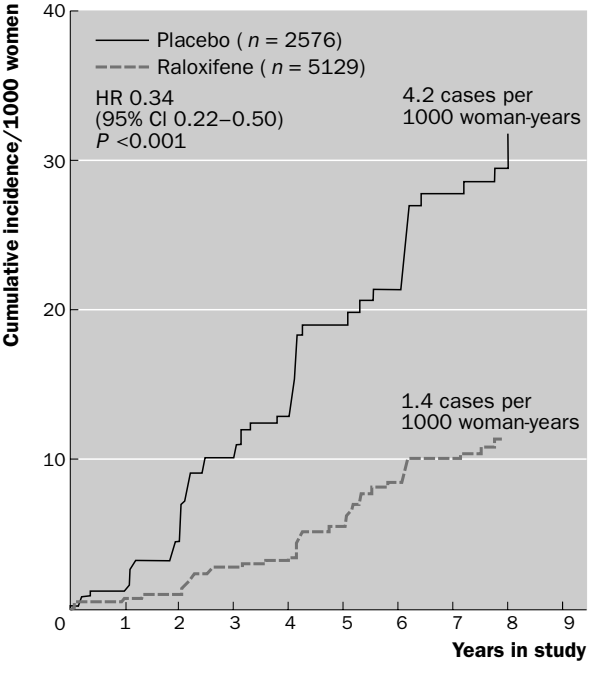


Fig. 13.9 Cumulative incidence of adjudicated breast cancers per 1000 women over the 8 years from randomization in the MORE trial to the end of the CORE trial for 7705 MORE participants. Source: Martino *et al*. (2004).

Figure 13.9 demonstrates the cumulative incidence of invasive cancers over the 8-year study period. There was no difference in the incidence of oestrogen receptor-negative breast cancer (Fig. 13.10). The relative risk of venous thromboembolism over the 4 years was 2.17 (95% CI 0.83–5.70). No new safety concerns were raised over the 4-year period.

Comment

While the outcome of this study relates to the incidence of invasive breast cancer and not to osteoporosis, this study offers the longest follow-up safety data (8 years) for raloxifene. It is therefore highly relevant to clinical practice for those prescribing raloxifene for its licensed indication, which is the prevention and treatment of postmenopausal osteoporosis. The results can be further taken as relevant to our clinical practice as women in the treatment group were prescribed the licensed dose of 60 mg of raloxifene, unlike the MORE trial, in which there was also a 120 mg group.

In interpreting the results, selection bias should be considered as women could choose whether to continue in the CORE trial after completion of MORE. There

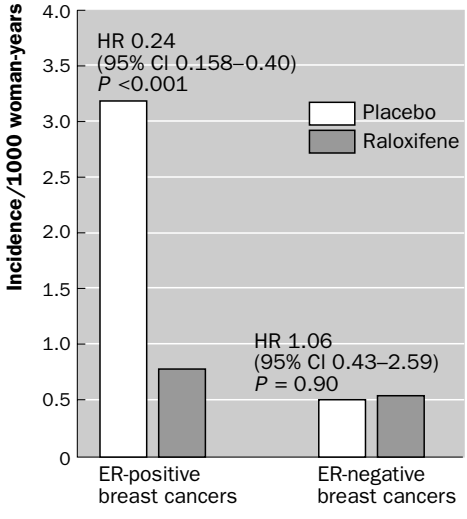


Fig. 13.10 Annual incidence rate per 1000 women-years of follow-up for adjudicated invasive breast cancers over the 8 years from the time of randomization in the MORE trial to the end of the CORE trial for the 7705 MORE participants. Source: Martino *et al.* (2004).

was also a gap (2.6–62 months) between the two trials when women could have used other therapy for osteoporosis, which may have affected the results.

Interestingly, the reporting of hot flushes and leg cramps as a side effect of raloxifene in the MORE trial was not significantly higher in the raloxifene group than in the placebo group during the CORE trial. This may be explained by women experiencing side effects not putting themselves forward to continue in the CORE trial, to women becoming used to the symptoms and therefore reporting less, or to women actually experiencing fewer side effects with longer-term use.

Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation

Grady D, Ettinger B, Moscarelli E, *et al.*; Multiple Outcomes of Raloxifene Evaluation Investigators. *Obstet Gynecol* 2004; **104**: 837–44

BACKGROUND. Some of the potential adverse events associated with raloxifene from the MORE trial have already been published [5], such as a significant increase in risk from venous thromboembolism and no early or overall increase in the risk of coronary events or stroke in women treated with raloxifene. The authors of this study (for the MORE investigators) used data from the 7705 women in the MORE study with the aim of examining the effect of raloxifene on the major adverse events that have

been documented to occur with HRT and tamoxifen. Outcomes included venous thromboembolism, cataracts, gall bladder disease and endometrial hyperplasia or cancer. The authors chose not to include coronary disease and stroke in this analysis because results showing no increased risk from these events had been published [19].

INTERPRETATION. During a mean follow-up period of 3.3 years, raloxifene was associated with an increased risk of venous thromboembolism (RR 2.1; 95% CI 1.2–3.8) and the number needed to treat to cause one event was 170 (95% CI 100–582) over 3.3 years. The risk in the raloxifene group decreased to about the same as that in the placebo group after the first 2 years. Raloxifene did not increase the risk of cataracts (RR 1.0; 95% CI 0.7–1.3), endometrial hyperplasia (RR 1.3; 95% CI 0.4–5.1) or endometrial carcinoma (RR 0.9; 95% CI 0.3–2.7). The authors conclude that there was an increased risk of venous thromboembolism but that there was no increased risk of cataracts, gall bladder disease, endometrial hyperplasia or malignancy.

Comment

This study addresses the previously unanswered question of the effect of raloxifene on cataracts and gall bladder disease. Whereas tamoxifen is associated with an increased incidence of cataract and oestrogen therapy with increased gall bladder disease, this study confirms that raloxifene does not increase the risk of either pathology.

This study confirms again that there is no evidence for raloxifene having an adverse effect on the endometrium.

It is not clear why the authors chose to reanalyse the data on venous thromboembolism but not on cardiovascular disease from the original MORE study. The analysis of the risk of venous thromboembolism with raloxifene is slightly different from the results published previously by the MORE investigators. For example, the relative risk of venous thromboembolism in the initial publication of the MORE results showed a relative risk of 3.1 (95% CI 1.5–6.2) after 40 months of treatment compared with this study, in which the relative risk was 2.1 (95% CI 1.2–3.8) after completion of the study (4 years). This may relate to a lower number of women presenting with venous thromboembolism in the later stages of the trial, as those with a particular tendency to venous thromboembolism may have developed it earlier in the course of treatment. However, both these results equate broadly to the 2–4% increase in venous thromboembolism in women taking HRT.

Risk–benefit profile for raloxifene: 4-year data from the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial

Barrett-Connor E, Cauley JA, Kulkarni PM, Sashegyi A, Cox DA, Geiger MJ.
J Bone Miner Res 2004; **19**: 1270–5

BACKGROUND. The MORE trial reported the reduction in the risk of vertebral fracture for raloxifene 60 mg/day (RR 0.7; 95% CI 0.5–0.8) and 120 mg/day

(RR 0.5; 95% CI 0.4–0.7), no significant reduction in non-vertebral fracture, and an increase in BMD compared with placebo in the femoral neck and spine for both doses. It also showed that women receiving raloxifene had a 3-fold increased risk of venous thromboembolism (RR 3.1; 95% CI 1.5–6.2) but a reduced incidence of breast cancer (RR 0.3; 95% CI 0.2–0.6) and no increase in vaginal bleeding or breast pain. The WHI trial was published subsequently and focused on defining the risks and benefits of conjugated equine oestrogen combined with medroxyprogesterone acetate for major disease outcomes in post-menopausal women. Outcomes included coronary heart disease, stroke, pulmonary embolism, hip fracture, invasive breast cancer, endometrial or colonic cancer and deaths from other causes, assessed using the global index. This paper takes the global index method from the WHI trial and applies it to the MORE trial data in a *post hoc* analysis to assess the risk–benefit profile of raloxifene. Intention-to-treat survival analysis of the time to first event was also performed, using a proportional hazards model.

INTERPRETATION. The annualized rate of global index events was 1.83% in the placebo group and 1.39% in the combined (60 and 120 mg) raloxifene groups (hazard ratio 0.75; 95% CI 0.62–0.92) (Table 13.2). The same results were found for analysis of the two different dose groups separately. Subgroup analysis showed that age and hysterectomy status did not have a significant interaction with the effect of raloxifene on the global index, but that the global index risk reduction was greater in obese compared with non-obese women. Figure 13.11 shows the rates of individual clinical outcomes included in the global index. The authors conclude that the 25% reduction in global index is compatible with a favourable risk–benefit safety profile when raloxifene is used for

Table 13.2 Global index events and individual clinical outcomes by treatment assignment*

	Number (annualized percentage)		
	Placebo (*n* = 2576)	**Raloxifene† (*n* = 5129)**	**Hazard ratio (95% CI)**
Global index	160 (1.83%)	244 (1.39%)	0.75 (0.62–0.92)
Coronary heart disease	28 (0.32%)	50 (0.28%)	0.88 (0.56–1.40)
Stroke	32 (0.37%)	44 (0.25%)	0.68 (0.43–1.07)
Pulmonary embolism	2 (0.02%)	16 (0.09%)	3.97 (0.91–17.3)
Invasive breast cancer	35 (0.40%)	17 (0.10%)	0.24 (0.13–0.43)
Endometrial cancer	5 (0.06%)	7 (0.04%)	0.69 (0.22–2.18)
Colorectal cancer	15 (0.17%)	26 (0.15%)	0.85 (0.45–1.61)
Hip fracture	29 (0.33%)	55 (0.31%)	0.94 (0.60–1.47)
Total mortality‡	36 (0.41%)	62 (0.35%)	0.85 (0.56–1.28)

*The global index includes the first occurrence of an event, whereas individual events include all occurrences reported during the trial. Because women could have had multiple events, individual event counts do not sum to the global index event count. Event counts do not include events reported after a patient discontinued from the trial. When events that were reported after study discontinuation were not censored, the hazard ratio (95% CI) for raloxifene compared with placebo was 0.77 (064–0.94).
†Combined 60 and 120 mg/day dose groups.
‡Includes fatal global index events and deaths from other causes.
Source: Barrett-Connor *et al.* (2004).

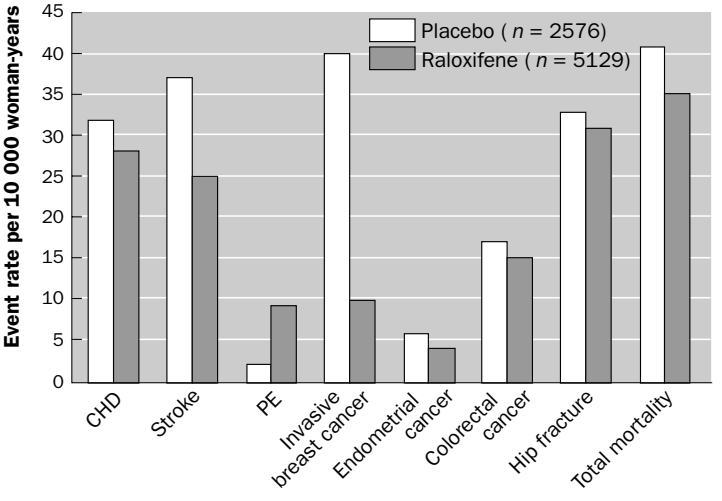


Fig. 13.11 Rate of clinical outcomes included in the global index. Source: Barrett-Connor *et al*. (2004).

osteoporosis treatment in post-menopausal women. Table 13.3 shows the rate of clinical outcomes in the placebo groups of the MORE and WHI trials. This demonstrates the fact that the study groups were significantly different at baseline. The MORE women were enrolled on the basis of osteoporosis defined by low BMD or previous vertebral

Table 13.3 Rate of clinical outcomes in the placebo groups of the MORE and WHI trials*

	MORE (n = 2576)	WHI** (n = 8102)
Global index	183†	151
Coronary heart disease	32	30
Stroke	37‡	21
Pulmonary embolism	2	8
Invasive breast cancer	40	30
Endometrial cancer	6	6
Colorectal cancer	17	16
Hip fracture	33§	15
Total mortality	41	53

*Rates expressed as number of events per 10 000 women per year. Placebo rates were compared between the MORE and WHI trials with an exact binomial test without adjusting for any covariates.
Writing Group for the Women's Health Initiative Investigators |6**|.
†P = 0.03 versus WHI placebo group (exact binomial test).
‡P = 0.005 versus WHI placebo group (exact binomial test).
§P = 0.0005 versus WHI placebo group (exact binomial test).
P >0.10 for all other comparisons.
Source: Barrett-Connor *et al*. (2004).

fracture and the women in the MORE trial were generally older and had a lower body mass index than those in the WHI trial. All the women in the WHI trial had an intact uterus, whereas some of the women in the MORE trial had had a hysterectomy.

Comment

The global index is a helpful tool in assessing the overall impact of treatments such as HRT and SERMs, which have different effects in different tissues, particularly SERMs, which have been developed for this specific difference in action at different sites.

The 25% reduction in the global index suggests a significant favourable risk–benefit profile of raloxifene in the treatment of osteoporosis in post-menopausal women.

The authors translate the risk reduction with raloxifene into an absolute figure of 150 fewer global index events per 10 000 women taking raloxifene for an average of 3.4 years. In the WHI the absolute excess risk of events included in the global index was 19 per 10 000 person-years in those taking HRT (approximately 100 more global events per 10 000 women were observed for the 5.2 years of follow-up). The difference relates to the increased rates of breast cancer diagnosis and finding of coronary heart disease and stroke with HRT and a decreased incidence of breast cancer and no effect on coronary heart disease or stroke associated with raloxifene. The venous thromboembolism effects are broadly equivalent for raloxifene and HRT.

The MORE trial was a well-designed, large, randomized, double-blinded study. However, caution should be exercised in making direct comparisons with the WHI trial for various reasons. The MORE trial enrolled women with established osteoporosis, whereas the WHI participants were enrolled regardless of osteoporosis status (more than 90% did not have osteoporosis at baseline). Moreover, the WHI set out to assess risk and benefit in terms of the global index, whereas this analysis was a *post hoc* analysis of data from a trial with primary outcomes of vertebral fracture and changes in BMD as well as the safety of long-term raloxifene use (secondary objectives were to assess the impacts on cardiovascular disease, breast and endometrial cancer).

Overall, the paper is informative in its results and supports the use of raloxifene as a treatment for osteoporosis, showing an overall reduction in the risk of global events.

Alendronate produces greater effects than raloxifene on bone density and bone turnover in post-menopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International

Sambrook PN, Geusens P, Ribot C, *et al*. *J Intern Med* 2004; **255**: 503–11

BACKGROUND. This study aimed to compare the efficacy and tolerability of once-weekly alendronate with those of raloxifene for the treatment of osteoporosis in

post-menopausal women with low bone density. Four hundred and eighty-seven women with T-score of –2.0 or lower at the lumbar spine or hip were enrolled in a randomized, double-blind, double-dummied, multicentre, international trial (the EFFECT International). Women received either alendronate 70 mg once weekly and daily placebo or raloxifene 60 mg daily and weekly placebo, for 12 months. Outcome measures were BMD at the lumbar spine and hip markers of bone turnover at 6 and 12 months, and adverse event reporting.

INTERPRETATION. Lumbar spine BMD increased by 4.8 versus 2.2% with raloxifene ($P<0.001$). Total hip BMD increased by 2.3% with once-weekly alendronate versus 0.8% with raloxifene ($P<0.001$) (Fig. 13.12). Bone turnover markers also declined significantly more with alendronate than with raloxifene. A similar number of women in each group reported gastrointestinal adverse events, whereas significantly more drug-related vasomotor symptoms were reported in the raloxifene group ($P<0.007$). The authors conclude that, in post-menopausal women with low bone density, the improvement in BMD and the decrease in markers of bone turnover were substantially greater with weekly alendronate than with raloxifene. The authors suggest that the difference shown in efficacy between raloxifene and alendronate is similar to that in earlier studies [**20**] and to meta-analysis data [**21,22**].

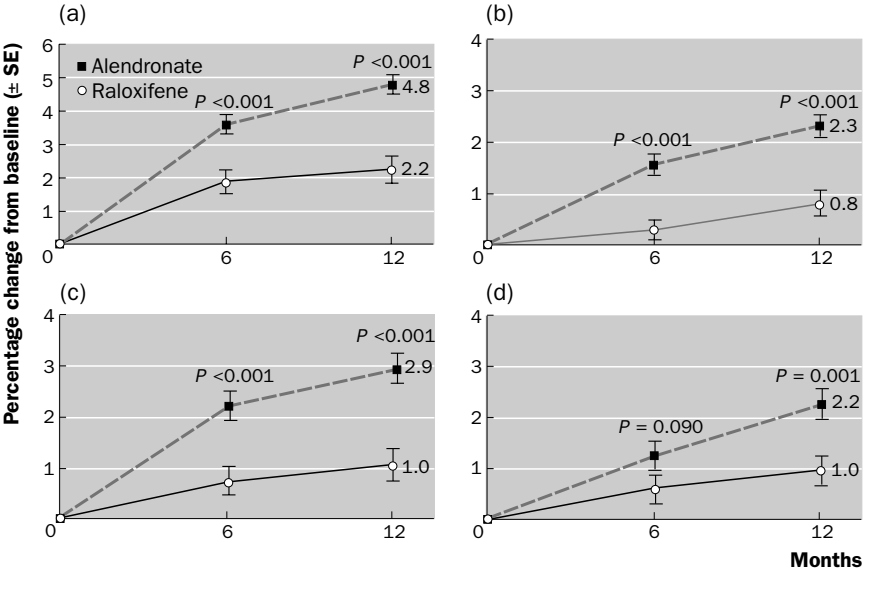


Fig. 13.12 (a) Changes in bone mineral density (BMD) at the lumbar spine. (b) Changes in total hip BMD. (c) Changes in BMD at hip trochanter. (d) Changes in BMD at femoral neck. Source: Sambrook *et al*. (2004).

Comment

A direct comparison of therapeutic regimes provides the best evidence of their comparative efficacy. Ideally, studies should assess the risk of fracture but smaller, short-term studies such as this again concentrate on changes in BMD and bone turnover markers as surrogates.

The evidence presented would suggest an advantage of alendronate over raloxifene in terms of osteoporosis benefit and fewer adverse effects.

The drug-related side effects are presented in Table 13.4. The only significant differences are that raloxifene seems to be associated with a higher number of vasomotor and drug-related vasomotor symptoms. However, the study does not explain how these symptoms were asked about, or how events were classified as 'drug-related' or not. Obviously, post-menopausal women are likely to suffer significant vasomotor symptoms and it may be difficult to reliably attribute symptoms to oestrogen deficiency or to establish that they are side effects of drug treatment. The study does not give details of the baseline reporting of vasomotor symptoms and yet reports an increased incidence of drug-related symptoms in the raloxifene group.

Women were included in this trial if they were 'able to accept either treatment'. It is not clear whether they were therefore excluded if they had any upper gastrointestinal disease (it is advised that alendronate should be used with caution in women with any upper gastrointestinal disease). Women with pre-existing gastrointestinal disease may have been excluded, whereas women with pre-existing hot flushes do not seem to have been excluded from entry.

Table 13.4 Summary of clinical, upper gastrointestinal and vasomotor adverse experiences

	Alendronate 70 mg once weekly (*n* = 246)	**Raloxifene 60 mg daily (*n* = 241)**	
	***n* (%)**	***n* (%)**	***P*-value***
Any adverse experience	154 (62.6)	157 (65.1)	0.573
Drug-related adverse experience†	56 (22.8)	65 (27.0)	0.296
Serious adverse experience	11 (4.5)	14 (5.8)	0.543
Discontinued due to an adverse experience	14 (5.7)	19 (7.9)	0.371
Upper gastrointestinal adverse experience	38 (15.4)	53 (22.0)	0.081
Drug-related gastrointestinal adverse experience†	23 (9.3)	39 (16.2)	0.029
Vasomotor adverse experience	9 (3.7)	23 (9.5)	0.010
Drug-related vasomotor adverse experience†	6 (2.4)	19 (7.9)	0.007

*Comparison between treatment groups.
†Determined by the investigator to be possibly, probably or definitely drug-related.
Source: Sambrook *et al.* (2004).

The other shortcoming of this trial is the short follow-up (1-year). Long-term regimes are usually indicated for women requiring treatment or prevention of osteoporosis and it would be important to know whether the difference in efficacy and adverse events continued with longer duration of use.

Effects of alendronate and hormone replacement therapy, alone and in combination, on bone mass and markers of bone turnover in elderly women with osteoporosis

Evio S, Tiitinen A, Laitinen K, Ylikorkala O, Valimaki MJ. *J Clin Endocrinol Metab* 2004; **89**: 626–31

BACKGROUND. The aim of this study was to compare alendronate, HRT and their combination in the treatment of osteoporosis in elderly post-menopausal women. Ninety women aged 65–80 with osteoporosis, shown by a T-score of BMD of –2.5 or less at the lumbar spine or femoral neck, were studied. They were randomized to receive daily 10 mg alendronate ($n = 30$), 2 mg oestradiol plus 1 mg norethisterone acetate ($n = 30$) or their combination ($n = 30$) for 2 years. The study was double-blinded and double-dummied. BMD and serum bone turnover markers were measured over the 2-year period.

INTERPRETATION. Lumbar spine BMD increased similarly (9.1–11.2%) in the three study groups. Total hip BMD also increased significantly in all groups. Only HRT increased femoral neck BMD significantly ($P < 0.0001$) at both 1 (+4.9%; $P =$ not significant versus other groups) and 2 years (+5.8%; $P < 0.05$ versus the other groups). The reduction in urinary and serum bone markers of bone turnover was less in the HRT group than in the other two groups. The authors conclude that in elderly women the combination of HRT and alendronate did not confer any benefit in increasing bone density over either treatment alone. The single treatments were equally effective but bone markers showed less reduction in the HRT alone group. They postulate that, in this elderly group, overall bone turnover is lower and therefore is more adequately suppressed with one drug alone, with no consequent benefit from the addition of a second drug.

Comment

The authors comment that previous studies show that women aged 52–62 gain an additive benefit from combining the two antiresorptive agents with different modes of action (alendronate is an osteoclast inhibitor at sites of bone resorption; oestrogen acts by decreasing the concentrations of circulating osteoclast-stimulating cytokines and upregulating transforming growth factor-β to inhibit osteoclast activity and increase osteoclast apoptosis). This is not seen in this study of older women. However, this is a small study (three groups of 30 women) and 21 women discontinued the study (eight, seven and six from the three groups) for a variety of reasons.

The results were also assessed after 2 years of treatment, so that longer-term benefits of the combination treatment are unknown.

In terms of relevance to clinical practice, HRT would be an unlikely first-line choice for the prevention of osteoporotic fracture in an elderly woman, as she would be unlikely to need the climacteric symptom relief. The more likely indication to use HRT in combination therapy would be in women who have not responded adequately to single-agent therapy. However, this study looks at the combination of alendronate and HRT in women who have not been chosen because of their previous lack of response to single agents, and thus its clinical usefulness is limited.

Conclusion

The papers discussed in this chapter cover a wide range of evidence related to the use of HRT and raloxifene for the prevention and treatment of osteoporosis. To summarize some important findings, the self-reported questionnaire study by Yates suggested an increased risk of fracture in women who have discontinued HRT in the last 5 years compared with never users. In contrast, the paper by Banks, from the Million Women Study, suggests that the fracture risk is similar to that for never users after stopping, and the paper by Bagger, which is smaller but relates to women in well-conducted randomized placebo-controlled trials, reports a decreased risk of fracture compared with the placebo group 5, 11 or 15 years after stopping treatment.

The paper by Rejnmark shows that increased age, a higher body weight, moderate alcohol consumption and low initial hip BMD are associated with a good response to oestrogen therapy. In addition, a study by Rapuri [23] has found that low endogenous oestradiol levels seem to be associated with better responses to HRT. This correlates well with the evidence that fracture reduction is known to be more significant in older women, though these women also have a higher risk of breast cancer and cardiovascular disease.

Pulsed once-daily intranasal 17β-oestradiol has been proved to effectively reduce bone turnover and maintain bone density.

With regard to raloxifene, the breast cancer reduction has been shown to persist with long-term use and no further adverse events have been reported over a longer duration of use.

Once-weekly alendronate had better efficacy than raloxifene in the comparison study, with an apparently better side effect profile. Although there is no apparent benefit in the combination of HRT with alendronate in improving bone mass, more evidence is needed on the effects of combination treatments. In the meantime, giving HRT or SERMs in combination with vitamin D, calcium or hip protectors makes sense and does not confer any obvious risk of harm.

Other areas for research

Lower doses of HRT are known to have significant bone-sparing effects [24–26] and may be associated with fewer adverse affects. Large trials would be needed to confirm whether fracture reduction from low doses is similar to that obtained with higher doses and whether the benefits outweigh the risks for low-dose preparations. Such trials are unlikely to be initiated in the current climate.

Ospemifine is a new SERM still undergoing clinical trials. It has been shown to significantly reduce markers of bone turnover and increase bone density in healthy post-menopausal women, in a dose-dependent fashion [27]. Bazedoxifene is another tissue-specific oestrogen receptor modulator undergoing Phase 3 clinical trials. Tofupill is a phytoselective oestrogen receptor modulator (ERM)-like substance. Phyto-oestrogen is a constituent of soya beans and the low incidence of osteoporosis in the Asian population has been attributed partly to high dietary consumption of phyto-oestrogen. The potential for this to treat menopausal symptoms has not yet been fully evaluated but one recent study shows some increase in bone density with a high dose of tofupill, and there has been no reporting of side effects or adverse events [28].

Prescribing HRT and raloxifene for the prevention and treatment of osteoporosis should be based, now more than ever, on individual factors and involve informed decision-making with the woman. The risks of venous thromboembolism, breast cancer and cardiovascular disease are all important in the assessment. For women experiencing premature menopause or who have significant climacteric symptoms, HRT should still be the agent of choice for osteoporosis prevention. Women intolerant of other therapies, such as bisphosphonates, should also consider HRT or raloxifene for osteoporosis prevention or treatment.

When HRT is indicated in post-menopausal women, general recommendations are for the lowest effective dose to be prescribed, for the shortest duration. An arbitrary maximum of 5 years is sometimes applied. With the evidence available, no long-term prevention of fractures should be assumed from short-duration HRT, and women who cease HRT once it is no longer needed for climacteric symptom relief should consider other forms of osteoporosis prevention or treatment if they are at high risk.

NICE published a technology appraisal for the secondary prevention of osteoporosis (after a fragility fracture) in January 2005 [29]. This included a review of the evidence for raloxifene for the secondary prevention of osteoporosis fractures in post-menopausal women. It concludes that raloxifene should be used for the secondary prevention of osteoporosis only where bisphosphonates are contraindicated, women are intolerant of bisphosphonates or physically unable to take them, or where there is an unsatisfactory response to bisphosphonates. This conclusion is drawn because their review suggests that raloxifene is less effective in treating osteoporosis (particularly non-vertebral fracture) and its use for breast cancer prevention has not been assessed against the use of other drugs that potentially reduce

the risk of breast cancer. It also suggests that the long-term risks of using raloxifene for more than 8 years are uncertain.

Publication of the NICE technology appraisal on the primary prevention of osteoporotic fragility fractures in post-menopausal women is expected in September 2006.

There is no doubt that HRT is not indicated as a treatment to prevent chronic disease in all women. However, it is still a very effective treatment in women needing relief from perimenopausal symptoms of oestrogen deficiency, and gives a significant reduction in osteoporotic fracture. The risk of coronary heart disease appears to be less in those taking it at a relatively young age and for a short duration.

Raloxifene is probably not as effective as bisphosphonates in reducing the risk of fracture but is suitable for those intolerant of other treatments and in those in whom the significant reduction in the risk of breast cancer may be important.

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14

Management of osteoporosis: bisphosphonates

SOCRATES PAPAPOULOS

Introduction

Bisphosphonates are very effective treatments for osteoporosis. Daily administration of alendronate and risedronate decreases the rate of bone turnover, increases bone mineral density (BMD) at relevant skeletal sites and significantly reduces the risk of vertebral and non-vertebral fractures, including those of the hip. Systematic reviews with meta-analyses have further shown that the antifracture efficacy of these two bisphosphonates is consistent among trials and populations. To improve patient convenience and long-term adherence to treatment, and to reduce potential gastrointestinal complications that may be associated with daily use, once-weekly regimens have been developed for both bisphosphonates. These regimens provide the sum of seven daily doses (alendronate 70 mg and risedronate 35 mg once a week) and are pharmacologically equivalent to the daily doses. The once-weekly administration of a bisphosphonate should be considered continuous treatment and should be distinguished from the administration of bisphosphonates at longer, drug-free intervals, commonly referred to as intermittent or cyclical regimens.

Following the demonstration of the efficacy and safety of bisphosphonate therapy, current studies address questions related primarily to the pharmacological properties of these compounds that are essential for their optimal clinical use. These studies can be classified into four broad areas: (i) mechanisms of antifracture efficacy; (ii) long-term safety and efficacy; (iii) use in therapies together with other anti-osteoporotic agents; and (iv) use at intervals longer than 1 week [1]. In this chapter, I will discuss studies published in the last year that have addressed these questions.

Mechanisms of antifracture efficacy

Changes in bone turnover and hip, non-spine and vertebral fracture in alendronate-treated women: the Fracture Intervention Trial

Bauer DC, Black DM, Gernero P, *et al. J Bone Miner Res* 2004; **19**: 1250–8

BACKGROUND. There are few data on the relationship between short-term changes in biochemical markers of bone turnover and non-spine fracture risk among bisphosphonate-treated women, and the clinical use of such measurements is unknown.

INTERPRETATION. The authors measured biochemical markers of bone turnover and BMD of the spine and hip at baseline and after 1 year of alendronate or placebo. During a mean follow-up of 3.6 years, 72 hip, 786 non-spine and 336 vertebral fractures were documented. Each SD reduction in 1-year change in bone-specific alkaline phosphatase (bone ALP) was associated with fewer spine (odds ratio 0.74; 95% confidence interval [CI] 0.63–0.87), non-spine (relative hazard [RH] 0.89; CI 0.78–1.00; $P<0.05$) and hip fractures (RH 0.61; 95% CI 0.63–0.78). Alendronate-treated women with at least a 30% reduction in bone ALP had a lower risk of non-spine (RH 0.72; 95% CI 0.55–0.92) and hip fractures (RH 0.26; 95% CI 0.08–0.83) relative to those with reductions of less than 30%.

The authors concluded that greater reductions in bone turnover with alendronate therapy are associated with fewer hip, non-spine and vertebral fractures, and that the effect is at least as strong as that observed in 1-year change in BMD.

Comment

It is well established that low BMD and increased rate of bone turnover are strong, independent risk factors for fractures. There is disagreement, however, regarding the relative contributions of changes in BMD to the antifracture efficacy of antiresorptive agents. This disagreement has stemmed from observations in clinical trials of antiresorptive agents showing reductions in the risk of vertebral fractures of a similar magnitude by agents with a small or a larger effect on BMD. Furthermore, the reported estimates of the proportion of the reduction in fracture risk that can be explained by changes in BMD range between 4 and 50% depending on the type of analysis. In order to understand the action of a therapeutic agent on a clinical outcome, in this case fracture incidence, we need first to consider the mechanism of action of this agent in relation to the pathophysiology of the disease. For example, in osteoporosis there is an imbalance between bone formation and bone resorption, resulting in bone loss with each remodelling cycle. When this imbalance is accompanied by an increase in the activation of new bone remodelling units, more bone will be lost within the same period. In addition, the latter will

adversely affect the structure of bone, further increasing the risk of fracture. This pathophysiological background provides the rationale for the use of agents that reduce bone resorption and bone turnover in the management of osteoporosis. Bisphosphonates are taken up selectively by the skeleton, primarily at active bone sites, where they suppress osteoclast-mediated bone resorption. This is their primary pharmacological action. The suppression of bone resorption occurs early after initiation of treatment and is followed by a slower decline in the rate of bone formation, due to the coupling of the two processes, until a new equilibrium between bone formation and resorption is achieved between 6 and 12 months at a slower rate of bone turnover. Increases in BMD are secondary to this action.

Earlier analyses of data from intervention studies with raloxifene and risedronate [2,3] showed that short-term decreases in bone turnover are associated with lower risk of vertebral fractures. The present study, which included the whole Fracture Intervention Trial cohort, reached the same conclusion using three different markers of bone turnover and showed, for example, that each SD reduction in the 1-year percentage change in bone ALP was associated with a 26% reduction in spine fractures (95% CI 13–37%). However, in contrast to the analysis performed by Eastell *et al.* [3] with risedronate, which reported that the relationship between decreases in bone resorption markers and the risk of vertebral fractures is non-linear, there was no evidence of non-linearity in this study. Thus, the previous suggestion that proportional reduction of bone resorption below a certain level (about 50%) by risedronate offers no additional antifracture benefit should not be extrapolated to treatment with alendronate. Whether this difference is due to methodological issues or to potential pharmacological differences, other than potency, between the two bisphosphonates cannot be decided from the data reported. In addition and, perhaps, more importantly, the present study also showed an association between reduction in bone ALP and the risk of non-vertebral and hip fractures (Table 14.1). Such a relationship has been reported previously in a meta-analysis of 18 placebo-controlled trials [4] but is shown for the first time by Bauer *et al.* in an analysis of individual patient data. Again, for this relationship there was no evidence for non-linearity. These relationships were further independent of the severity of osteoporosis assessed either by the presence of a prevalent vertebral fracture or by a BMD T-score below –2.5.

Taken together, these data suggest that greater reductions in bone turnover are required for a reduction in the risk of all fractures, whereas this may not be the case for vertebral fractures only. This is consistent with available evidence from clinical trials of antiresorptives. Compounds with a weak antiresorptive action (calcitonin) reduce the risk of vertebral fractures but have no effect on the risk of non-vertebral fractures. Conversely, more potent inhibitors of bone resorption (alendronate, risedronate, oestrogens) reduce the risk of both vertebral and non-vertebral fractures. In addition, this study provides further support for the use of analyses based on individual patient data in exploring associations between effects on surrogate end-points and the antifracture efficacy of antiresorptive agents [5]. However, such analyses are difficult to perform because in clinical trials samples for

Table 14.1 Fracture risk per SD of 1-year decrease in marker or 1-year increase in BMD among alendronate-treated women

Variable	SD of change over 1 year (%)	Spine fracture OR (95% CI)*	Non-spine fracture RH (95% CI)*	HIP fracture RH (95% CI)*
Bone ALP	22.1	0.74 (0.63–0.87)	0.89 (0.78–1.00)	0.61 (0.46–0.80)
P1NP	30.8	0.77 (0.66–0.90)	0.90 (0.80–1.03)	0.78 (0.51–1.19)
S-CTX	31.1	0.83 (0.73–0.95)	0.94 (0.84–1.06)	0.89 (0.61–1.31)
Fasting at baseline subgroup	35.5	0.77 (0.58–1.03)	1.02 (0.75–1.37)	—
BMD spine	3.9	0.92 (0.76–1.11)	1.05 (0.92–1.20)	0.94 (0.56–1.58)
BMD total hip	2.6	0.74 (0.61–0.89)	1.03 (0.90–1.17)	0.74 (0.47–1.17)

*Fracture risk per 1 SD decrease in 1-year percentage change in bone ALP, P1NP or S-CTX, and per 1 SD increase in 1-year percentage change in spine or total hip BMD (age-adjusted).
Source: Bauer *et al.* (2004).

measurements of bone markers are generally obtained only from subgroups of patients, mainly for economic reasons.

Bauer *et al.* attempted further to estimate a cut-off point for the reduction in bone ALP that can predict antifracture efficacy and thus provide some guidance for clinical practice. A reduction of more than 30% (corresponding closely to the least significant change in this marker) was associated with significant reductions in non-vertebral and hip fractures, whereas a lower reduction was not. However, this analysis did not take into consideration the prevalent rate of bone turnover which can differ considerably among patients, and did not attempt to define treatment targets of bone markers in absolute values or in T-scores, as previously reported by Eastell *et al.* [3]. Apart from this reservation, the study of Bauer *et al.* suggests an easy-to-follow biochemical target in osteoporotic women treated with alendronate in daily practice.

Relationship between pre-treatment bone resorption and vertebral fracture incidence in post-menopausal osteoporotic women treated with risedronate

Seibel MJ, Naganathan V, Barton I, Grauer A. *J Bone Miner Res* 2004; **19**: 323–9

BACKGROUND. Earlier studies, using BMD as primary end-point, have suggested that the therapeutic response to antiresorptive therapies may be influenced by pre-treatment bone turnover but it is unclear whether this is true for their antifracture efficacy.

INTERPRETATION. The authors analysed *post hoc* the relationship between urinary excretion of deoxypyridinoline (uDPD) as an index of bone resorption and the incidence of

vertebral fractures in a subset of women with post-menopausal osteoporosis who participated in the risedronate phase III clinical programmes. A total of 1593 patients from the placebo and risedronate groups who had both baseline uDPD measured and paired spine radiographs were stratified by the uDPD pre-menopausal normative median. In all four groups, the proportion of patients with new vertebral fractures was higher in patients with baseline uDPD levels above compared with those with levels below the normative median. The incidence of vertebral fractures was significantly lower in groups assigned to risedronate compared with placebo. This effect was independent of pre-treatment bone resorption: in patients with high baseline bone resorption the relative risk (RR) of vertebral fractures after 1 year of risedronate was 0.33 ($P<0.001$ compared with controls; absolute risk reduction 7.1%). In patients with low baseline bone resorption the RR of fracture after 1 year was 0.28 ($P = 0.030$; absolute risk reduction 4%). After 3 years, the RR of fracture was 0.54 ($P = 0.002$; absolute risk reduction 8.3%) in patients with high and 0.52 ($P = 0.042$; absolute risk reduction 6.4%) in patients with low pre-treatment bone resorption. [Data in the published abstract do not correspond exactly to those described in the text. I have quoted those reported in the paper.] Results were similar after adjusting for age, baseline lumbar spine BMD and prevalent fractures. The number needed to treat (NNT) to avoid one vertebral fracture at 12 months was 15 and 25 in the groups with high and low pre-treatment bone resorption respectively. During the first year of treatment, women with high baseline bone resorption gained lumbar spine BMD at a faster rate than patients with low baseline bone resorption. Treatment × baseline bone resorption interactions were not significant over time. The authors concluded that the efficacy of risedronate in reducing incident vertebral fractures in women with post-menopausal osteoporosis is largely independent of pre-treatment bone resorption rate.

Comment

In clinical practice it is frequently assumed that patients with prevalent high rates of bone turnover are better candidates for treatment with antiresorptive agents whereas those with low rates of bone turnover should ideally be treated with a bone-forming agent. Earlier studies using BMD as the primary end-point support this notion by showing greater increases in patients with high baseline rates of bone turnover. The question is whether this relationship translates also into differences in fracture incidence, the clinically relevant end-point. This is the first study that has systematically addressed this question, and it showed that the efficacy of risedronate in reducing the risk of vertebral fractures was independent of the prevalent rate of bone resorption. Importantly, the relative risk reduction in vertebral fracture risk during the first year was 67 and 72% in patients with high and low baseline bone resorption respectively. Thus, not only was there no difference between the two groups but the effect was equally rapid and substantial.

The lack of difference in response to risedronate between the two groups was also documented after 3 years. What was different between the two groups was the absolute risk reduction and consequently the NNT to prevent one fracture. NNT is calculated as the fraction of 100 divided by the absolute risk reduction and depends, therefore, both on the efficacy of the intervention and the risk of the placebo group.

The efficacy of risedronate was the same but the fracture risk in the group with high baseline bone resorption was clearly higher, accounting for an NNT after 1 year of 15 in this group compared with 25 in the group with low baseline bone resorption (Table 14.2). After 3 years, this difference was considerably smaller (NNT 13 versus 16). These findings indicate that the excess risk of patients with high bone turnover is removed early during treatment by the quick suppression of bone resorption and the resulting preservation of trabecular microarchitecture.

An additional finding of clinical relevance was the higher fracture incidence after 1 year in the groups with high baseline bone resorption independently of the treat-

Table 14.2 Incidence of new vertebral fractures by treatment group and pre-treatment bone resorption

	Placebo	5 mg risedronate	5 mg risedronate vs placebo
0–1 years			
Urinary deoxypyridinoline ≤15.4 nm/mm			
n/N*	11/199	4/238	–
Percentage†	5.7	1.7	–
RR (95% CI)‡	–	–	0.28 (0.09–0.89)
P-value§	–	–	0.030
NNT¶	–	–	25
Urinary deoxypyridinoline >15.4 nm/mm			
n/N*	42/397	14/362	–
Percentage†	11.1	4.0	–
RR (95% CI)‡	–	–	0.33 (0.18–0.62)
P-value§	–	–	<0.001
NNT¶	–	–	15
0–3 years			
Urinary deoxypyridinoline ≤15.4 nm/mm			
n/N*	30/210	21/241	–
Percentage†	16.7	10.3	–
RR (95% CI)‡	–	–	0.52 (0.30–0.92)
P-value§	–	–	0.042
NNT¶	–	–	16
Urinary deoxypyridinoline >15.4 nm/mm			
n/N*	75/403	41/369	–
Percentage†	21.5	13.2	–
RR (95% CI)‡	–	–	0.54 (0.36–0.80)
P-value§	–	–	0.002
NNT¶	–	–	13

*Number of patients with an incident new vertebral fracture/number of patients with evaluable paired radiographs; †cumulative proportion of patients with incident new vertebral fractures based on Kaplan–Meier estimate; ‡based on Cox regression model, stratified for trial; §based on stratified log-rank test, stratified for trial. RR, relative risk; ¶NNT, number need to treat.
Source: Seibel *et al*. (2004).

ment they received (Table 14.2). This illustrates further the important and independent effect of bone resorption on bone strength. This risk could be reduced by risedronate, underscoring the need for early intervention in patients with vertebral fractures and high bone turnover.

Long-term safety and efficacy

Ten years' experience with alendronate for osteoporosis in post-menopausal women

Bone HG, Hosking D, Devogelaer J-P, *et al.*, for the Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 2004; **350**: 1189–99

BACKGROUND. Antiresorptive agents are widely used in the treatment of post-menopausal osteoporosis but there are no data on the effects of prolonged therapy under clinical trial conditions.

INTERPRETATION. The authors examined the effects of alendronate on BMD, biochemical markers of bone turnover and fracture incidence in women with post-menopausal osteoporosis treated for up to 10 years. This is the third extension of the study reported by Liberman *et al.* [**6**], in which three daily doses of alendronate were compared with placebo over 3 years. In years 4 and 5, women in the original placebo group received alendronate and were discharged, whereas those in the original active treatment groups continued to receive alendronate. In the two further extensions (years 6 and 7 and 8–10) women who had received 5 or 10 mg of alendronate daily continued on the same treatment. Women in the discontinuation group received 20 mg of alendronate daily for 2 years and 5 mg daily in years 3, 4 and 5 followed by 5 years of placebo. Randomized group assignment and blinding were maintained throughout the 10 years. The study reports results for 247 women who participated in all four phases of the study. Compared with baseline, treatment with 10 mg of alendronate daily produced mean increase in BMD of 13.7% at the lumbar spine, 10.3% at the trochanter, 5.4% at the femoral neck and 6.7% at the proximal femur. Smaller gains occurred in the group given 5 mg daily. The discontinuation of alendronate resulted in a gradual loss of effect, as measured by BMD and markers of bone turnover. Safety data, including fractures and stature, did not suggest any loss of benefit with prolonged treatment.

The authors concluded that the therapeutic effects of alendronate were sustained and the drug was well tolerated over a 10-year period. The discontinuation of alendronate resulted in the gradual loss of its effects.

Comment

Bisphosphonates suppress osteoclast-mediated bone resorption at the surface of bone. After exerting their action, they are embedded in the bone, where they remain for a long period. With the resumption of bone remodelling in these areas,

bisphosphonates will be released from bone and will be excreted in urine, but their metabolic fate locally is currently unknown. It is not known, for example, whether and to what extent the released bisphosphonate can again suppress bone resorption. Clarifying this pharmacological action of the bisphosphonates is of obvious clinical relevance, as it may indicate how long we should treat patients with bisphosphonates. The unique property of the bisphosphonates of being able to concentrate exclusively in the skeleton and to specifically suppress bone resorption allows the use of pharmacodynamic approaches to explore further their actions on bone metabolism. In addition, there are concerns that long-term exposure of the skeleton to bisphosphonates may have an adverse effect on bone metabolism and quality, leading to the so-called frozen bone. The study of Bone *et al.*, the longest ever reported for a bisphosphonate, addressed a number of these issues in osteoporotic women treated with alendronate for up to 10 years. It should be noted that this study was not designed to examine long-term antifracture efficacy, the endpoints being efficacy with regard to surrogate parameters and safety. Furthermore, because of recent suggestions that there may be differences among clinically used bisphosphonates in their affinity for bone mineral, the results obtained with alendronate may not be readily extrapolated to the whole class.

The study shows that alendronate reduced bone turnover into the premenopausal range early in the course of treatment and the effect was sustained throughout 10 years of treatment (Fig. 14.1a). For example, mean levels of urinary NTX (N-terminal crosslinking telopeptide of type I collagen) in the 10 mg group declined from 66.6 to 22.0 nmol BCEq/mmol Cr (bone collagen equivalent/mmol creatinine) and mean serum bone ALP from 17.8 to 9.1 ng/ml at the end of 10 years. Thus, despite the accumulation of the bisphosphonate in the skeleton, there was no indication of a cumulative effect on bone turnover, a result consistent with numerous other studies of bisphosphonates given daily for shorter periods. These changes in bone remodelling were associated with increases in BMD at all skeletal sites measured (Fig. 14.1b). In patients who discontinued treatment after 5 years, there was an increase in bone turnover within 1 year, but the values remained well below baseline values. The magnitude of this increase cannot be assessed as there was no parallel placebo group for comparison, but the response is clearly different from that following discontinuation of oestrogens.

The most important finding of this study is the absence of an adverse effect on skeletal integrity with long-term exposure to the bisphosphonate. This was illustrated by the incidence of non-vertebral fractures, which was similar to that observed during the first 3 years of the study. However, the women were older and were therefore at higher risk of fracture. Cortical bone has a lower rate of remodelling than trabecular bone and any potential adverse effect by an agent which reduces it would be seen primarily in such bones. The findings of the present study provide reassurance about the safety of long-term treatment with alendronate, but do not answer the question regarding the optimal length of treatment.

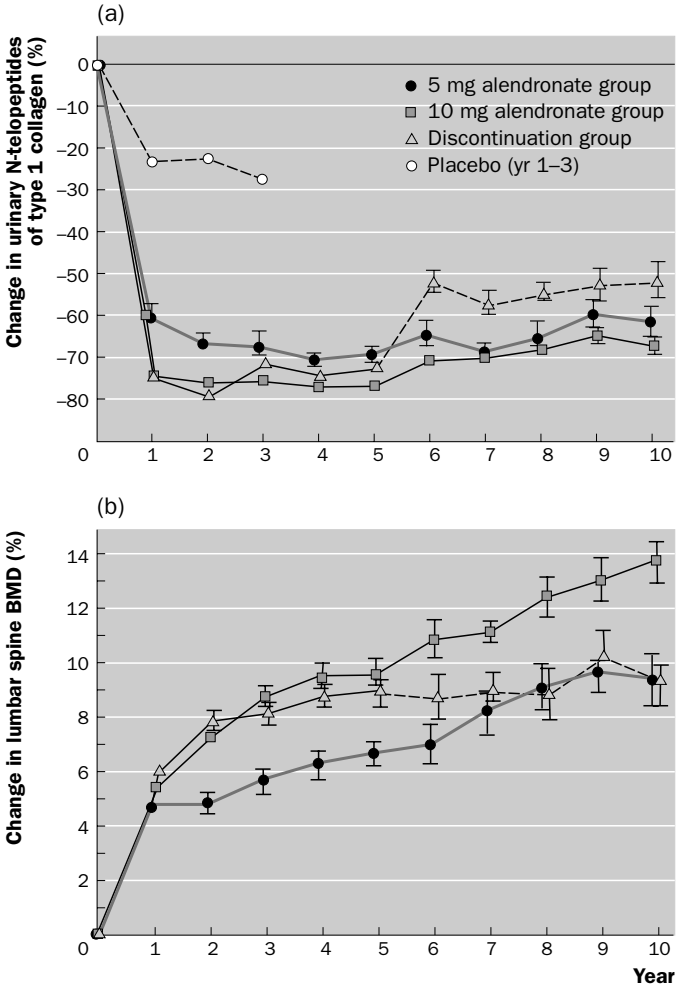

Fig. 14.1 Mean (± SE) percentage change in bone mineral density (BMD) in values for urinary N-telopeptides of type I collagen (a) and at the lumbar spine (b) over a 10-year period. The discontinuation group was treated with 20 mg of alendronate per day for 2 years and then 5 mg daily for 3 years, followed by placebo for 5 years. The 10-mg group was treated with 10 mg of alendronate daily for 10 years, and the 5-mg group was treated with 5 mg of alendronate daily for 10 years. Ten years of alendronate treatment resulted in significant dose-dependent increases in BMD at the lumbar spine. In the discontinuation group, some net effects on BMD and markers of bone turnover persisted to year 10, in a manner that was consistent with the cumulative dose received. *Solid lines* indicate the period during which alendronate was administered and *dashed lines* the period of placebo administration. Source: Bone *et al*. (2004).

Seven years of treatment with risedronate in women with post-menopausal osteoporosis

Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. *Calcif Tissue Int* 2004; **75**: 462–8

BACKGROUND. The antifracture efficacy of risedronate has been demonstrated in controlled studies up to 5 years. There is no information concerning its longer-term efficacy.

INTERPRETATION. The authors report the results of a second 2-year extension of a 3-year randomized, placebo-controlled study of daily risedronate in women with post-menopausal osteoporosis. The primary objective was to determine the safety and tolerability of this bisphosphonate. For the first 5 years of the study women received risedronate 5 mg/day or placebo according to the original randomization with maintenance of blinding. All women who entered the 6–7 years extension study received risedronate 5 mg/day. End-points included vertebral and non-vertebral fracture assessment, changes in biochemical markers of bone turnover and BMD measurements. A total of 164 women entered the 6–7 years extension study (placebo/risedronate group 81, risedronate group 83) and 136 (83%) completed the study. All received 1000 mg calcium daily and vitamin D up to 500 IU daily if baseline serum 25-hydroxyvitamin D levels were below 40 nmol/l. The annualized incidence of new vertebral fractures during the 6–7 years was similar in the two treatment groups (3.8%). The incidence of vertebral fractures did not change in the risedronate group during years 6–7 compared with years 4–5, while a significant reduction was observed in the placebo group, which switched to risedronate treatment for years 6–7. The incidence of non-vertebral fractures was 7.4 and 6.0% in the placebo/risedronate and risedronate groups respectively during years 6–7. Urinary NTX had decreased from baseline by 54 and 63% at 3 months and 7 years respectively in the risedronate group. The increases in BMD from baseline after 5 years of risedronate treatment were maintained or increased further during years 6–7; lumbar spine BMD after 5 and 7 years of risedronate treatment increased from baseline by 8.8 and 11.5% respectively. Risedronate was well tolerated. The authors concluded that 7 years of risedronate treatment of osteoporotic women is associated with significant increases in BMD and decreases in bone turnover to within pre-menopausal levels and that there was no indication of any loss of antifracture efficacy.

Comment

This is an extension of the 5-year study with risedronate, which was the first to provide information about the antifracture efficacy of a bisphosphonate during a period longer than 4 years. The original VERT (Vertebral Efficacy with Risedronate Therapy) multinational study examined the antifracture efficacy of daily oral risedronate in post-menopausal women with severe osteoporosis. Of the 814 women originally randomized in the 3-year study, 265 entered the first 2-year extension. This smaller number was partly due to the inclusion criteria, requiring only centres

that enrolled more than 10 patients during the first 3 years to participate, and partly to the number of patients who completed the first 3 years of the study ($n = 472$). Of the 220 patients who completed 5 years of treatment, 164 agreed to participate in the second, open-label, 2-year extension. The characteristics of the extension cohort at the time of enrolment into the original study were similar to those of the original cohort.

Like the alendronate study discussed above, this extension was not designed to assess antifracture efficacy of risedronate but rather safety and tolerability. The data on fracture incidence and bone metabolism reported are reassuring for the long-term use of risedronate in a particularly clinically relevant population of women with severe osteoporosis (mean number of 4.0 prevalent fractures). The incidence of both vertebral and non-vertebral fractures was sustained (Fig. 14.2) during years 6–7, bone resorption showed no evidence of a further decline with time (Fig. 14.3), and BMD at the lumbar spine showed a further increase.

Despite some methodological weaknesses regarding particularly the limited participation of women in the extension studies, the present and the 10-year alendronate studies are among the few examples of long-term controlled intervention studies in chronic diseases. Moreover, these studies illustrate a remarkable similarity of long-term responses to daily bisphosphonate therapy in osteoporosis and allow the general conclusion that long-term treatment is safe.

Supporting evidence

These clinical data are supported by two studies of paired bone biopsies obtained from a small number of women participating in the risedronate trial after 3 and 5 years of treatment. In the first study [7], bone biopsies taken before and after

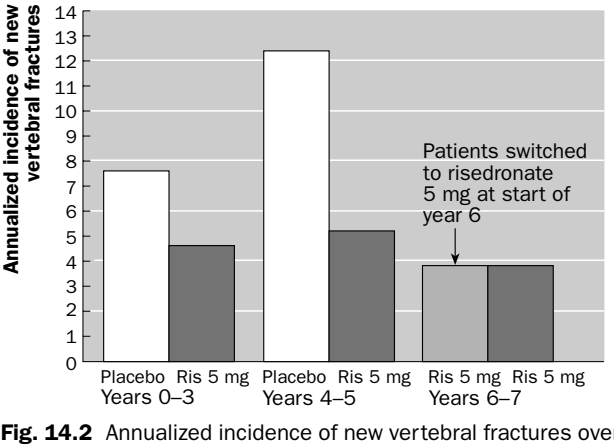

Fig. 14.2 Annualized incidence of new vertebral fractures over entire 7 years of the trial. Source: Mellstrom *et al.* (2004).

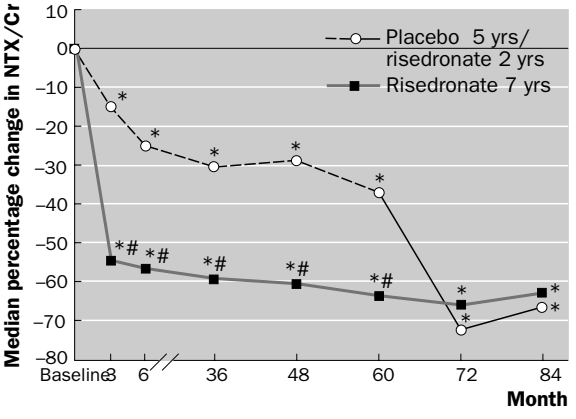

Fig. 14.3 Median percentage change from baseline in urine NTX/Cr. Dotted line denotes when patients were on placebo treatment. **P* <0.05 percentage change from baseline values. †*P* <0.001 versus placebo. Source: Mellstrom *et al*. (2004).

3 years of treatment were analysed by 3-D microcomputed tomography. Results showed that trabecular architecture deteriorated significantly in osteoporotic women who had high bone turnover at baseline and were treated with placebo. This deterioration was prevented by 3 years of risedronate treatment, presumably because of the reduction in bone turnover. Preservation of architecture by bisphosphonate treatment may contribute to its antifracture efficacy. In the second study [8], bone biopsies obtained after 5 years of treatment with risedronate 5 mg/day were examined histologically and histomorphometrically. Histological evaluation revealed no pathological findings in all biopsies examined. Consistent with the effect of the bisphosphonate on bone resorption and bone turnover, histomorphometry showed a 77% reduction in activation frequency and the presence of double tetracycline labels in all specimens examined.

Use of bisphosphonates in combination therapies

Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate

Ettinger B, San Martin J, Pavo I. *J Bone Miner Res* 2004; **19**: 745–51

BACKGROUND. The combination of a bone-forming with an antiresorptive agent represents the more rational approach to a combination therapy for osteoporosis. As teriparatide (human parathyroid hormone [PTH] peptides 1–34) is currently the only

bone-forming agent available, studies have focused on its use together with antiresorptive agents, mainly bisphosphonates. The question, however, is how these agents should be administered. Concurrently or sequentially? And if sequentially, in which sequence? Studies reviewed in the previous volume of *The Year in Osteoporosis* [1] showed that concurrent administration of PTH with alendronate to either men or women with osteoporosis does not offer any advantage over monotherapy and this is now generally accepted. I discuss here two articles reporting on sequential therapy. In the first, teriparatide was given after treatment with either raloxifene or alendronate; in the second bisphosphonates were given after teriparatide treatment.

INTERPRETATION. Fifty-nine post-menopausal women, who had been treated with either alendronate or raloxifene for 18–36 months, received teriparatide 20 μg per day for 18 months. All received calcium (1000 mg) and vitamin D (400 IU) daily. In patients treated with alendronate, median baseline turnover markers were about one-half those in patients treated with raloxifene. During teriparatide treatment, bone markers in the alendronate-treated patients increased later and peaked at about one-third lower levels compared with those of raloxifene-treated patients. During the first 6 months of teriparatide treatment, changes in BMD at the spine and the hip were significantly different between the two groups (0.5 vs 5.2% and –1.8 vs 0.5% for the alendronate and the raloxifene groups respectively). The positive slopes in hip and lumbar spine BMD were similar when compared between the two groups between 6 and 18 months of teriparatide treatment. After 18 months, mean lumbar spine BMD increased by 10.2 and 4.1% in patients treated previously with raloxifene and alendronate respectively. The authors concluded that teriparatide stimulates bone turnover in patients pre-treated with either raloxifene or alendronate. However, although increases in BMD after teriparatide in raloxifene-treated patients are similar to those induced by teriparatide alone, alendronate prevents these increases, particularly in the first 6 months.

Comment

This study is of obvious clinical significance as many women with severe osteoporosis, the target group for teriparatide treatment, are already treated with an antiresorptive agent, mainly a bisphosphonate. Data such as those reported in the present study are needed in order to guide decisions in daily practice. Results show that osteoporotic patients respond to teriparatide independently of the type of antiresorptive therapy they previously received (Fig. 14.4). Although the percentage increase in bone turnover was similar in the two groups of patients, the magnitude of the increase was clearly greater in the raloxifene-treated patients and very similar to that observed in naive patients treated with teriparatide. However, these changes induced different BMD responses in the two groups. Whereas lumbar spine BMD increased as expected in patients previously treated with raloxifene, it did not change during the first 6 months of treatment in patients previously treated with alendronate. Thereafter, the changes were similar in the two groups. There was, therefore, a 6-month delay in response in the alendronate group, a result difficult to interpret because bone turnover responded readily to teriparatide treatment. Either a certain absolute level of bone turnover must be reached for the full action of teriparatide on bone, an unlikely explanation, or other mechanisms are responsible

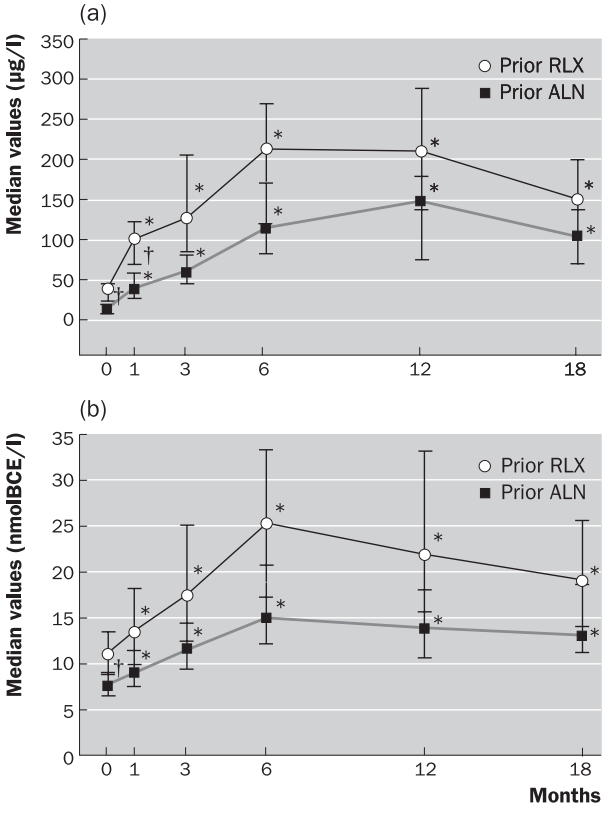

Fig. 14.4 Median values of serum bone turnover markers according to previous treatment with alendronate or raloxifene. (a) N-propeptide of type I procollagen; (b) N-telopeptide of collagen. Error bars indicate 25–75% interquartile range. *P<0.05 change from baseline; †P<0.05 difference between groups. Source: Ettinger *et al.* (2004).

for this apparent discrepancy. An explanation of the mechanism of action of alendronate is needed. As discussed above, the bisphosphonate concentrates preferentially at sites of increased bone turnover, whereas there is no such indication for teriparatide. Therefore, after teriparatide administration, sites that have not been exposed to alendronate previously are normally stimulated by the hormone, leading to increases in BMD. However, this increase may be initially compensated for by the removal of calcium and a decrease in the mineralization of sites previously exposed to alendronate. Therefore, the obvious suggestion – to delay the administration of teriparatide for 6 months in alendronate-treated patients to achieve a better early BMD response – is invalid if this hypothesis is correct. Clearly,

more studies are needed to test this and other hypotheses, and it may be that the response of such patients to teriparatide should be followed by bone markers (preferably P1NP [collagen type I N-terminal propeptide]) rather than by BMD. This is supported by a cryptic statement in the paper that is not further explained and appears to have escaped the attention of the reviewers: 'There were no differences in the group comparisons for bone density at the lumbar spine or hip when the results were repeated with data restricted to per-protocol analysis'. Finally, the results of the present study provide reassurance to clinicians that bone previously exposed to alendronate responds readily to teriparatide. This provides additional evidence against the concern of inducing frozen bone by treatment and distinguishing this sequential regimen from the concurrent administration of PTH with alendronate.

The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone (1–34)]

Kurland ES, Heller SL, Diamond B, McMahon J, Cosman F, Bilezikian JP. *Osteoporos Int* 2004; **15**: 992–7

BACKGROUND. The authors followed 21 men with idiopathic osteoporosis for up to 2 years after discontinuation of teriparatide treatment. Twelve men chose treatment with bisphosphonate immediately after teriparatide withdrawal while nine opted for no pharmacological treatment. At the end of 1 year, lumbar spine BMD increased by an additional 5.1% in the bisphosphonate group whereas it declined by 3.7% in those on no medication. For the entire 2-year post-PTH period, the gain was 8.9%. These men showed a total 4-year (2 years of teriparatide and 2 years of bisphosphonate treatment) gain in lumbar spine BMD of 23.6%.

INTERPRETATION. The authors conclude that the immediate use of bisphosphonates after teriparatide withdrawal may help to optimize gains in bone density at the lumbar spine.

Comment

This is a small, non-randomized study performed in men rather than in women with osteoporosis. It is, however, a proof-of-concept investigation, the concept being currently tested in ongoing larger studies. As there is no evidence of a difference in skeletal response between men and women to either teriparatide or bisphosphonate, these results can be extrapolated to women with post-menopausal osteoporosis. There are two very important observations in this study (Fig. 14.5). The first is that the gains in BMD induced by teriparatide are not maintained after discontinuation of treatment, which is similar to that which is observed after cessation of treatment with oestrogens or raloxifene but different from that which is observed after discontinuation of bisphosphonates. The second is that

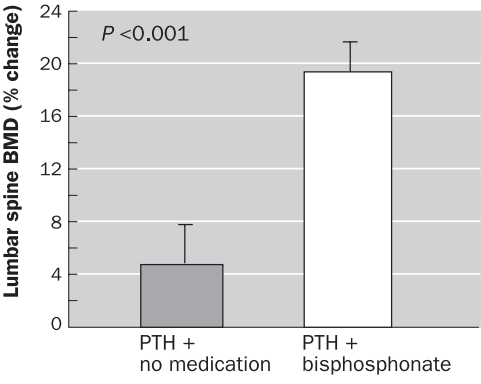

Fig. 14.5 Cumulative lumbar spine bone density change: baseline to 1 year after withdrawal of human PTH (1–34). Cumulative percentage change ± SEM in lumbar spine density for men who took bisphosphonates immediately after completing human PTH (1–34) ($n = 12$, white bar) and men who took no medication for 1 year after withdrawal of human PTH ($n = 7$, grey bar). Comparison is from baseline, prior to beginning human PTH (1–34) treatment, until 1 year after discontinuing human PTH (1–34) ($P < 0.001$). Source: Kurland *et al.* (2004).

continuation of teriparatide treatment with a bisphosphonate not only maintains the gain in BMD but increases it further, as reported previously in women treated with PTH 1–84 followed by 1 year of alendronate treatment [**9**]. The magnitude in total BMD gain during the whole treatment period with the two agents cannot be achieved by any currently available monotherapy, and this treatment with two agents is the most promising form of combination therapy currently available for osteoporosis.

The practical question, with significant economic implications, is whether treatment with teriparatide for 18 to 24 months is really needed. The study of Kurland *et al.* suggested that a shorter treatment period with teriparatide followed by bisphosphonate may give an even better BMD response. This suggestion was based on data from a few patients treated with teriparatide for 18 months compared with some treated for 30 months. In addition, it is now well established that the increase in bone turnover induced by teriparatide does not reach a plateau but appears to start decreasing after 9–12 months of treatment. It may therefore be that teriparatide treatment, when followed by bisphosphonate, should not last longer than a few months. In pilot studies of sequential treatment with human PTH 1–34 given for only 6 months followed by oral pamidronate for another 6 months we have previously shown dramatic changes in external calcium balance after 1 year [**10**]. Such studies, which are unlikely to be financed by the industry, are urgently needed.

Use of bisphosphonates at intervals longer than one week

Effects of oral ibandronate administered daily or intermittently on fracture risk in post-menopausal women

Chesnut CH III, Skag A, Christiansen C, *et al*. for the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). *J Bone Miner Res* 2004; **19**: 1241–9

BACKGROUND. The efficacy of bisphosphonate therapy given daily to patients with osteoporosis is well established. Less frequent, intermittent dosing of bisphosphonate, which can increase patient convenience and may improve long-term adherence to treatment, has not been adequately studied.

INTERPRETATION. The authors assessed the efficacy and safety of oral ibandronate given either daily or intermittently with a dose-free interval of more than 2 months in a randomized, double-blind, placebo-controlled, parallel group study of 2946 women with post-menopausal osteoporosis. Selection criteria were a BMD T-score of –2.0 or lower at the lumbar spine in at least one vertebra (L1–L4) and one to four vertebral fractures (T4–L4). Patients received placebo or oral ibandronate administered either daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months) and daily calcium (500 mg) and vitamin D (400 IU) supplementation. After 3 years, the rate of new vertebral fractures was reduced in patients receiving oral daily (4.7%) and intermittent ibandronate (4.9%), relative to placebo (9.6%). Thus, daily and intermittent ibandronate were associated with significant reductions in new vertebral fractures, by 62% ($P = 0.0001$) and 50% ($P = 0.0006$) respectively. Both treatments also produced a statistically significant reduction in the risk of clinical vertebral fractures (49 and 48% for daily and intermittent ibandronate respectively). Significant and progressive increases in lumbar spine (6.5, 5.7 and 1.3% for daily ibandronate, intermittent ibandronate and placebo respectively at 3 years) and hip BMD, normalization of bone turnover and significantly less height loss than in the placebo group were also observed for both ibandronate regimens. The overall population was at low risk of osteoporotic fractures. Consequently, the incidence of non-vertebral fractures was similar between the ibandronate and placebo groups after 3 years. However, a *post hoc* analysis showed that the daily regimen reduces the risk of non-vertebral fractures (69%; $P = 0.012$) in a higher-risk subgroup (femoral neck T-score below –3.0). In addition, oral ibandronate was well tolerated.

The authors concluded that oral ibandronate, whether administered daily or intermittently with an extended between-dose interval of more than 2 months, is highly effective in reducing the incidence of osteoporotic fractures in post-menopausal women. This is the first time that significant fracture efficacy has been shown prospectively with an intermittently administered bisphosphonate in the overall study population of a randomized, controlled clinical trial. Oral ibandronate holds promise as an effective and convenient alternative to current bisphosphonate therapies.

Comment

Bisphosphonate administration at intervals longer than 1 week is an attractive therapeutic option but it has failed to show concrete evidence of antifracture efficacy in controlled clinical trials. This is largely due to the empirical design of the regimens examined in such trials. The pharmacodynamics of bisphosphonates given at drug-free intervals longer than 1 week may differ from those induced by daily treatment. Such regimens induce a fast decrease in bone resorption which reaches a nadir within a few days. Thereafter, resorption starts to increase slowly towards baseline until the administration of the following dose. The result is a fluctuating rate of bone resorption. Thus, different doses lead not only to different levels of bone resorption but also to differences in the fluctuation in resorption. Dosing amount and interval are, therefore, of primary importance for the design of such regimens. This was illustrated in the initial studies with ibandronate given by intravenous injections at inadequate doses of 0.5 and 1.0 mg every 3 months to osteoporotic women [**11**]. These regimens increased BMD to some extent (about 4% after 3 years) but the magnitude of suppression of bone resorption at the end of each 3-month interval was insufficient. For example, after 3 years the dose of 1 mg every 3 months reduced median CTX (C-terminal crosslinking telopeptide of type I collagen)/creatinine (Cr) excretion by 10.8% compared with placebo and 45% compared with baseline. These changes were associated with a non-significant decrease in the risk of vertebral fractures (by about 24%). These results indicated that either higher doses or shorter dosing-free intervals are required for the development of an effective treatment regimen with intravenous ibandronate. This hypothesis was tested in a double-blind, placebo-controlled, randomized study that compared the effectiveness of intravenous ibandronate 1 and 2 mg with that of placebo over 1 year [**12**]. The higher dose was clearly more efficacious; it increased lumbar spine BMD by 5.0% and decreased urinary CTX/Cr by 61% after 1 year. The corresponding changes with the lower dose were 2.8% and 42%. Whether this dose of ibandronate and/or treatment-free interval are optimal for the intravenous administration of this bisphosphonate is currently investigated in a phase III non-inferiority clinical trial against daily oral ibandronate.

In the study of Chesnut *et al.* ibandronate was given orally. On the basis of animal data showing that the total cumulative dose rather than the treatment schedule is more important for the efficacy of ibandronate with respect to bone strength and quality, these authors examined an intermittent dosing regimen with a drug-free interval of 9–10 weeks that provided about the same total dose as daily ibandronate over 3 months (approximately 225 mg for daily and 240 mg for intermittent). This regimen reduced the incidence of vertebral fractures significantly, demonstrating for the first time in a prospective, specifically designed study that this is feasible with an intermittent oral bisphosphonate regimen (Fig. 14.6). However, upon examination of the data of this and of a more detailed analysis of bone marker results published at the same time [**13**], it is apparent that the intermittent regimen, despite its efficacy, appeared to be (arithmetically at least) less effective than the daily regimen. For example, lumbar spine BMD increased by

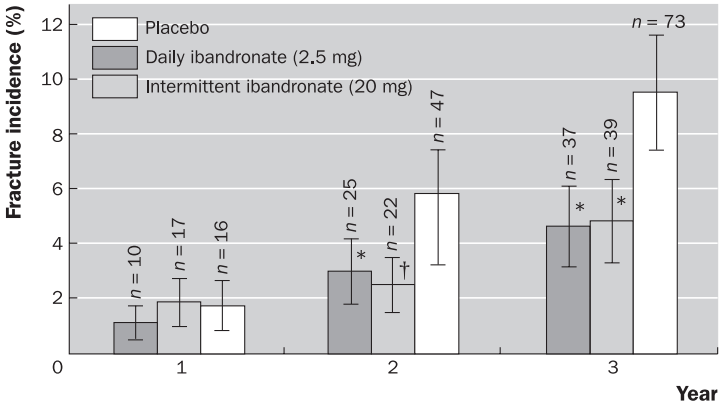

Fig. 14.6 Cumulative effect of oral daily and intermittent ibandronate on new vertebral fractures during each year of the study. *P<0.001 vs placebo; †P<0.0017 vs placebo. Source: Chesnut *et al*. (2004).

6.5% with daily ibandronate versus 5.7% with intermittent ibandronate; urinary CTX/Cr decreased by 65.3% with daily ibandronate versus 52.7% with intermittent ibandronate (Fig. 14.7); and vertebral fracture reduction was 62% with daily ibandronate versus 50% with intermittent ibandronate after 3 years. Similar trends

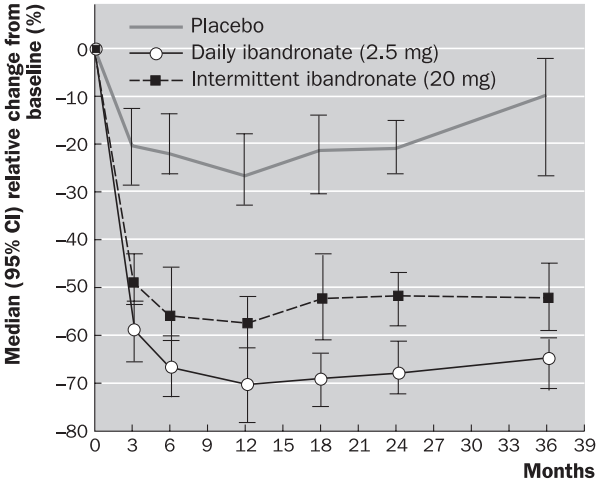

Fig. 14.7 Median (95% CI) relative change from baseline for urinary CTX/creatinine in patients receiving placebo, oral daily and oral intermittent ibandronate over 3 years. Source: Delmas *et al*. (2004) [**13**].

were observed by histomorphometric analysis of bone biopsies obtained during this trial [14]. As stated above, the total dose provided by daily ibandronate was 225 mg, whereas that provided by intermittent ibandronate was 240 mg. These results strongly suggest that the total dose concept, at least for this bisphosphonate, is not fully applicable and that for optimal efficacy the dose should be increased to fully compensate for the prolongation of the dosing-free interval. Indeed, this approach was tested with oral once-monthly ibandronate doses that were 25 or 100% higher than the daily cumulative dose (e.g. 100 and 150 vs 75 mg, respectively).

The studies of varying ibandronate treatment regimens not only provide the basis for the development of clinically relevant regimens with this bisphosphonate but also improve our understanding of the relationships between the pharmacodynamics of bisphosphonates given intermittently and antifracture efficacy.

New data with an old bisphosphonate

Clodronate reduces vertebral fracture risk in women with post-menopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study

McCloskey E, Selby P, Davies M, *et al. J Bone Miner Res* 2004; **19**: 728–36

BACKGROUND. The antifracture efficacy of clodronate has never been evaluated by a properly designed clinical trial.

INTERPRETATION. Women with a lumbar spine BMD T-score –2.5 or lower and/or at least one prevalent vertebral fracture were included in a 3-year double-blind, placebo-controlled study. A total of 593 patients were randomized to two strata comprising women with post-menopausal osteoporosis (I, $n = 483$) and secondary osteoporosis (II, $n = 110$). They received clodronate 800 mg daily orally or placebo. All patients received calcium 500 mg daily. Treatment with clodronate was associated with a significant increase in mean spine BMD over 3 years (percentage change from baseline 4.35 vs 0.64% in the placebo group; $P<0.0001$). At the hip, clodronate maintained total BMD, whereas a significant decrease was observed in the placebo group (percentage change from baseline 0.70 vs –3.03% in the placebo group; $P<0.0001$). The changes at the spine and the hip were similar in the two strata. Incident vertebral fractures at 3 years were observed in 63 women in the placebo group and 33 patients in the clodronate group (relative risk 0.54; 95% CI 0.37–0.80; $P = 0.001$) Clodronate significantly reduced vertebral fracture risk in both strata and in women with or without prior vertebral fractures at baseline. Non-vertebral osteoporosis-associated fractures occurred in 21 women in the placebo group and in 14 women treated with clodronate. Treatment was well tolerated with no significant differences in adverse event rates. The authors concluded that clodronate 800 mg daily is a safe and

effective treatment to reduce fracture risk in women with osteoporosis, regardless of causation.

Comment

This is another study that demonstrates the efficacy of a bisphosphonate given daily to patients with osteoporosis. Clodronate does not have a nitrogen atom in its molecule and suppresses osteoclastic resorption by a mechanism different from that of nitrogen-containing bisphosphonates (e.g. alendronate, ibandronate, pamidronate, risedronate and zoledronate). Furthermore, it is less potent, as also evidenced by the effective oral dose used in this trial (800 mg daily versus 150, 10, 5 and 2.5 mg daily for pamidronate, alendronate, risedronate and ibandronate respectively). The changes in BMD were predictable and their magnitude was intermediate to those observed in the studies of raloxifene and alendronate. Clodronate reduced significantly the incidence of vertebral fractures in a population of patients with an overall high risk, but it appeared to be also effective in subgroups with variable fracture risk. Finally, the number of non-vertebral fractures that occurred during the study was too small to draw any conclusions. Despite the recent completion of the study, these data are of historical value as developments in the use of bisphosphonates in osteoporosis have overtaken the concept of the daily administration. The effective oral doses of clodronate in osteoporosis preclude development of regimens with drug-free intervals with this bisphosphonate. The development of parenteral regimens is, however, possible as this bisphosphonate can be administered not only intravenously but also intramuscularly. This needs to be further tested in clinical trials.

Conclusion

Bisphosphonates are the most commonly used treatment of patients with osteoporosis and current research addresses questions related to their optimal clinical use. For example, is it possible to offer a 'treatment holiday' to a patient? Which long-term results obtained with one bisphosphonate can be extrapolated to other members of the class? Will intermittent regimens with newer bisphosphonates increase the likelihood that patients will persist with their treatment? How can bisphosphonates be best used in combination with other anti-osteoporotic treatments, particularly PTH? Answering these questions will help in the individualization of treatment, which should be the primary aim of the management of any chronic disease.

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15

Strontium and parathyroid hormone

JONATHAN ADACHI, ALEXANDRA PAPAIOANNOU

Introduction

The treatment of osteoporosis has focused on antiresorptive therapies, in particular the bisphosphonates and, to a lesser extent, oestrogen and selective oestrogen receptor modulators, calcitonin, calcium and vitamin D. More recently there has been regulatory approval of therapies that are either anabolic, as is the case for teriparatide, or that have mixed antiresorptive and anabolic activity, as is the case for strontium. Pivotal trials have been published for both therapies [1,2].

Strontium

The SOTI (Spinal Osteoporosis Therapeutic Intervention) trial, a pivotal randomized, double-blind, placebo-controlled trial of strontium, has been published and has demonstrated vertebral fracture efficacy [1]. This article was reviewed in the first volume of these reviews. SOTI was the first trial to demonstrate vertebral fracture benefit; a second large trial, TROPOS (Treatment of Peripheral Osteoporosis), confirmed both vertebral fracture benefits and demonstrated non-vertebral and hip fracture efficacy (Reginster *et al.* below). This trial is reviewed in this chapter and provides us with the full breadth of the clinical effects of strontium to date. A second article has been reviewed to help in the understanding of the mechanism by which strontium increases bone strength and thus prevents fractures (Ammann *et al.* below).

Parathyroid hormone

More recent publications providing supportive evidence or a better understanding of the optimal use of these therapies have appeared. For example, concomitant use of parathyroid hormone (PTH) with a bisphosphonate appears to suppress the bone mineral density (BMD) gains seen with PTH alone in both men and women [3,4]. As a result, the concomitant initiation of these therapies is not advised at

present [5]. Perhaps the more relevant question for the practising clinician concerns the use of PTH after antiresorptive therapy. The specific questions addressed by the articles that are reviewed in this chapter are the following: Are there differences in the response to PTH between prior therapy with different antiresorptive treatments (Ettinger *et al.* and Cosman *et al.*)? How important is antiresorptive therapy following PTH treatment (Kurland *et al.* and Black *et al.*)? Does PTH prevent fracture in men as it does in women (Kaufman *et al.*)? Does PTH prevent fractures in those with multiple fractures or in those with severe fractures (Gallagher *et al.*)? When and how much calcium and vitamin D should be given in those on PTH (Licata)?

Strontium ranelate reduces the risk of non-vertebral fractures in post-menopausal women with osteoporosis: TROPOS study

Reginster JY, Seeman E, De Vernejoul MC, *et al. J Clin Endocrinol Metab* 2005; **90**: 2816–22

BACKGROUND. The purpose of reviewing this study is to examine the effects of strontium on non-vertebral fractures. In an earlier study by Meunier *et al.* [1], strontium ranelate was shown to reduce vertebral fracture risk in post-menopausal women with osteoporosis. In a second study, the TROPOS study, strontium was assessed for its efficacy and safety in preventing vertebral and non-vertebral fractures. Strontium ranelate (2 g/day) and placebo were randomly allocated to 5091 post-menopausal women with osteoporosis in a double-blind, placebo-controlled 5-year study with a main statistical analysis over 3 years of treatment. While vertebral fracture efficacy is always of interest, the efficacy of strontium ranelate at non-vertebral sites is of greater interest as it often differentiates between the many different therapies that we have for the treatment of osteoporosis. Non-vertebral fracture efficacy has been demonstrated in this study. All non-vertebral fractures were reduced by 16% ($P = 0.04$), and major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus) by 19% ($P = 0.031$) in strontium ranelate-treated patients compared with placebo. At the request of the European regulatory agency, a high-risk subset of women was examined for hip fracture benefit. Among women at high risk of hip fracture, as defined by age 74 years or older and femoral neck BMD T-score –3 or lower, there was a 36% reduction in hip fractures ($P = 0.046$) (Fig. 15.1). The relative risk of vertebral fractures was reduced by 39% ($P < 0.001$) in the 3640 patients with spinal X-rays and by 45% in the subgroup without prevalent vertebral fracture (Fig. 15.2). Strontium ranelate increased BMD throughout the study, with the following changes at 3 years ($P < 0.001$): +8.2% at the femoral neck and +9.8% for the total hip. The incidence of adverse events was similar in the two groups.

INTERPRETATION. Strontium ranelate reduces the risk of vertebral and non-vertebral fractures. In a high-risk subset it reduces hip fractures. Strontium reduces fracture rates in a variety of subsets of individuals, including the elderly and those without prior vertebral fracture.

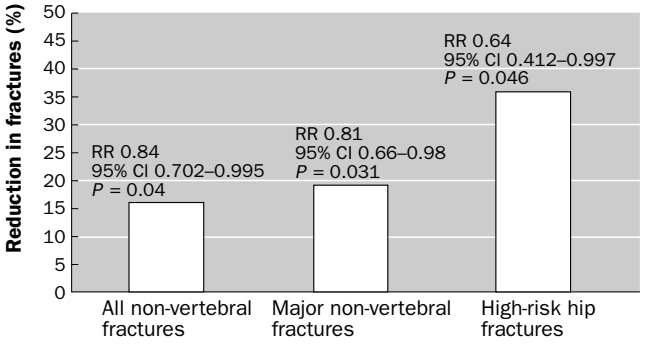

Fig. 15.1 The first column illustrates the risk reduction of 16% for all non-vertebral fractures. The second column represents a 19% risk reduction in major non-vertebral fractures, including hip, wrist, pelvis and sacrum, ribs and sternum, clavicle and humerus. The third column is the risk reduction in hip fractures in the high-risk subset of subjects. Source: Reginster *et al*. (2005).

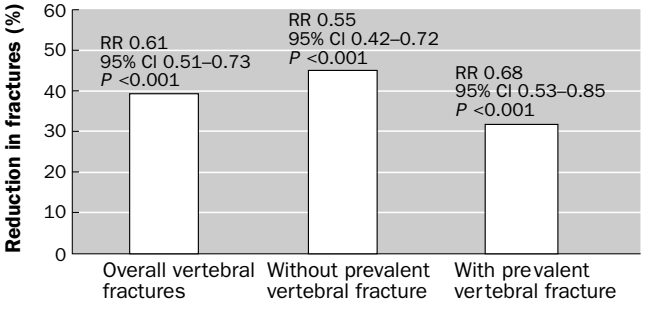

Fig. 15.2 The first column illustrates the overall risk reduction of 39% for vertebral fractures. The second column represents a 45% risk reduction in vertebral fractures in those who did not have a baseline vertebral fracture. The third column shows a 32% risk reduction in vertebral fractures in those without a baseline vertebral fracture. Source: Reginster *et al*. (2005).

Comment

This study shows that strontium ranelate significantly reduces the risk of all non-vertebral fractures and, in a high-risk subgroup, hip fractures over a 3-year period. It confirms that strontium ranelate reduces vertebral fractures. Strontium ranelate offers a safe and effective means of reducing the risk of fracture associated with osteoporosis. It does have side effects, including venous thromboembolism and seizures, that physicians will need to be aware of when treating at-risk populations. It offers another therapy for the treatment of osteoporosis, one that has antiresorptive activity

and possibly anabolic activity. The exact mechanism of action in humans has yet to be established, although safety over 3 years is established. Well-designed Phase 4 studies will help to better define the long-term benefits and risks.

Strontium ranelate improves bone resistance by increasing bone mass and improving architecture in intact female rats

Ammann P, Shen V, Robin B, Mauras Y, Bonjour JP, Rizzoli R. *J Bone Miner Res* 2004; **19**: 2012–20

BACKGROUND. The reason for reviewing this study is to examine the mechanism of action of strontium. Bone strength is said to be the sum of BMD and bone quality. While many have monitored treatment efficacy by measuring changes in BMD, it has recently been shown to account for only a small proportion of the benefit a treatment gives in reducing fractures. As a result, researchers have turned their attention to measurements of bone quality and structure to explain fracture efficacy. Strontium ranelate was tested for its influence on bone quality and quantity in intact female rats. Doses of 0, 225, 450 and 900 mg/kg/day were studied for 2 years. In another experiment, the effects of 625 mg/kg/day were evaluated in intact male and female rats over the same time period. Bone mineral mass and mechanical properties were evaluated at the spine and femur. Bone microarchitecture was evaluated by static histomorphometry at a cortical site, the tibiofibular junction, and at a trabecular site, the tibial metaphysis. Alkaline phosphatase activity and serum levels of insulin-like growth factor-1 (IGF-1) were also assessed.

In female rats treated with strontium ranelate over 2 years, dose-dependent increases in bone strength and bone mass at a predominantly trabecular site (the vertebral body) and at a cortical site (the midshaft femur) were detected without change in stiffness. Dose-dependent increases in bone strontium were seen in the L_4 vertebral body. At higher doses, both sites exhibited an increase in bone size. Similar effects were observed in males at the level of the vertebra. The improvements in mechanical properties were associated with improvements in microarchitecture, as assessed by increases in trabecular and cortical bone volumes and trabecular number and thickness. Total alkaline phosphatase activity and IGF-1 were increased in treated rats; this is compatible with strontium ranelate having bone-forming activity.

INTERPRETATION. Bone size and mass, bone microarchitecture and maximal deformation are important determinants and reflections of bone strength. All were improved in this study.

Comment

Our understanding of the fracture benefits and potential mechanism of action reported in the two large Phase 3 clinical trials may be explained by this study. This animal study provides supportive evidence that strontium ranelate not only increases bone mass but also improves bone architecture without compromising bone stiffness. These bone biopsy studies need to be replicated in humans. This rat

model used high doses of strontium compared with that used in humans. This was necessary in order to obtain blood levels equivalent to those seen in humans. Whether this results in effects of strontium on bone similar to those seen in humans has to be shown.

Summary of the strontium ranelate studies

The prevention of non-vertebral fractures is of primary interest as a means of differentiating among therapies. In particular, hip fracture prevention is very important as hip fracture is a well-recognized cause of morbidity and mortality. It is a fracture that is readily diagnosed and as a result has pharmaco-economic consequences that can be quantified. In the primary analysis of TROPOS, hip fracture efficacy was not demonstrated and as a result the European regulatory agency asked that data also be presented for the subset with established osteoporosis at high risk of fracture. In response to the request, a revised target population for hip fracture prevention was proposed: women older than 74 years and with a femoral BMD T-score below –3. In this subset, there were 32 and 51 hip fractures in strontium ranelate and placebo groups, respectively (relative risk 0.64; 95% CI 0.412–0.997). For vertebral fractures the TROPOS study provided corroboration of the SOTI study. Relative risks of new vertebral fracture in the overall TROPOS population treated with strontium ranelate and for subsets with a prevalent vertebral fracture and without a prevalent vertebral fracture were all clinically and statistically significantly reduced compared with the placebo-treated population.

BMD and bone turnover markers were qualitatively similar in both SOTI and TROPOS. For the reduction of the risk of new vertebral fracture, relevant efficacy has been convincingly shown in patients with and without prevalent vertebral fracture. SOTI provided robust evidence of the efficacy of strontium ranelate 2 g/day in reducing the risk of new vertebral fracture in a population characterized by established post-menopausal osteoporosis and at high risk of recurrent vertebral fracture. The magnitude of the effect appears comparable with that achieved with bisphosphonates in similar populations.

A subset analysis of pooled data from the TROPOS and SOTI treatment trials indicated that strontium ranelate 2 g/day reduces the risk of new vertebral fracture in elderly post-menopausal women with baseline BMD in the osteopenic range, at both the lumbar spine and the femoral neck.

Treatment with strontium ranelate is associated with an increase of approximately 50% in the annual risk of venous thromboembolism, including pulmonary embolus. Reports of some nervous system disorders were more frequent with strontium ranelate than with placebo. Reports of CNS effects, such as mental impairment, disturbed consciousness, memory loss/amnesia and seizures, create some concern. No mechanism has been elucidated. Strontium ranelate therapy is associated with gastrointestinal intolerance, but there are no indications of serious gastrointestinal complications and these problems are considered clinically manageable.

The clinical programme in osteoporosis, especially the contribution of data on the elderly and very elderly, is important. Strontium ranelate has an indication for the treatment of post-menopausal osteoporosis, to reduce the risk of vertebral and hip fractures. For the vertebral fracture indication, the demonstrated effect of strontium ranelate 2 g/day appears comparable with that of bisphosphonates. The *post hoc* analysis of those at high risk of hip fracture is not novel and has regulatory precedent in the licensing of bisphosphonates. Increased risks of venous thromboembolism and nervous system dysfunction have been reported. Despite these adverse events, an acceptable benefit/risk ratio is felt to be present.

Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate

Ettinger B, San Martin J, Crans G, Pavo I. *J Bone Miner Res* 2004; **19**: 745–51

BACKGROUND. This study was chosen for review to examine the effects of prior antiresorptive therapy on the response to teriparatide therapy. Teriparatide has been shown to increase BMD and reduce the risk of fracture in post-menopausal women with osteoporosis. This study investigates the effects of teriparatide on bone turnover markers and bone densitometry after 18 months of treatment in women whose osteoporosis was previously treated with either alendronate or raloxifene. Teriparatide 20 μg daily was administered for 18 months to 59 post-menopausal women, 60–87 years of age, with BMD T-scores of –2.0 or lower who had previously received either alendronate or raloxifene therapy for 18–36 months. All received supplementation with calcium 1000 mg/day and vitamin D 400 IU/day. The primary outcome measure was change in lumbar spine BMD and secondary outcome measures included changes in bone turnover markers, total hip BMD and safety.

As expected, median levels of baseline bone turnover markers in patients who had been receiving alendronate were about one-half of those of patients who had been receiving raloxifene. During teriparatide treatment, bone markers in patients previously receiving alendronate increased later and peaked at about one-third lower levels compared with patients previously receiving raloxifene. During the first 6 months, there were statistically significant ($P<0.05$) group differences in BMD change at the hip: patients previously receiving alendronate showed a decline of 1.8% whereas patients previously receiving raloxifene showed an increase of 0.5%; at the spine, BMD showed an increase of 0.5% in patients previously treated with alendronate and an increase of 5.2% in those previously treated with raloxifene. The positive slopes in hip and lumbar spine BMD were similar in the two groups between 6 and 18 months. After 18 months, mean lumbar spine BMD had increased by 10.2% in patients who had been treated with raloxifene previously compared with 4.1% in those who had been treated with alendronate ($P<0.05$). Furthermore, at 18 months the mean total hip BMD had increased significantly, by 1.8% ($P<0.05$), in patients previously treated with raloxifene but was not different from baseline in patients who had been treated with alendronate. The difference between the groups previously receiving alendronate and raloxifene was not significant.

INTERPRETATION. Treatment with teriparatide resulted in an increase in bone turnover and an increase in BMD in patients who had undergone prior treatment with raloxifene and alendronate. Prior therapy with alendronate blunted the BMD treatment response seen historically with teriparatide in treatment-naive patients. In contrast, prior raloxifene treatment was followed by the expected increase in BMD seen in treatment-naive individuals; the increase was more than double that seen in the group previously treated with alendronate.

Comment

This study suggests that there are differences in response to teriparatide depending upon on prior antiresorptive therapy. However, it is important to note that, based on historical observations, the response in raloxifene-treated individuals is as one might expect for a treatment-naive population. The response with prior alendronate is not as great but it is still better than one might expect from ongoing alendronate therapy. Whether these differences in responsiveness result in differences in long-term fracture reduction remains to be seen.

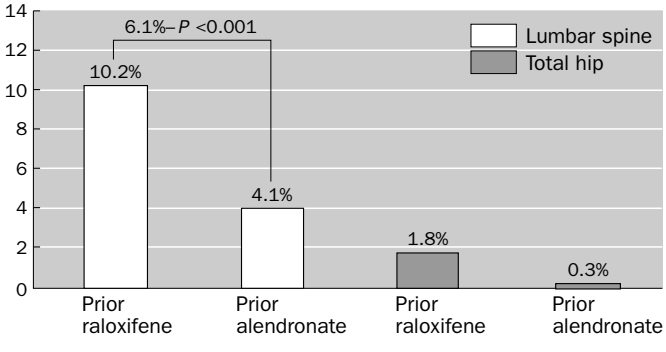

Fig. 15.3 Changes in lumbar spine and hip BMD in response to teriparatide therapy, compared with baseline, in individuals who had previously been treated with raloxifene. Source: Ettinger *et al*. (2004).

Daily and cyclic parathyroid hormone in women receiving alendronate

Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. *N Engl J Med* 2005; **353**: 566–75

BACKGROUND. This is an interesting study that examines the effects of daily and cyclic teriparatide therapy in women on long-term alendronate therapy. It was also chosen to demonstrate the effects of teriparatide in those receiving alendronate concomitantly. Patients with osteoporosis receiving long-term alendronate treatment have a response to teriparatide treatment, and the authors assessed whether short,

3-month cycles of teriparatide therapy could be as effective as daily administration. They randomly assigned 126 women with osteoporosis who had been taking alendronate for at least 1 year to continued alendronate plus teriparatide subcutaneously daily, continued alendronate plus teriparatide subcutaneously daily for three 3-month cycles alternating with 3-month periods without teriparatide, or alendronate alone for 15 months. In both teriparatide groups, bone formation indexes rose swiftly. Among the women who were receiving cyclic teriparatide, bone formation declined during cycles without teriparatide and increased again during cycles with teriparatide. Bone resorption increased in both teriparatide groups but increased progressively more in the daily treatment group than in the cyclic therapy group. BMD of the spine rose by 6.1% in the daily treatment group and 5.4% in the cyclic therapy group (P <0.001 for each teriparatide group compared with the alendronate group). There were no significant differences between the teriparatide groups. One woman in the daily treatment group, two in the cyclic therapy group and four in the alendronate group had new or worsening vertebral deformities.

INTERPRETATION. This study suggests that a regimen of 3-month cycles of teriparatide alternating with 3-month cycles without teriparatide causes the early phase of action of teriparatide, which is characterized by pure stimulation of bone formation, to be dissociated from the later phase—the activation of bone remodelling. The early phase may be more important to the increase in spinal BMD. In patients with persistent osteoporosis after prior alendronate treatment, both daily treatment and cyclic treatment with teriparatide increase spinal BMD.

Comment

This study is of particular interest. Today, most patients with osteoporosis who are on therapy are on an antiresorptive therapy with a bisphosphonate. Many wonder if the effects of PTH will be abrogated in those on concurrent alendronate therapy. This study suggests that the addition of PTH in those on established alendronate therapy has therapeutic benefit. This is very different from the results seen in those initiating concomitant PTH and alendronate therapy, in whom the combination of PTH and alendronate does not seem to bring any benefit beyond PTH alone. It also suggests that intermittent PTH may have a role in the therapy of those with osteoporosis.

The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone(1–34)]

Kurland E, Heller SL, Diamond B, McMahon DJ, Cosman F, Bilezikian JP. *Osteoporos Int* 2004; **15**: 992–7

BACKGROUND. Important questions remain regarding the management strategy beyond the recommended 18- to 24-month course of teriparatide treatment. This study examines this question. Twenty-one men were followed for up to 2 years after discontinuing teriparatide. Twelve men (57%) chose treatment with bisphosphonate

immediately after teriparatide withdrawal, while nine (43%) opted for no pharmacological agent. At the end of 1 year lumbar spine bone density had increased by an additional 5.1 ± 1.0% in the bisphosphonate group, whereas it had declined by 3.7 ± 1.7% in those on no medication (P<0.002). In six men who delayed initiation of bisphosphonate until 1 year after teriparatide withdrawal, their subsequent gain in the second year (2.6 ± 1.7%) still placed them below the peak gains they achieved on teriparatide. In contrast, the twelve men who began bisphosphonates immediately and continued treatment for the entire 2-year post-PTH period had continued gains at the lumbar spine (8.9 ± 1.5%) above their post-PTH values (P = 0.002). For the 4-year period, including 2 years of teriparatide and 2 years of bisphosphonate, the total gain at the lumbar spine was 23.6 ± 2.9%. Men who received bisphosphonate in only the second year after teriparatide had a cumulative gain of 11.1 ± 3.4%. Three men who did not receive any bisphosphonate at any time during the post-PTH period had a cumulative gain of only 5.5 ± 3.7%.

INTERPRETATION. These findings suggest that the use of bisphosphonates following teriparatide is an important component of any strategy using this anabolic drug for osteoporosis in men. The immediate use of bisphosphonates after teriparatide withdrawal may help to optimize gains in bone density at the lumbar spine.

Comment

While the numbers of patients are small, the findings are similar to those seen in post-menopausal women. Given these findings, it is reasonable to offer bisphosphonate therapy immediately after teriparatide withdrawal. Indeed, the magnitude of the increase in BMD and presumed improvement in structural parameters may be interpreted as normalizing osteoporotic bone. Whether this results in a greater reduction in fractures compared with those who are not treated with a bisphosphonate remains to be demonstrated. However, if the loss of bone mass while off bisphosphonate therapy is associated with an increased risk of fractures, it would follow that an increase in bone mass on bisphosphonate therapy following teriparatide would be associated with a fracture benefit.

One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis

Black DM, Bilezikian JP, Ensrud KE, *et al. N Engl J Med* 2005; **353**: 555–65

BACKGROUND. This study was chosen as it examined the effects of antiresorptive therapy following PTH (1–84). Since the use of PTH as a treatment for osteoporosis is limited to 2 years or less, the question of whether antiresorptive therapy should follow PTH therapy is important. Previously reported results after the first year of this randomized trial compared the use of full-length PTH (1–84) alone, alendronate alone, and or both in combination. In the continuation of this trial, it was asked whether antiresorptive therapy is required to maintain gains in BMD after 1 year of therapy with PTH (1–84). Women who had received PTH (1–84) monotherapy (100 μg daily) in year 1 were randomly reassigned to one additional year with either placebo or alendronate.

Subjects who had received combination therapy in year 1 received alendronate in year 2; those who had received alendronate monotherapy in year 1 continued with alendronate in year 2. BMD at the spine and hip was assessed with the use of dual energy X-ray absorptiometry and quantitative computed tomography (CT). Over 2 years, alendronate therapy after PTH therapy led to significant increases in BMD in comparison with the results for placebo after PTH therapy. Measuring BMD in trabecular bone at the spine using quantitative CT, there was an increase of 31% in the PTH–alendronate group compared with 14% in the PTH–placebo group. During year 2, subjects receiving placebo lost substantial BMD. After 1 year of PTH (1–84), densitometric gains appeared to have been maintained or increased with alendronate but lost if PTH was not followed by an antiresorptive agent.

INTERPRETATION. These results have clinical implications for therapeutic choices after the discontinuation of PTH. Indeed, in those treated with PTH subsequent alendronate results in a significant and substantive increase in BMD when compared with PTH-treated individuals who receive placebo following their course of PTH therapy.

Comment

This study provides further evidence that antiresorptive therapy is important in maintaining and even increasing BMD in PTH-treated individuals. The average increase in BMD may take a person with a T-score of –3 to –3.5 in the spine to near normal BMD ranges. The hope would be that bone structure is improved to a similar extent. The increases in BMD seen in this trial were large and offer the hope that sequential therapy with an anabolic such as PTH and an antiresorptive therapy may one day cure osteoporosis.

Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy

Kaufman J-M, Orwoll E, Goemaere S, *et al*. *Osteoporos Int* 2005; **16**: 510–16

BACKGROUND. Teriparatide increases BMD in men and women, and reduces the risk of fractures in women with osteoporosis. Fracture efficacy has not yet been confirmed in men. In addition, there is limited information on the effect of withdrawal of teriparatide. BMD and vertebral fracture incidence are reported during a 42-month observation period, from the baseline of the previously reported treatment study in men to 30 months of post-treatment follow-up. Three hundred and fifty-five men who were treated with placebo or 20 or 40 μg of teriparatide participated in the follow-up study. BMD gradually decreased following discontinuation of teriparatide therapy; however, it remained significantly higher than baseline after 30 months of follow-up ($P<0.001$). Antiresorptive treatment prevented the decline and tended to further increase BMD. Lateral thoracic and lumbar X-rays obtained at baseline and 18 months after discontinuation of teriparatide were available for 279 men. Of these men, 11.7% assigned to placebo, 5.4% treated with teriparatide 20 μg and 6.0% treated with

teriparatide 40 μg had an incident vertebral fracture. In the combined teriparatide-treated groups versus placebo, the risk of vertebral fracture was reduced by 51% ($P = 0.07$). The incidence of moderate or severe fractures was significantly reduced, by 83% ($P = 0.01$). In conclusion, men who received teriparatide and who may have received follow-up antiresorptive therapy had a decreased risk of moderate and severe vertebral fractures.

INTERPRETATION. Teriparatide results in large increases in BMD. Withdrawal of therapy results in a gradual decline in BMD; however, in this study BMD remained significantly higher than baseline after 30 months of follow-up. As in a previous trial in post-menopausal women with osteoporosis, antiresorptive therapy prevented declines in BMD and tended to result in further increases. While the overall reduction in vertebral fractures was not statistically significant, the reduction seen is clinically relevant. A clinically relevant and statistically significant reduction in moderate and severe vertebral fractures was seen.

Comment

This study provides further evidence that teriparatide increases BMD and reduces vertebral fractures. It confirms the benefits of antiresorptive therapy following teriparatide in increasing BMD.

Teriparatide prevents the fracture risk associated with increasing number and severity of osteoporotic fractures

Gallagher JC, Genant HK, Crans GC, Vargas SJ, Krege JH. *J Clin Endocrinol Metab* 2005; **90**: 1583–7

BACKGROUND. This study was chosen to highlight the influence of the severity and number of fractures on the risk of further fractures. Perhaps the greatest risk for fracturing is having had a previous fracture. Indeed, there is evidence that the severity of a prevalent vertebral fracture is associated with an increased risk of both vertebral and non-vertebral fracture. In addition, individuals with greater numbers of fractures are more likely to have an incident fracture. In this study, the relationship between prior fractures and the risk of new fractures was evaluated in 931 post-menopausal women with prior vertebral fractures who were randomized to daily placebo or teriparatide 20 μg. The median observation period was 21 months. Among placebo patients with one, two or three or more prior vertebral fractures, 7, 16 and 23%, respectively, developed vertebral fractures ($P < 0.001$), with 3, 9 and 17% developing moderate or severe vertebral fractures ($P < 0.001$). Among placebo patients with mild, moderate or severe prior vertebral fractures, 10, 13 and 28%, respectively, developed vertebral fractures ($P < 0.001$), with 4, 8 and 23% developing moderate or severe vertebral fractures ($P < 0.001$). Among placebo patients with no, one or two or more prior non-vertebral fragility fractures, 4, 8 and 18%, respectively, developed non-vertebral fragility fractures ($P < 0.001$). Among teriparatide patients having a greater number/severity of prior vertebral fractures or a greater number of prior non-vertebral fractures, there was no significant increase in vertebral or non-vertebral fracture risk, respectively.

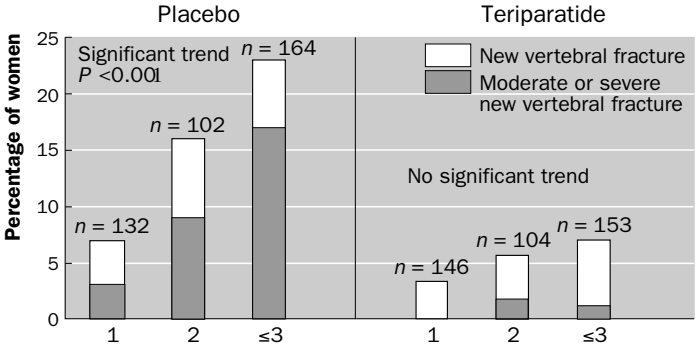

Fig. 15.4 The number of prevalent vertebral fractures increases the risk of incident vertebral fractures. This trend is no longer apparent with teriparatide treatment. Source: Gallagher *et al*. (2005).

INTERPRETATION. While a low baseline BMD measurement is a well-established risk factor for incident fracture, this study demonstrates the importance of the number of both vertebral and non-vertebral fractures and the degree of vertebral fracture deformity in the determination of fracture risk. This study demonstrates that the number and severity of prior vertebral fractures independently predict the risk of new vertebral fractures, and that the number of prior non-vertebral fractures predicts the risk of new non-vertebral fractures. Of further importance, teriparatide significantly reduces the increased risk of fracture seen in these individuals.

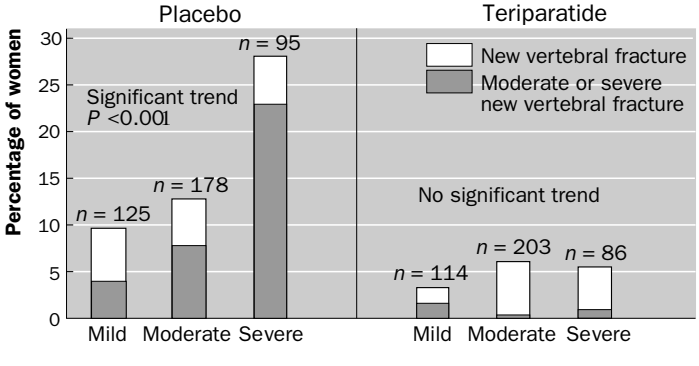

Fig. 15.5 The severity of prevalent vertebral fracture is associated with an increased risk of incident vertebral fracture. This increased risk is not seen with teriparatide. Source: Gallagher *et al*. (2005).

Comment

Fracture risk increases with both the number and severity of vertebral fractures and the number of non-vertebral fractures. These are important risk factors to bear in mind when making decisions about fracture risk and the urgency of therapy. Teriparatide prevents fractures in these high-risk individuals.

Osteoporosis, teriparatide, and dosing of calcium and vitamin D

Licata AA. *N Engl J Med* 2005; **352**: 1930–1

BACKGROUND. Teriparatide represents a new class of therapeutic options for osteoporosis. Since it is a PTH derivative, many practitioners are concerned about hypercalcaemia, which is seen in hyperparathyroidism, and about how best to monitor their patients receiving this therapy. A major study of teriparatide stated that transient and chronic hypercalcaemias were rare, that changes in vitamin D metabolism occurred, and that manipulation of mineral or drug doses helped lower serum calcium levels.

Dr Licata reported that in his initial use of this drug persistent hypercalcaemia developed in three patients. This finding prompted closer surveillance of a subsequent group of twelve treated patients. All twelve patients took extra elemental calcium (mean [± SD] daily dose, 1100 mg) and ten of them took vitamin D (mean daily dose, 355 ± 200 IU). At baseline and after receiving treatment (i.e. 1–3 months into therapy), serum levels of calcium, intact PTH, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were checked more than 6 h after injection of the teriparatide, since most patients were given the drug at bedtime. Levels of intact PTH decreased and those of 25-hydroxyvitamin D showed a downward trend. Levels of 1,25-dihydroxyvitamin D and total serum calcium increased. In two-thirds of the measurements, the values for 1,25-dihydroxyvitamin D level exceeded the 95% confidence limit (mean, 98.9 ± 26.4 pg/ml); in the remaining levels, the values were below the confidence limit (36.5 ± 6.6 pg/ml). The change in serum calcium levels tended to correlate positively with 1,25-dihydroxyvitamin D levels (Spearman's *r* = 0.65; one-tailed *P*-value 0.08) and inversely with 25-hydroxyvitamin D (Spearman's *r* = 0.66; one-tailed *P*-value 0.054). The substantial rise in serum 1,25-dihydroxy-vitamin D levels in the presence of decreased levels of intact PTH and increased levels of calcium suggested that teriparatide affected the serum concentration of the vitamin even in the presence of physiological signals that normally decrease its concentration.

INTERPRETATION. From the clinical perspective, the guidelines of the National Osteoporosis Foundation and other medical specialty guidelines for calcium and vitamin D use may suggest doses that are too high for some patients taking this drug. When teriparatide therapy is begun, it is suggested that daily elemental calcium be maintained at 1000 mg or less, to keep the level of serum calcium below 10 mg/dl. Supplementary vitamin D is not given if the basal level is greater than 20 ng/ml. In the absence of directives for the use of vitamins and minerals in the treatment of patients taking teriparatide, this approach may be useful for practitioners as a way to prevent hypercalcaemia in clinical practice.

Comment

This letter to the editor provides some practical advice to those who are interested in initiating teriparatide therapy. It should be noted that the number of individuals is small and further observations of this nature would be helpful in confirming these findings.

Summary of the PTH studies

Parathyroid hormone is the most potent anabolic therapy that we have for the treatment of osteoporosis. While fracture reduction is similar to that given by current antiresorptive therapy, the mechanism of action is very different, with improvement in both bone mass and bone architecture.

Pivotal trials with PTH demonstrate reductions in the risk of vertebral and nonvertebral fracture relative to placebo in women with severe osteoporosis. In men who may or may not have had subsequent antiresorptive therapy, PTH decreased the risk of moderate and severe vertebral fractures. Prior therapy with a bisphosphonate may blunt the BMD response normally seen in treatment-naive patients. Changes in the volumetric density of trabecular bone, the cortical volume at the hip and levels of markers of bone turnover suggest that the concurrent use of a bisphosphonate may reduce the anabolic effects of PTH in those initiating osteoporosis with both a bisphosphonate and PTH. Prior long-term use of a bisphosphonate may or may not have an effect on BMD in those initiating PTH. Indeed, a more recent study in those on prior alendronate suggests that both continuous and intermittent PTH significantly increase BMD. Therapy following oestrogen or raloxifene therapy does not seem to blunt the response. Longer-term studies of fractures are needed to determine whether and how antiresorptive drugs can be optimally used in conjunction with PTH therapy.

Therapy with a bisphosphonate immediately following completion of PTH therapy is recommended. This strategy appears to result in the greatest overall gains in bone density and maintenance of the improved structure seen with PTH therapy. Theoretically, this should result in a long-term reduction in fractures greater than that seen with antiresorptive therapy alone. The amount of calcium and vitamin D may need to be limited compared with those who are not treated with PTH.

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Part IV

Therapeutic issues

16

How to identify therapeutic targets—from the bench to the bedside

JONATHAN TOBIAS

Introduction

This chapter aims to illustrate the different types of approach taken to identify therapeutic targets for osteoporosis, by reviewing a selection of recent papers in this area. One of the most important features is whether the target in question is involved in regulating osteoblast or osteoclast activity, the cells responsible for bone formation and resorption respectively. Historically, drugs which inhibit osteoclast activity and hence suppress bone resorption, such as the bisphosphonates, have provided the mainstay of therapy for osteoporosis. However, with the recent advent of anabolic therapies such as teriparatide [1], it is now clear that stimulation of osteoblast activity, leading to enhanced bone formation, represents a useful alternative approach which may confer greater efficacy.

Drug targets in osteoporosis generally consist of mechanisms which play a major physiological role in bone cell function. In particular, targets are generally selected on the basis of non-redundancy; i.e. alterations in their activity are not replaced by compensatory changes in other mechanisms. One strategy for identifying novel non-redundant mechanisms is to define genetic mutations responsible for familial skeletal disorders. As discussed in the previous issue, these include sclerosing dysplasias such as familial high bone mass caused by activating mutations in low-density lipoprotein receptor-related protein (LRP)-5, and sclerosteosis caused by loss-of-function mutations in sclerostin [2]. Other examples include the osteopetroses, in which excessive accumulation of trabecular bone occurs, leading to suppressed bone marrow function. The latter disorders generally result from mutations that inhibit osteoclast function, such as pycnodysostosis caused by cathepsin K deficiency [3]. Non-redundant pathways involved in regulating osteoblast or osteoclast activity, which are of potential interest as a drug target in osteoporosis, can also be demonstrated in animal models. In particular, the finding that transgenic over- or under-expression of a gene of interest in mice leads to a skeletal

phenotype as a consequence of altered levels of bone formation or resorption generally implies that the gene in question is part of a non-redundant pathway.

Another important consideration is whether the pathway in question is widely involved in different biological systems, or largely restricted to the skeleton. As discussed below, several extracellular pathways have been identified which appear to have a relatively specific role in regulating bone cell function, and as such represent potential drug targets for osteoporosis. Distinct intracellular pathways have also been found to play a critical role in regulating bone cell function. Although several of these are relatively generic, suggesting that their targeting may cause unwanted extraskeletal side effects, experience with bisphosphonates suggests that this limitation can be overcome by the use of pharmacological agents whose tissue distribution is restricted to bone.

A further issue is how amenable the potential drug target is likely to be to pharmacological manipulation. In the case of teriparatide therapy, the G-protein-coupled cell membrane PTHR1 receptor, which mediates the biological actions of parathyroid hormone, is targeted by administration of recombinant peptide sharing the first 34 amino acids of parathyroid hormone. As described below, a variety of other extracellular targets have since been identified which are likely to be amenable to manipulation using a similar approach. Alternatively, as also illustrated below, several programmes are based on drug targets for osteoporosis that are likely to be modifiable using small molecules. This offers advantages over recombinant therapy in terms of cost of manufacture and ease of administration.

Extracellular targets

Several extracellular pathways have been identified which are thought to play an important role in regulating bone cell function but to lack important effects elsewhere, and which therefore represent potentially useful therapeutic targets for osteoporosis. As described below, these include regulatory pathways such as LRP-5/Wnt and RANK (receptor activator of NF-κB)/RANKL (receptor activator of NF-κB ligand), which play a critical role in regulating osteoblast and osteoclast function respectively; osteoclastic enzymes such as cathepsin K, which are required for bone resorption; and integrin antagonists, which inhibit interactions between osteoclasts and the extracellular matrix.

LRP-5/Wnt pathway

As discussed above, reports that LRP-5 gene mutations affect bone density suggest that this protein forms part of a critical pathway involved in regulating osteoblast function, which may prove a useful drug target for osteoporosis. LRP-5 forms part of a cell membrane receptor which also includes the frizzled G-protein-coupled receptor. Activation of this co-receptor complex stimulates the intracellular canonical pathway, leading to stabilization of β-catenin, which then translocates into the nucleus, where it binds to and activates a wide range of transcription factors, ultimately leading to

enhanced osteoblastic activity. Extracellular Wnt proteins are thought to be the primary endogenous ligand for this LRP-5–frizzled receptor complex; although previous studies have demonstrated the importance of Wnt signalling in skeletal development, it is only recently that the importance of this pathway in regulating osteoblast function and bone formation in the adult has been realized.

The Wnt antagonist secreted frizzled-related protein-1 is a negative regulator of trabecular bone formation in adult mice

Bodine PV, Zhao W, Kharode YP, *et al. Mol Endocrinol* 2004; **18**: 1222–37

BACKGROUND. Many extracellular and intracellular proteins control Wnt signalling. The former include secreted frizzled-related proteins (sFRPs), which represent soluble forms of the frizzled receptor that bind Wnt proteins, thereby preventing them from binding to and activating LRP-5–frizzled cell membrane receptor complexes. Though several forms of sFRP exist, preliminary studies have suggested that sFRP-1 plays a specific role in regulating Wnt signalling in osteoblasts. In order to explore this possibility, Bodine *et al.* determined whether sFRP-1 regulates osteoblast function and bone formation at the level of the whole animal, by investigating the effect of knocking out the *sFRP-1* gene.

INTERPRETATION. As expected, *sFRP-1*$^{-/-}$ knockout mice had undetectable levels of SFRP-1 in bone and other tissues, while other sFRPs, such as sFRP-2 and -4, were still present. Despite the fact that sFRP-1 is expressed in many different tissues, *sFRP-1*$^{-/-}$ mice appeared normal; fertility and viability were unaffected, as were the gross appearance and the weights of the total body and most organs. In addition, the overall skeletal morphology of *sFRP-1*$^{-/-}$ mice was normal, as was cortical bone mass. Trabecular bone mineral density (BMD) of the distal femur, as measured by peripheral quantitative computed tomography (pQCT), was also similar in the two groups of animals at age 13 weeks. However, between 28 and 52 weeks of age, trabecular BMD showed a significant increase in *sFRP-1*$^{-/-}$ mice relative to wild-type *sFRP-1*$^{+/+}$ littermate controls, particularly in females. Histological analysis at the proximal femur confirmed that this gain in BMD was secondary to increased osteoblast activity, as measured by calcein double labelling (Fig. 16.1). In terms of the mechanisms involved in this effect, the proportion of osteoblasts and osteocytes undergoing apoptosis (programmed cell death) was reduced by approximately 50% in *sFRP-1*$^{-/-}$ mice. In addition, the rate of osteoblastic differentiation was increased approximately 4-fold in bone marrow cultures obtained from *sFRP-1*$^{-/-}$ mice compared with *sFRP-1*$^{+/+}$ littermates.

Comment

These findings demonstrate that loss of sFRP-1 function results in increased osteoblast activity within trabecular bone at the level of the whole animal. This effect appears to reflect two distinct actions: an increased rate of osteoblast formation and a reduced rate of osteoblast programmed cell death. Since no other changes were observed, these results suggest that sFRP-1 has a bone-specific

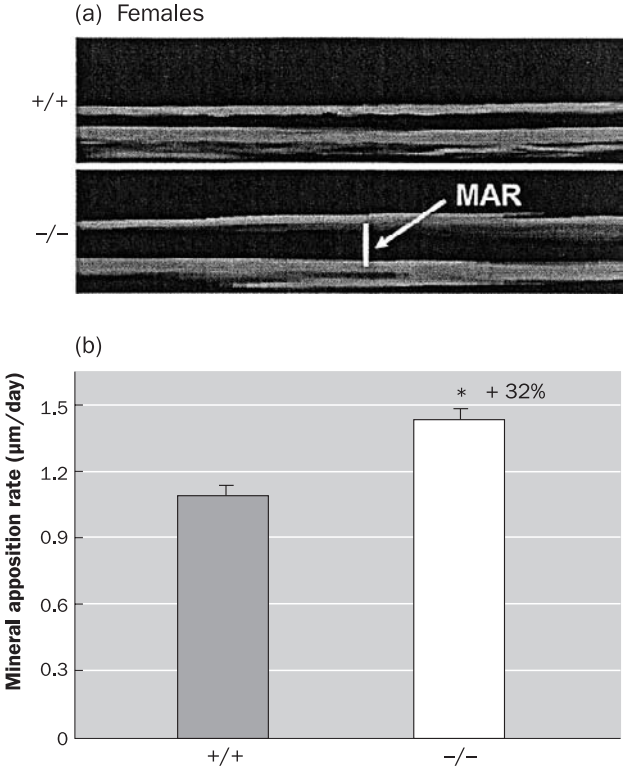

Fig. 16.1 Deletion of sFRP-1 increases femoral trabecular bone formation. This was assessed by measuring mineral appositional rate (MAR), which was derived from the distance between calcein labels deposited at the formation front after serial calcein injections. (a) Double calcein labelling of distal femurs from control (+/+) and knockout (–/–) 35-week-old females. (b) Quantification of double calcein labelling results demonstrates an increase in trabecular bone MAR in sFRP-1 knockout females compared with controls. Results are presented as mean ± SEM. $*P<0.001$ versus controls. Source: Bodine *et al.* (2004).

function, and thus represents a suitable drug target for therapies for osteoporosis. Furthermore, the fact that sFRP-1 is an extracellular protein may make it more amenable to pharmacological manipulation by orally active small molecules compared with other components of the Wnt signalling pathway, such as the LRP-5–frizzled cell membrane receptor complex or the canonical intracellular pathway. In terms of possible disadvantages, sFRP-1 exerted relatively little influence on cortical bone, which contrasts with the effects of LRP-5 activation since LRP-5 also acts to increase cortical thickness [4]. Therefore, though sFRP-1 represents a promising drug target for anabolic therapies for osteoporosis, a

potential limitation is that this approach is unlikely to exploit the stimulatory effect of Wnt signalling on cortical as well as trabecular bone.

RANK/RANKL pathway

RANKL is well known to play an important role in regulating osteoclast activity, and has been implicated in the pathogenesis of many diseases associated with increased bone resorption, including osteoporosis. RANKL consists of an extracellular protein which stimulates osteoclast function by binding to RANK, a cell surface receptor expressed by osteoclasts and osteoclast precursors. Following its discovery, it was recognized that the RANKL pathway represents a useful drug target for new antiresorptive therapies for osteoporosis.

A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in post-menopausal women

Bekker PJ, Holloway DL, Rasmussen AS, *et al. J Bone Miner Res* 2004; **19**: 1059–66

BACKGROUND. One of the initial approaches to targeting the RANK/RANKL pathway pharmacologically was to administer osteoprotegerin, which is a soluble form of RANK that acts as an endogenous extracellular inhibitor of RANKL signalling. However, although osteoprotegerin was highly effective in suppressing bone resorption |5|, it was reported to induce an immune response in one subject. Therefore, an alternative approach to targeting this pathway was developed using AMG 162, a human monoclonal antibody to RANKL, the effects of which on bone resorption were evaluated in 49 post-menopausal women randomized to receive either a single injection of placebo or different doses of AMG 162.

INTERPRETATION. A single subcutaneous injection of AMG 162 led to a dose-dependent decrease in bone resorption, as assessed by urinary excretion of the resorption marker NTX (N-terminal cross-linking telopeptide of bone collagen) (Fig. 16.2). Relatively marked inhibition of bone resorption was observed, which in the case of the maximal dose tested (3.0 mg/kg) consisted of a decrease in urinary NTX of 84% after 3 months. Bone resorption following a single injection remained suppressed for a period ranging from 4 to 9 months according to dose. Significant decreases were also seen in serum markers of bone resorption (NTX) and bone formation (alkaline phosphatase), although their magnitude was smaller than those in urinary NTX. No cases of antibody formation against AMG162 were observed. Pharmacokinetic studies revealed that a single injection of AMG162 led to a prolonged elevation in serum level, the concentration profile of which closely mirrored the suppression of bone resorption as reflected by urinary NTX levels.

Comment

This study demonstrated that AMG 162 causes marked suppression of bone resorption, which if anything was of greater magnitude than that seen after

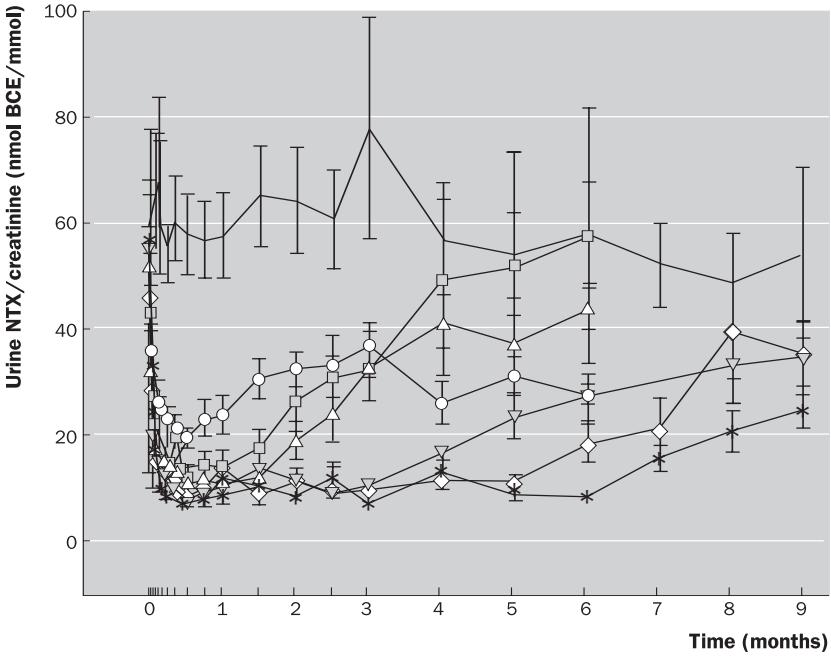

Fig. 16.2 The effect of AMG 162 treatment on bone resorption as reflected by changes in second morning void urinary NTX/creatinine. Data are mean and SEM. Placebo, *no symbol*; 0.01 mg/kg AMG, *open circle*; 0.03 mg/kg AMG 162, *open square*; 0.1 mg/kg AMG 162, *open triangle*; 0.3 mg/kg AMG 172, *inverted open triangle*; 1.0 mg/kg AMG 162, *diamond*; 3.0 mg/kg AMG 162, *asterisk*. Source: Bekker *et al*. (2004).

treatment with bisphosphonates. In the light of this finding, AMG 162 would appear to have strong potential as a treatment not only for osteoporosis, but also for other conditions in which bone loss occurs secondary to elevated bone resorption. Since no patient was found to develop antibodies against AMG 162, this approach to targeting the RANKL pathway would appear to be safer than the administration of osteoprotegerin. In addition, the authors point out that even if antibodies to AMG 162 were to develop, since this is structurally very different to osteoprotegerin, these would not be expected to cross-react with endogenous osteoprotegerin. Another potential risk with targeting RANKL is that RANK is also expressed by a subset of lymphocytes, and partial inhibition of early T- and B-lymphocyte development has previously been observed in RANKL-deficient mice. However, in the present study no clinically significant effect of AMG 162 on lymphocyte counts was observed.

Cathepsin K

Cathepsin K is a cysteine proteinase enzyme primarily expressed by osteoclasts during bone resorption. That cathepsin K is an essential requirement for bone resorption was demonstrated by the observation that pycnodysostosis, a rare genetic disorder associated with osteopetrosis, results from mutation of the cathepsin K gene [3].

Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption *in vivo* in a non-human primate

Stroup GB, Lark MW, Veber DF, *et al. J Bone Miner Res* 2001; **16**: 1739–46

BACKGROUND. On the basis that these findings suggested that cathepsin K is a potential drug target for osteoporosis, a small-molecule inhibitor of human cathepsin K, SB-357114, was developed which potently and selectively inhibits this enzyme. The study by Stroup *et al.* tested the ability of SB-357114 to inhibit bone loss in a non-human primate model of post-menopausal bone loss.

INTERPRETATION. In initial *in vitro* studies, SB-357114 was found to cause dose-dependent suppression of cathepsin K activity and of the bone-resorptive activity of isolated human osteoclasts. Subsequently, SB-357114 was administered by daily subcutaneous injection for 5 days in a non-human primate model of post-menopausal osteoporosis, consisting of cynomolgus monkeys rendered oestrogen-deficient by the administration of a gonadotrophin-releasing hormone agonist. Over the period of administration, a significant decrease in bone resorption, as reflected by serum levels of NTX and CTX (C-terminal cross-linking telopeptide of bone collagen), was seen (Fig. 16.3).

Comment

This study demonstrates that SB-357114 has significant *in vivo* antiresorptive activity in a non-human primate animal model. Since cathepsin K is identical in primates and humans, this compound is predicted to exert a similar antiresorptive action in humans. In the absence of any clinical data, the safety and side effect profile of this agent is currently unclear. One potential concern with this agent is the fact that SB-357114 also inhibits cathepsin L, the absence of which in knockout mice has been reported to cause hair loss [6]. Another limitation is that, although significant antiresorptive activity was observed, the extent of resorption suppression may not be as great as that engendered by other compounds in development, such as AMG 162, described above.

Integrin antagonists

Binding of bone cells to the extracellular matrix is an essential requirement for processes such as osteoclastic bone resorption. Of the extracellular proteins involved in cell adhesion, the most important are proteins such as osteopontin,

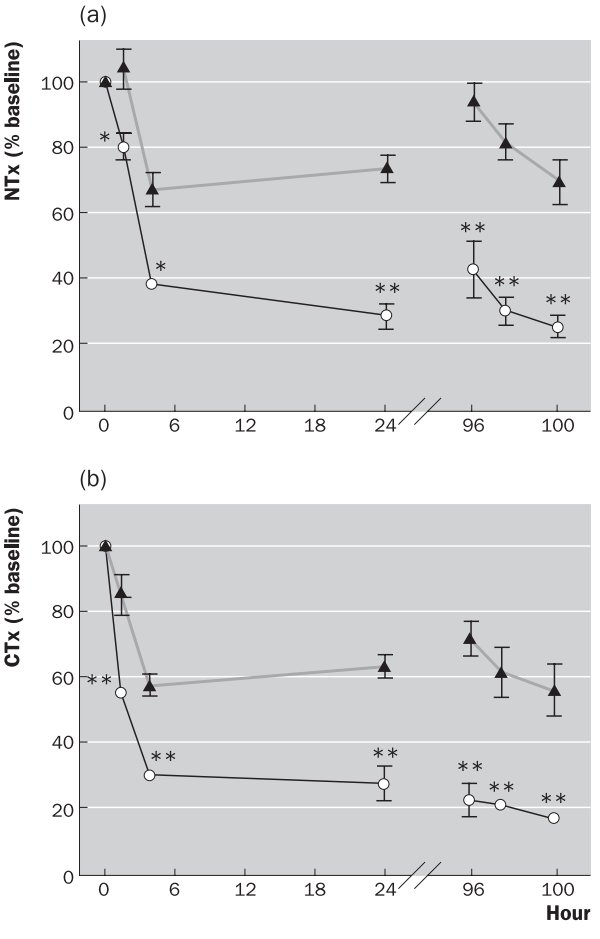

Fig. 16.3 SB-357114 reduces bone resorption in medically ovariectomized monkeys, as reflected by serum (a) NTX and (b) CTX. Data are mean and SEM. *Triangle*, vehicle treatment; *circle*, SB-357114. $*P<0.05$; $**P<0.01$. Source: Stroup *et al.* (2001).

which contain the arginine–glycine–aspartic acid (RGD) sequence. This sequence mediates binding between the bone surface and cells such as osteoclasts via transmembrane adhesion receptors known as integrins, which are expressed on the surface of many different cell types. The most abundant integrin in osteoclasts is $\alpha_v\beta_3$, the loss of which leads to osteosclerosis in animal models as a consequence of defective osteoclast activity [7].

Effect of L-000845704, an alphaVbeta3 integrin antagonist, on markers of bone turnover and bone mineral density in post-menopausal osteoporotic women

Murphy MG, Cerchio K, Stoch SA, Gottesdiener K, Wu M, Recker R; L-000845704 Study Group. *J Clin Endocrinol Metab* 2005; **90**: 2022–8

BACKGROUND. Since integrin-dependent osteoclast attachment to the extracellular matrix appears to play an essential role in osteoclastic bone resorption, there has been considerable interest in examining whether this pathway represents a useful therapeutic target for osteoporosis. Support for this concept has been provided by animal studies in which $\alpha_v\beta_3$ antibodies, echistatin (an RGD-containing peptide) and orally active RGD inhibitors were found to inhibit bone resorption without significant adverse effects. The study by Murphy *et al.* examined whether L-000845704, an orally active potent inhibitor of $\alpha_v\beta_3$ integrin, is effective in reducing bone resorption and increasing BMD in patients with post-menopausal osteoporosis (as defined by a lumbar or femoral neck T-score below –2). Two hundred and twenty-seven women were randomized to receive 12 months of treatment with placebo, L-000845704 100 mg daily, L-000845704 400 mg daily, or L-000845704 200 mg twice daily.

INTERPRETATION. The two markers of bone resorption that were assessed, namely urinary NTX and serum CTX, were significantly reduced by 30–50% within 2 weeks of the onset of treatment with L-000845704, with suppression maintained over the 12-month treatment period (Fig. 16.4). Similar changes were observed with all three treatment regimens. Bone formation markers (alkaline phosphatase and osteocalcin) were also suppressed in the three active treatment groups. These effects on bone resorption were associated with significant increases in BMD at the lumbar spine (Fig. 16.5). In contrast to lumbar BMD, which increased in all three treatment regimes relative to placebo, a significant increase in total hip and femoral BMD was observed only in the group given 200 mg twice daily, whereas no effect was observed for total body BMD in any group. The study drug was found to be generally well tolerated.

Comment

These findings support the suggestion that $\alpha_v\beta_3$ integrin is a useful therapeutic target for osteoporosis. In particular, L-000845704 led to increments in BMD of a magnitude similar to those observed after conventional bisphosphonate therapy. However, one limitation of this compound is that in order to achieve maximal efficacy, twice daily oral dosing appears to be necessary, reflecting the fact that the half-life of L-000845704 in humans is relatively short. Therefore, although $\alpha_v\beta_3$ integrin antagonists are an interesting approach for the treatment of osteoporosis, alternative agents with a longer half-life are likely to be needed before this strategy produces a viable therapeutic option.

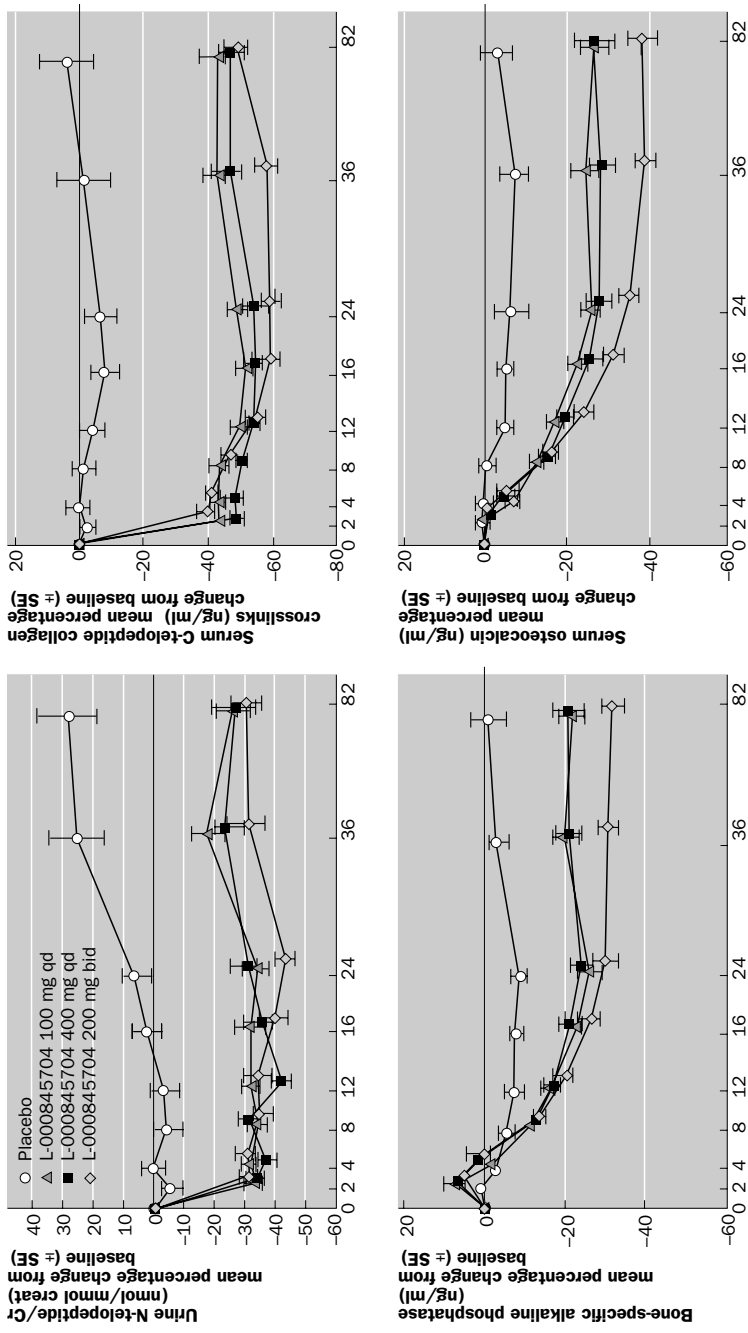

Fig. 16.4 Mean percentage change (± SE) from baseline in four biochemical markers of bone turnover during 12 months of treatment with L-000845704 or placebo. *P*, placebo; *triangle*, L-000845704 100 mg; *square*, L-000845704 400 mg; *diamond*, L-000845704 200 mg twice daily. Source: Murphy *et al.* (2005).

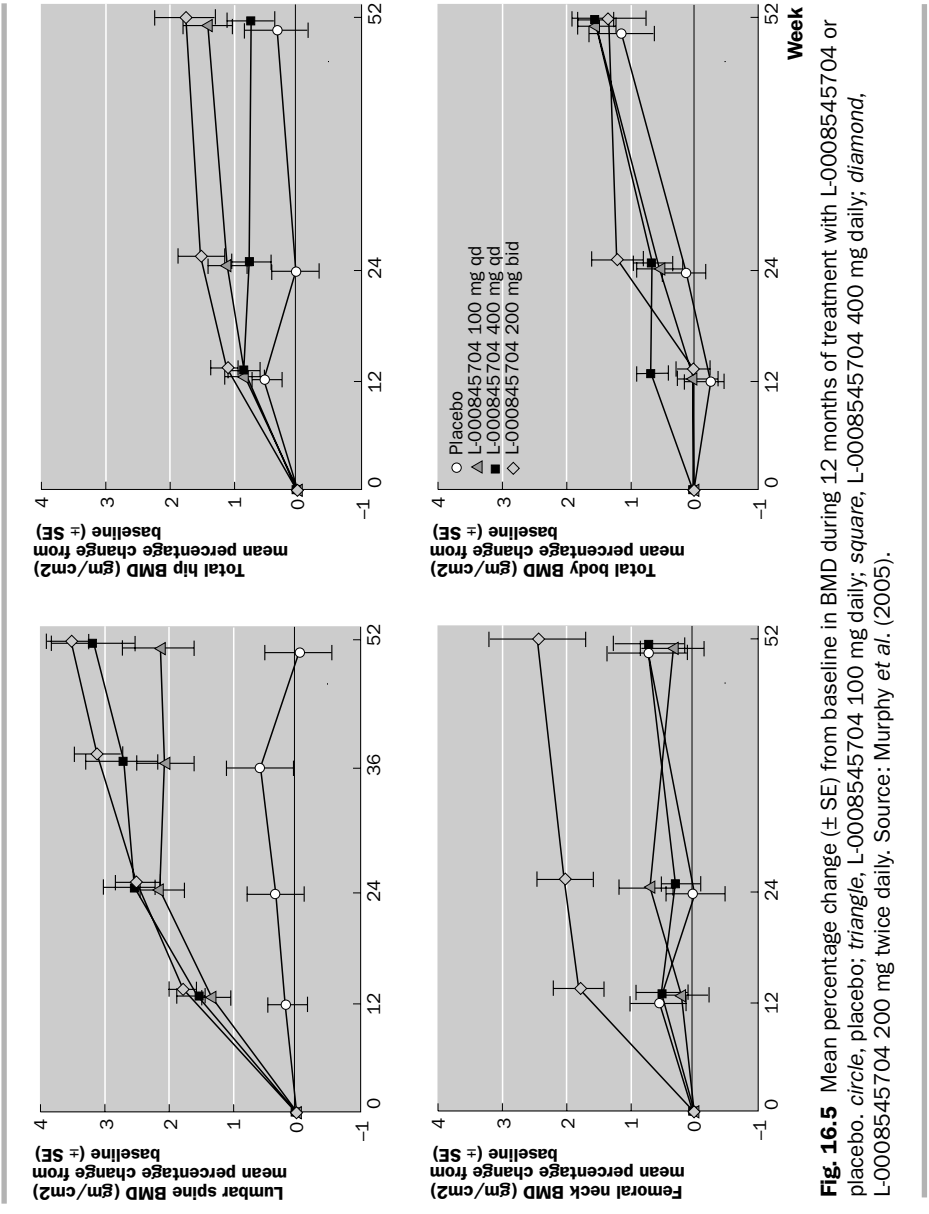

Fig. 16.5 Mean percentage change (± SE) from baseline in BMD during 12 months of treatment with L-000845704 or placebo. *circle*, placebo; *triangle*, L-000845704 100 mg daily; *square*, L-000845704 400 mg daily; *diamond*, L-000845704 200 mg twice daily. Source: Murphy *et al.* (2005).

Intracellular targets

Several intracellular mechanisms have been identified as playing critical roles in regulating osteoblast and osteoclast function. For example, as described below, cytoplasmic enzymes involved in mevalonate synthesis have been implicated in osteoclast survival; nuclear oestrogen receptors are known to influence both osteoblast and osteoclast activity; a ubiquitination-regulatory factor termed Smurf has been found to modulate bone morphogenetic protein (BMP)-dependent osteoblast stimulation; Gab2 (Grb2-associated binding protein 2) has been identified as an important factor in mediating RANK-induced cell signalling. Although several of these intracellular mechanisms are relatively generic, it may be possible to target them in a bone-selective manner by the use of pharmacological agents which are preferentially distributed in bone, as exemplified by the bisphosphonates.

Mevalonate synthesis

It is now well recognized that nitrogen-containing bisphosphonates suppress bone resorption by inducing osteoclast apoptosis as a consequence of inhibition of post-translational prenylation of small GTPases. This activity is in turn due to suppression of mevalonate synthesis as a result of inhibition by nitrogen-containing bisphosphonates of the enzyme farnesyl diphosphate (FPP) synthase, which plays a key role in the mevalonate pathway. Although the latter cytoplasmic pathway is required for the survival of many cell types, bisphosphonates preferentially act on bone by virtue of their preferential uptake into the skeleton as a consequence of their chemical structure, which is similar to that of pyrophosphate.

Identification of a bisphosphonate that inhibits isopentyl diphosphate isomerase and farnesyl diphosphate synthase

Thompson K, Dunford JE, Ebetino FH, Rogers MJ. *Biochem Biophys Res Commun* 2002; **290**: 869–73

BACKGROUND. Thompson *et al.* examined whether other enzymes involved in the mevalonate pathway, such as isopentenyl diphosphate (IPP) isomerase, the enzyme immediately proximal to FPP synthase, might also represent a useful pharmacological target in the development of new antiresorptive therapies for osteoporosis.

INTERPRETATION. A novel nitrogen-containing bisphosphonate, NE21650, was synthesized which inhibited both FPP synthase and IPP isomerase, in contrast to alendronate, which inhibited FPP synthase only (Fig. 16.6). NE10571, an inactive stereoisomer of NE21650, inhibited FPP synthase at high concentrations only, and had no effect on IPP isomerase activity (Fig. 16.6). When these compounds were tested for their ability to inhibit osteoclast function *in vitro*, NE21650 was found to be significantly more potent than alendronate, while NE10571 was without effect (Fig. 16.7). As well as

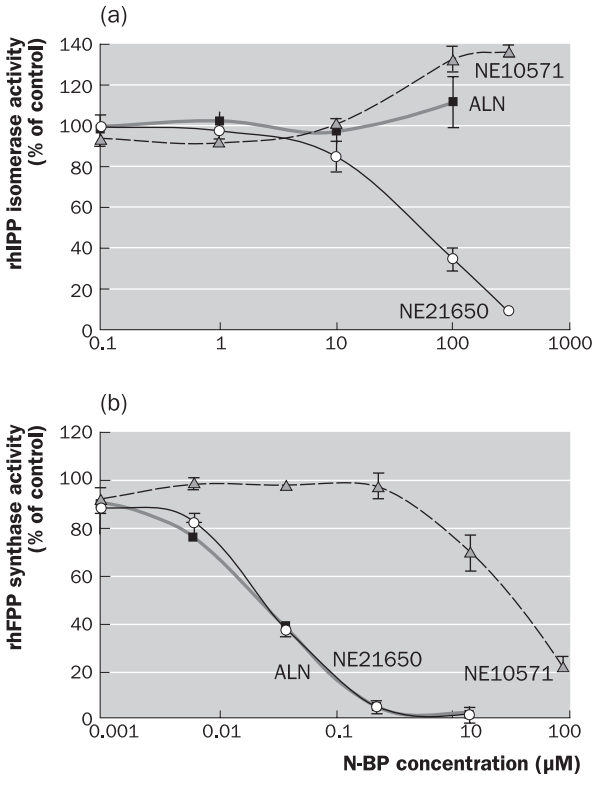

Fig. 16.6 (a) Inhibition of IPP isomerase by NE21650 but not NE10571 or alendronate (ALN). (b) Inhibition of FPP synthase by NE21650 and ALN. Results are mean ± SEM. Source: Thompson *et al*. (2002).

the greater anti-osteoclast activity of NE21650 compared with alendronate, the former was also found to be more effective in inhibiting protein prenylation.

Comment

Taken together, these findings suggest that it may be possible to develop newer bisphosphonates with enhanced antiresorptive activity by targeting additional enzymes in the mevalonate pathway, thereby leading to greater inhibition of protein prenylation and suppression of osteoclast activity.

Oestrogen receptor

Another important intracellular target for osteoporosis therapies is the oestrogen receptor, which is a nuclear transcription factor that becomes activated after binding oestrogen. Two types of oestrogen receptor are recognized, which together act

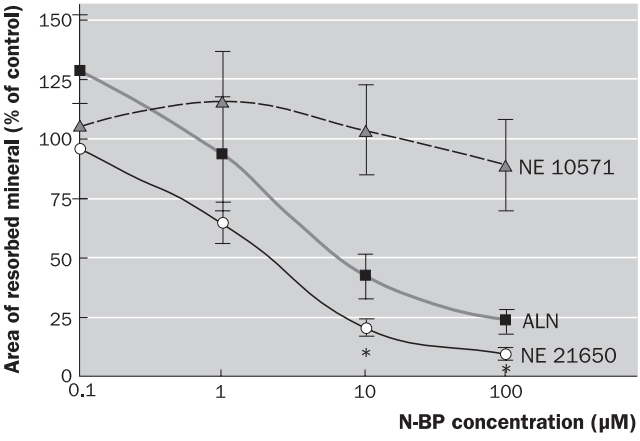

Fig. 16.7 Inhibition of osteoclastic bone resorption in rabbit osteoclasts. Cells were treated with bisphosphonates for 48 h prior to quantification of resorbed mineral by light microscopy. Data are mean ± SEM, expressed as a percentage compared with untreated cultures. NE21650 was significantly more potent than alendronate (ALN), whereas NE10571 was without effect. Source: Thompson *et al*. (2002).

to protect the skeleton from bone loss through a combination of anti-osteoclastic and pro-osteoblastic activities [8]. It is well recognized that the oestrogen receptor can be targeted in bone by the use of selective oestrogen receptor modulators (SERMs), which act as oestrogen agonists in bone but as antagonists in reproductive tissues such as the breast and uterus.

Long-term treatment of lasofoxifene preserves bone mass and bone strength and does not adversely affect the uterus in ovariectomized rats

Ke HZ, Foley GL, Simmons HA, Shen V, Thompson DD. *Endocrinology* 2004; **145**: 1996–2005

Background. The only SERM currently licensed for the treatment of osteoporosis is raloxifene, on the basis that this compound reduces the risk of vertebral fracture [9]. Since raloxifene may not entirely reproduce the beneficial effect of oestrogen on bone, further SERMs are being developed which may prove more efficacious. One such agent is lasofoxifene, which is a new SERM that has been suggested in phase II studies published as yet in abstract form only, to increase BMD in post-menopausal women [10]. The study by Ke *et al*. illustrates the therapeutic potential of lasofoxifene, as assessed in an animal model of osteoporosis, namely ovariectomized female rats.

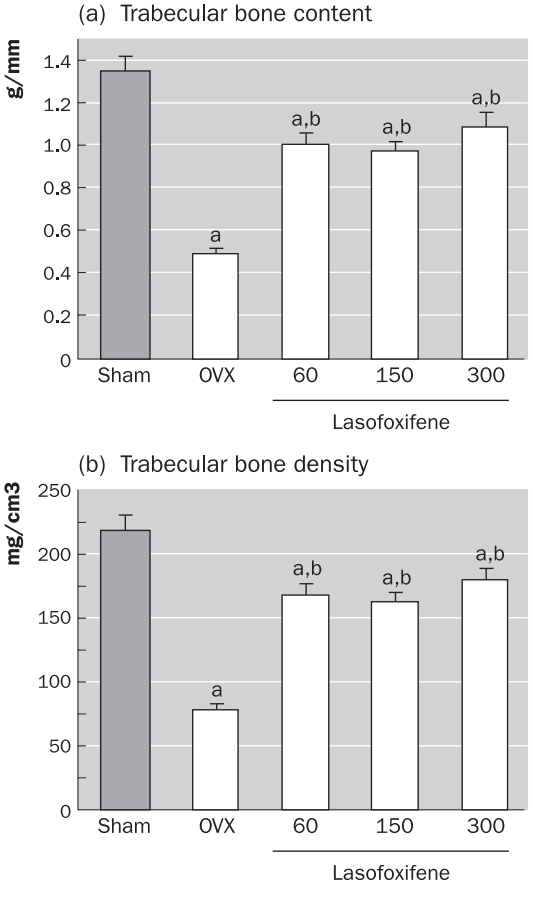

Fig. 16.8 Trabecular bone content and density of proximal tibial metaphysis determined by pQCT in sham controls, ovariectomized (ovx) controls and ovariectomized rats treated with lasofoxifene 60, 150 and 300 μg/kg/day. Data are mean ± SEM. (a) $P < 0.05$ versus sham; (b) $P < 0.05$ versus ovx controls. Source: Ke *et al*. (2004).

INTERPRETATION. Ke *et al*. examined the effect of treatment with lasofoxifene for 52 weeks in ovariectomized rats. As expected, this treatment led to a significant increase in trabecular bone mass compared with untreated controls, although levels remained below those observed in animals subjected to sham ovariectomy (Fig. 16.8). In addition, loss of bone strength following ovariectomy, as assessed at the lumbar vertebrae, was prevented by treatment with lasofoxifene. Increases in biochemical markers of bone turnover engendered by ovariectomy were reduced by treatment with lasofoxifene to a variable extent. In keeping with the bone-specificity of this SERM compound, lasofoxifene had minimal uterine-stimulatory activity, as assessed by measurement of uterine weight (Fig. 16.9).

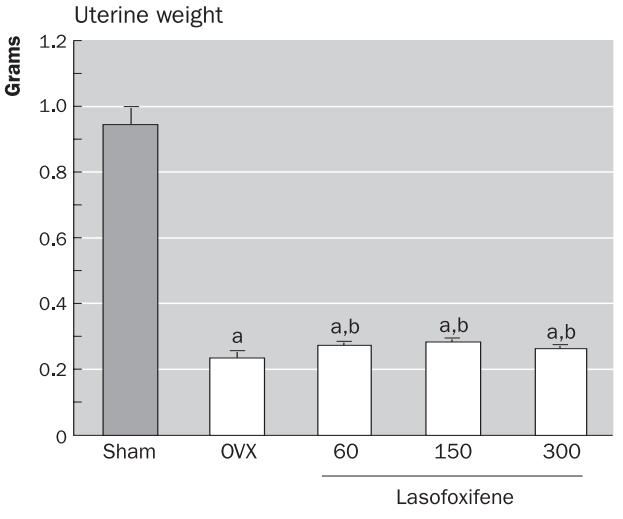

Fig. 16.9 Uterine weight in sham controls, ovariectomized (ovx) controls and ovariectomized rats treated with lasofoxifene 60, 150 and 300 μg/kg/day. Data are mean ± SEM. (a) $P < 0.05$ versus sham; (b) $P < 0.05$ versus ovx controls. Source: Ke *et al.* (2004).

Comment

Taken together, these data support the long-term efficacy and safety of lasofoxifene for the prevention and treatment of post-menopausal osteoporosis. However, the extent to which this compound offers advantages over existing SERMs, such as raloxifene, in terms of safety and efficacy can only be determined by the results of clinical trials which are currently ongoing.

Smurf

The ubiquitin/proteasome system inactivates a wide range of intracellular proteins, and as such is thought to play an important role in modulating intracellular signalling pathways involved in a number of different cellular processes. For example, Smad ubiquitin regulatory factor (Smurf) is thought to modulate transforming growth factor (TGF)-β and BMP signalling, thereby influencing the stimulatory actions of TGF-β and BMPs on osteoblast differentiation.

Ubiquitin ligase Smurf1 controls osteoblast activity and bone homeostasis by targeting MEKK2 for degradation

Yamashita M, Ying SX, Zhang GM, *et al*. *Cell* 2005; **121**: 101–13

BACKGROUND. On the basis of evidence that ectopic expression of Smurf1 prevents osteoblast differentiation, Yamashita *et al*. examined the effect of disruption of the Smurf1 gene on skeletal development in mice.

INTERPRETATION. *Smurf*$^{-/-}$ mice were found to be entirely normal morphologically, and to have normal fertility and lifespan. However, histological analysis revealed a significantly greater amount of both cortical and trabecular bone in knockout mice compared with *Smurf*$^{+/+}$ littermates, which was more marked in older animals. Further analyses indicated that the higher bone mass of *Smurf*$^{-/-}$ mice was a result of greater osteoblast activation (Fig. 16.10).

Comment

Even though *Smurf*$^{-/-}$ mice showed increased levels of Smurf 2 expression, this was unable to compensate for the loss of function of Smurf1, suggesting that the latter plays a non-redundant role in modulating osteoblast activity. Furthermore, the normal morphological appearance of *Smurf*$^{-/-}$ mice raises the possibility that Smurf plays a specific role in regulating bone cell function. However, although these studies suggest that Smurf 1 represents a possible therapeutic target for osteoporosis, it is currently unclear whether strategies can be developed for manipulating this pathway pharmacologically.

Gab2

Grb2-associated binding (Gab) proteins are a family of adapter molecules which are involved in signalling by receptors to a wide range of regulatory factors. Three family members, Gab1, Gab2 and Gab3, have been identified.

The molecular scaffold Gab2 is a crucial component of RANK signaling and osteoclastogenesis

Wada T, Nakashima T, Oliveira-dos-Santos AJ, *et al*. *Nat Med* 2005; **11**: 394–9

BACKGROUND. This paper describes the serendipitous finding that this family plays a previously unsuspected role in regulating bone cell activity, based on the phenotypic characterization of *Gab2*$^{-/-}$ mice.

INTERPRETATION. In the course of isolating bone marrow cells from *Gab2*$^{-/-}$ mice, a reduction in the cellularity of long bones was observed compared with wild-type *Gab2*$^{+/+}$ littermates, as well as an increase in trabecular and cortical bone mass (Fig. 16.11). A

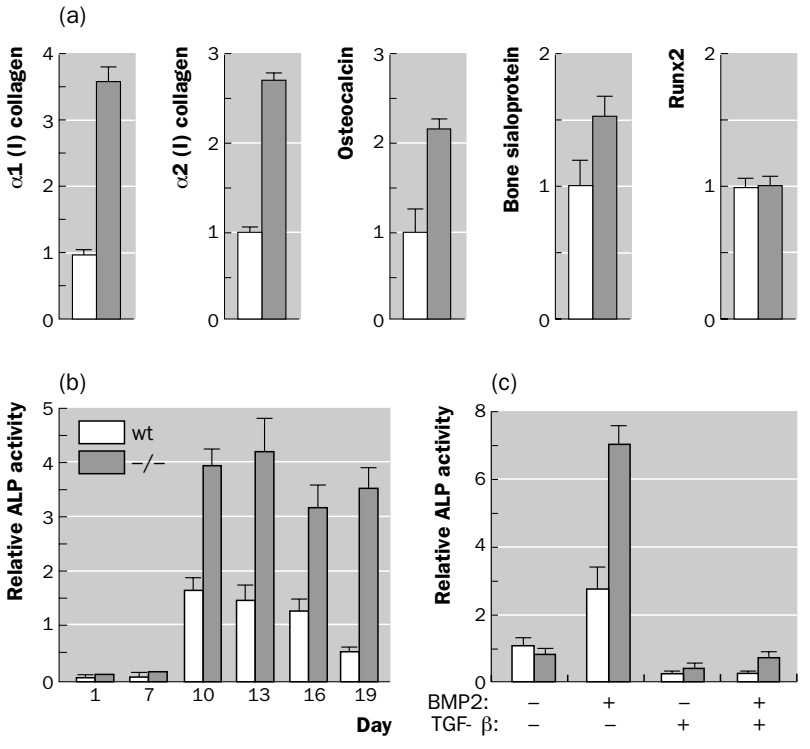

Fig. 16.10 Enhanced extracellular matrix production in Smurf knockout mice and BMP sensitivity of Smurf knockout osteoblasts. (a) Expression of osteoblast marker genes in long bones from control (*white column*) and Smurf knockout (*black column*) mice (assessed by real-time PCR of long-bone mRNA). Values are presented as relative expression. (b) Time course of alkaline phosphatase (ALP) activity in differentiating calvarial cultures established from control and knockout mice. (c) ALP activity of calvaria-derived cells after differentiation for 7 days in the presence of exogenous BMP-2 or TGF-β. Source: Yamashita *et al.* (2005).

decrease in osteoclast numbers in *Gab2*$^{-/-}$ mice was subsequently observed. The authors then investigated whether Gab2 interacts with the RANK/RANKL pathway, which, as described above, plays a central role in regulating osteoclast function. Osteoclast differentiation in response to RANKL was found to be significantly reduced in bone marrow cells derived from *Gab2*$^{-/-}$ mice compared with *Gab2*$^{+/+}$ littermates. Similarly, stimulation of osteoclast differentiation by RANKL in human peripheral blood monocyte cultures was significantly impaired following inhibition of Gab2 protein expression by small interfering RNAs, whereas inhibition of Gab1 was without effect. Further studies demonstrated that Gab2 directly associates with RANK, and impairs RANK-induced

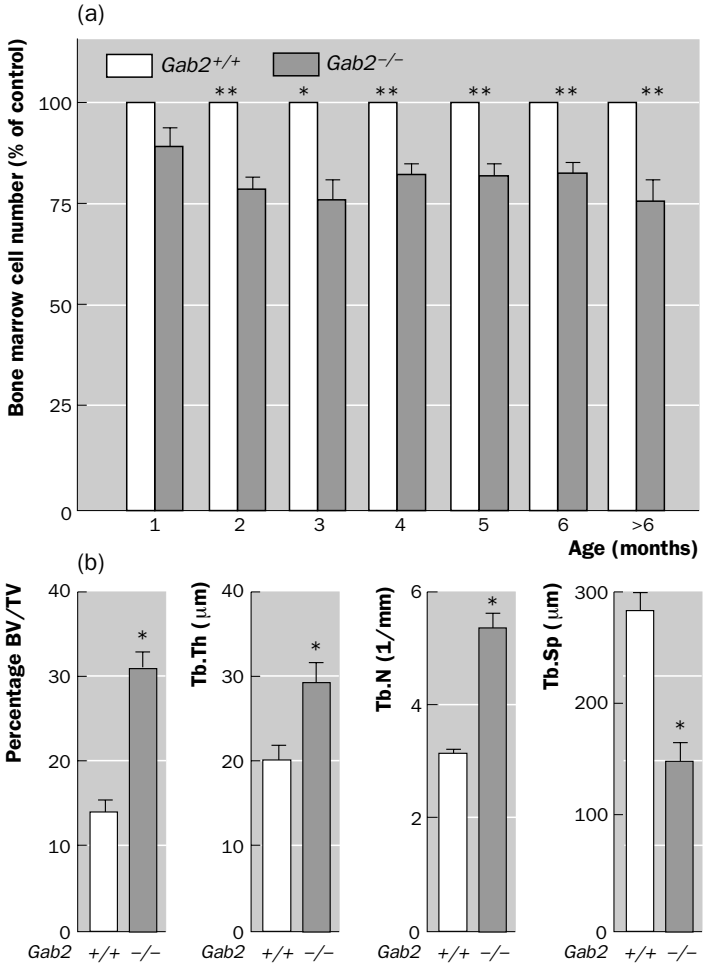

Fig. 16.11 Gab2-deficient mice develop osteopetrosis. (a) Reduced cellularity of long bones of *Gab2*$^{-/-}$ mice. Shown are total bone marrow cell numbers obtained from *Gab2*$^{-/-}$ mice and wild-type (*Gab2*$^{+/+}$) littermates at the ages given. (b) Bone histomorphometric analyses of femurs from *Gab2*$^{-/-}$ and *Gab2*$^{+/+}$ mice. BV/TV, bone volume/total volume; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation. Data are mean ± SE. Panel (b) shows data from 10-week-old mice. *P<0.05, **P<0.01 by Student's *t* test. Source: Wada *et al.* (2005).

phosphorylation of the intracellular signalling proteins Jnk, c-Jun and Akt. Taken together, these findings suggest that Gab2 plays a specific role in RANK-mediated signal transduction.

Comment

Findings from this paper, which suggest that Gab2 plays an important role in RANK/RANKL signalling, raise the possibility that the RANK/RANKL pathway can be targeted by manipulation of mechanisms involved in RANK signal transduction. Whether Gab2 represents a possible therapeutic target for osteoporosis is currently unclear, since Gab2 is expressed relatively widely, and loss of Gab2 has also been found to affect immune function. However, this avenue of research may lead to the identification of further mechanisms involved in RANK signalling which are specific to bone, and represent viable drug targets for osteoporosis.

Conclusion

Taken together, the papers discussed in this chapter illustrate how mechanisms which have been found to play a critical role in regulating either osteoblast or osteoclast function can potentially serve as therapeutic targets for osteoporosis. Having identified these mechanisms, whether they can be exploited as drug targets depends on several different considerations. A major issue is whether pharmacological manipulation of the target in question is likely to lead to bone-specific effects. Bone specificity is generally anticipated if the target in question is preferentially involved in regulating bone cell function, as illustrated by the Wnt and RANK/RANKL pathways, cathepsin K and $\alpha_v\beta_3$ integrin. On the other hand, it may be possible to use alternative strategies in which bone specificity is a property of the pharmacological agent rather than the target itself. This approach is illustrated by the bisphosphonates, which target the ubiquitous enzyme FPP but exert a bone-specific action as a consequence of their high affinity for bone.

With the new era of biological therapy, it is now possible to manipulate cell surface receptors and extracellular proteins by delivering peptides and antibodies, as illustrated by compounds such as teriparatide and AMG 162 respectively. In other cases, strategies for developing small orally active molecules designed to manipulate the target in question have been developed, as exemplified by several therapies in early clinical development, such as $\alpha_v\beta_3$ integrin inhibitors and novel SERMs.

Although laboratory studies have enabled a significant number of new drug targets for osteoporosis to be developed, translating these into effective therapies is a tortuous and costly process. For example, having identified the RANK/RANKL pathway as a therapeutic target for osteoporosis, the initial approach to manipulating this mechanism by administering recombinant osteoprotegerin was terminated because of safety concerns over host immune responses. Similarly, despite the fact that $\alpha_v\beta_3$ integrin represents an attractive bone-specific target, the half-life of the orally active inhibitors that have been developed to date appears to be too short for clinical use. Nevertheless, with the recent advances in understanding of the molecular regulation of bone cell function and the consequent identification of several new potential therapeutic targets, it is anticipated that significant numbers of new therapies for osteoporosis will become available in the foreseeable future.

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17

Preventing fractures in the very elderly

STEVEN BOONEN, WALTER PELEMANS, PATRICK HAENTJENS, DIRK VANDERSCHUEREN

Introduction

Osteoporosis – a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture – is a major public health problem of the elderly. Most types of osteoporotic fractures increase in incidence steadily with age [1–3], and the number of elderly individuals affected with osteoporosis is expected to increase dramatically in the coming years [4,5].

Although hip fractures are considered the most severe and economically important type of osteoporotic fracture [6], vertebral fractures also lead to adverse health outcomes, including back pain [7], height loss [8] and kyphosis [9]. These changes may result in significant declines in physical performance and function and ultimately loss of independence [10]. Vertebral fractures frequently require hospitalization or prolongation of hospital stays, particularly in elderly individuals [11] Each additional vertebral fracture leads to further functional limitation and substantially increases the risk of additional vertebral and hip fractures [12]. Vertebral fractures are even associated with an excess rate of mortality [13], and relative survival rates after fracture decline with age at the time of fracture [14].

Available pharmacological therapies for the treatment of osteoporosis include antiresorptive drugs, such as bisphosphonates, calcitonin and raloxifene, and the bone-forming drug teriparatide (rhPTH 1-34). However, despite the debilitating effects of osteoporosis fractures and the availability of therapies to reduce the incidence of fracture, many elderly patients do not receive treatment [15,16]; treatment rates range from 5% to 69% [17] and decrease with increasing age [18]. One explanation for this decrease is the perception that it is too late to alter the course of the disease in its late stage.

Given the known antifracture efficacy of the available drugs in calcium- and vitamin D-controlled trials, lack of appropriate and needed therapy in patients with osteoporosis may result in costly and debilitating fractures. However, when considering antiresorptive or anabolic treatment in the very elderly, a number of questions remain.

First, until recently no studies had provided evidence for a benefit from osteoporosis treatment in addition to that afforded by calcium and vitamin D in a geriatric population (of women 80 years of age or older) with osteoporosis. Treatment of very elderly women with combined calcium and vitamin D supplements has been shown to reduce the risk of fracture [19,20]. Fracture end-point trials in women 80 years of age or older with documented osteoporosis should assess whether and to what extent antiresorptive or anabolic treatment continues to provide an antifracture benefit in addition to that afforded by calcium and vitamin D. These trials should provide an answer to the critically important question of whether, even in the very elderly, reducing the bone resorption rate or increasing the bone formation rate remains an effective treatment strategy for osteoporosis.

Secondly, there is the question of the safety of osteoporosis treatment in the oldest old. This question may be particularly relevant to the use of bisphosphonates, given the age-associated increase in comorbid conditions. The comorbidities in older women with osteoporosis include a higher prevalence of underlying gastrointestinal diseases [21] and of renal insufficiency [22].

Thirdly, the question remains whether fall prevention in the very elderly could potentially be optimized by complementing bone-directed strategies with fall-directed strategies or even, paradoxically, by targeting osteoporosis treatment in old age to those individuals who have an increased propensity to falls. Currently, the prevention of osteoporotic fractures is based mostly on drug therapies that have been proved to lower the risk of fractures in well-defined patients with low bone density or a prevalent vertebral fracture. Patient selection for drug treatment relies, therefore, almost exclusively on bone-related risk factors for fracture. Although low bone mass is considered a major risk factor for fractures, it alone is generally not sufficient to predict fractures [23–25]. There is a large overlap in bone mineral density (BMD) between patients with and without fractures, particularly in old age [26]. Falling appears to be a major risk factor for fractures, especially appendicular fractures [23–25,27]. For predicting hip fracture, risk factors for falls and low bone density act as independent and additive risk factors [28].

The risk of falling increases with age; thus, a large proportion of elderly have one or more falls per year [29]. However, only 5–10% of falls result in a fracture [29], for several reasons. First, the orientation of the fall and the effectiveness of protective responses influence the risk of fracture in the elderly [24,25,30]. Secondly, interaction has been documented between osteoporosis and falls in the occurrence of fractures. In a European prospective cohort study of risk factors for hip fracture, falls and risk factors for falls (low physical activity or disturbed body balance) were related to the occurrence of humerus fractures in patients with osteoporosis but not in subjects with normal BMD [27]. In line with these findings, a retrospective study of post-menopausal women showed an increased risk of fractures during the preceding year in women who reported a fall during that period and had low BMD, but not in women with a history of falling and normal BMD, or in women who reported no falls irrespective of their BMD [31]. These results suggest that the risk of clinical, mainly appendicular, fractures is increased only in women with a combin-

ation of low BMD and incident falls. These findings could also explain why even women with osteopenia may have an increased risk of fracture if they fall.

Studies of fall prevention have shown varying results, but none has shown a decrease in the number of fractures [29]. This apparent lack of antifracture efficacy might reflect the fact that these studies were not performed in patients selected on the basis of low BMD. As shown by Kannus *et al.* [32], hip protectors may decrease the risk of hip fractures in frail elderly subjects who are wearing the device when falling. In their study, selection of patients was not based on low BMD but on advanced age (>80 years) in combination with frailty—both factors that are related to an increased risk of low BMD [33] and falls [29].

On the other hand, in the Fracture Intervention Trial [34], post-menopausal women with low BMD or prevalent vertebral fracture were studied without selection on the basis of the risk of falls. In these women, alendronate decreased the risk of vertebral and non-vertebral fractures. In the same study, however, alendronate had no effect in another cohort of women with normal baseline BMD [34], suggesting that bone-directed therapy is effective for reducing fracture risk only in patients with documented osteoporosis. Findings have been similar with risedronate, the first bisphosphonate to be studied with prevention of hip fracture as a primary endpoint [35]. Risedronate decreased the risk of hip fracture in women with established osteoporosis but not in women selected mainly on the basis of risk factors for falls but without proven low BMD. Thus, bisphosphonates seem to reduce the risk of fracture only in women who have low BMD or prevalent vertebral fractures. It remains to be clarified whether measures to prevent falls – in combination with drug therapy – might further reduce the risk of fracture.

Considered together, these observations provide evidence for an interaction between osteoporosis and falls in the occurrence of clinical fractures. An increased number of falls may have contributed to the age-standardized increase in the incidence of appendicular fractures during past decades [36,37]. An increased risk of falls is likely to be the main risk factor for the occurrence of fracture in subjects whose bone mass is not decreased to the level of osteoporosis. In addition to measuring BMD, risk evaluation for falls might, therefore, enhance the identification of elderly patients at the greatest risk of fractures. Further studies are needed to evaluate the effect of combined bone- and fall-directed strategies in patients with osteoporosis and an increased propensity to falls.

In recent months, a number of studies have addressed the occurrence of osteoporosis and osteoporotic fracture in old age. Some of these will be reviewed in more detail in this chapter. The aim was primarily to select papers with immediate implications for the practising clinician. Priority was given to studies addressing the key questions discussed above: the potential benefit of osteoporosis treatment in addition to that afforded by calcium and vitamin D in a geriatric population; the safety of osteoporosis treatment in the oldest old; and the interaction between osteoporosis and falls in the occurrence of clinical fractures in elderly individuals.

Risedronate reduces the risk for non-vertebral fractures within 6 months in women with post-menopausal osteoporosis

Harrington JT, Ste-Marie LG, Brandi ML, *et al. Calcif Tissue Int* 2004; **74**: 129–35

BACKGROUND. Although vertebral fractures are the fractures most commonly associated with osteoporosis, occurring in over 24% of women 75–79 years of age, fractures at other skeletal sites are also related to low bone density and collectively account for a substantial proportion of all osteoporotic fractures, particularly in elderly individuals. Therefore, prevention of non-vertebral fractures is an important goal of osteoporosis treatment in old age.

INTERPRETATION. In this population of post-menopausal women with low BMD, defined as a lumbar spine T-score below –2.5 with or without vertebral fractures, risedronate 5 mg daily significantly reduced the incidence of non-vertebral fractures within 6 months compared with the control group. After 1 year, the incidence of non-vertebral fracture was reduced by 74% compared with control ($P = 0.001$), and the number of women who needed to be treated with risedronate 5 mg to prevent one non-vertebral fracture was 30. After 3 years, the reduction in non-vertebral fractures was

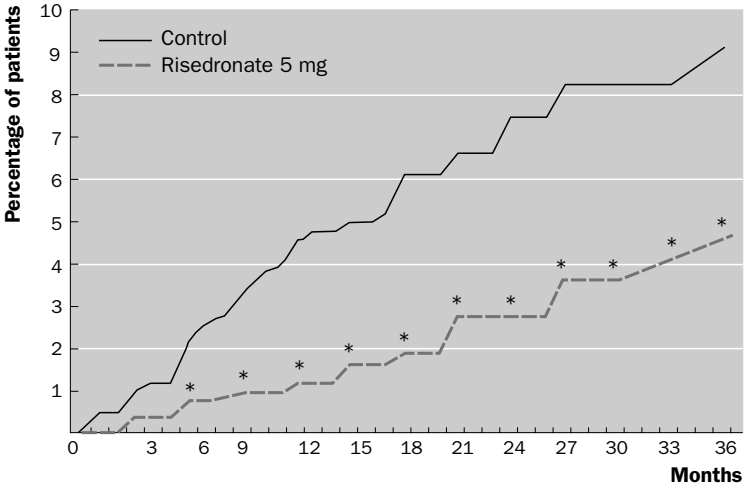

Fig. 17.1 Incidence of new osteoporosis-related non-vertebral fractures (Kaplan–Meier method) in patients treated with placebo or risedronate 5 mg for up to 3 years. *Significantly less than placebo group ($P \leq 0.01$). The 0–3 year fracture incidence was 9.1% in the placebo group compared with 4.6% in the risedronate 5 mg group. The treatment effect of risedronate 5 mg was 59% (95% confidence interval 27–77%; $P = 0.002$). Source: Harrington et al. (2004).

59% ($P = 0.002$) and the number needed to treat was 22. The results indicate that risedronate significantly reduces the incidence of osteoporosis-related non-vertebral fractures within 6 months.

Comment

Previous studies have shown that risedronate treatment decreases the incidence of clinical vertebral fractures within 6 months and radiographic vertebral fractures within 1 year. These new analyses indicate that risedronate 5 mg/day also reduces the incidence of non-vertebral fractures within 6 months. A rapid onset of fracture protection is important for optimal pharmacological treatment of osteoporosis. This is particularly true for elderly patients diagnosed with osteoporosis on the basis of a new vertebral fracture or non-vertebral fragility fracture rather than bone density measurement. For example, among osteoporosis patients who have suffered a vertebral fracture, more than 25% will suffer another new fracture within 1 year when taking only calcium and vitamin D.

The early reduction in vertebral and non-vertebral fractures associated with risedronate treatment is consistent with the concept that the benefits of risedronate – and other antiresorptive agents – are attributable to factors in addition to increases in BMD. Significant reductions in fracture risk are observed after 6 months of risedronate therapy, yet BMD increases are not at their peak at this time-point. Recent studies of risedronate, alendronate and raloxifene have demonstrated that increases in BMD do not explain treatment-associated reductions in fracture risk. These observations suggest that factors other than BMD, such as bone quality, may help explain the observed reduction in fracture risk.

The need for clinical guidance in the use of calcium and vitamin D in the management of osteoporosis: a consensus report

Boonen S, Rizzoli R, Meunier P, *et al. Osteoporos Int* 2004; **15**: 511–19

BACKGROUND. Calcium and vitamin D are crucial for bone health throughout life. Calcium intake is one of the main determinants of the development of peak bone mass during adolescence and also slows the subsequent age-related bone loss. In the presence of vitamin D deficiency, calcium absorption is impaired and there is a compensatory increase in parathyroid hormone levels, with a consequent stimulation of bone resorption and accelerated bone loss.

INTERPRETATION. Calcium and vitamin D, when given in appropriate doses, have been shown to be pharmacologically active (particularly in patients with dietary deficiencies), safe and effective for the prevention and treatment of osteoporotic fractures. Indeed, calcium and vitamin D are a first-line medication in the prevention and treatment of osteoporosis, although most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive agent. The use of calcium and vitamin D in the prevention and treatment of osteoporosis is cost-effective.

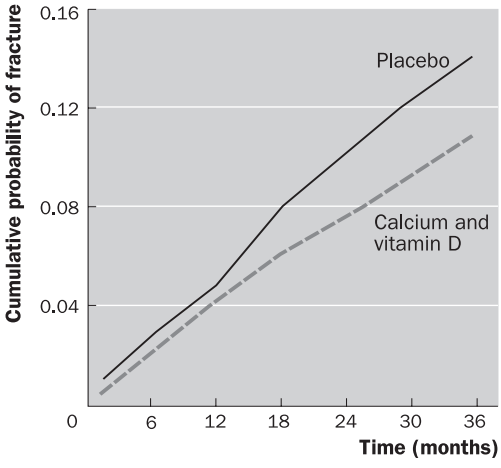

Fig. 17.2 Reduction in hip fractures achieved with calcium and vitamin D supplementation. Source: Boonen *et al.* (2004).

Comment

This consensus report summarizes the rationale for calcium and vitamin D supplementation in the prevention and treatment of osteoporotic fractures. Two musculoskeletal risk factors are implicated in osteoporotic fractures in the elderly: the loss of bone mass due to secondary hyperparathyroidism and the increased propensity to falls. Treatment with calcium and vitamin D reverses secondary hyperparathyroidism with beneficial effects on BMD. Additionally, calcium and vitamin D supplementation significantly improves body sway and lower extremity strength, reducing the risk of falls. The effects of combined calcium and vitamin D on parathyroid function and BMD provide a strong rationale for the use of calcium and vitamin D combination therapy in the prevention and treatment of osteoporosis and osteoporotic fractures. Evidence from randomized studies in both institutionalized and community-dwelling elderly demonstrates that calcium and vitamin D reduce the risk of osteoporotic fracture in both populations, particularly in the presence of dietary deficiencies. Although most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive agent, calcium and vitamin D should be a first-line strategy for the prevention and treatment of osteoporosis.

Musculoskeletal rehabilitation in osteoporosis: a review

Pfeifer M, Sinaki M, Geusens P, Boonen S, Preisinger E, Minne HW; ASBMR Working Group on Musculoskeletal Rehabilitation. *J Bone Miner Res* 2004; **19**: 1208–14

BACKGROUND. Most antifracture strategies have focused on increasing the biomechanical competence of bone by reducing bone turnover. The efficacy of these interventions in reducing the risk of fracture has been consistently documented in well-defined patients with confirmed osteoporosis (low BMD or prevalent vertebral fracture). Fractures in the elderly – particularly fractures of the appendicular skeleton – result from two processes: a loss of skeletal integrity and an increased risk of falls. However, little attention has been given to the targeting of extraskeletal factors to prevent fractures in selected individuals.

INTERPRETATION. Fractures due to osteoporotic fragility may be prevented with multidisciplinary intervention programmes, including education, environmental modifications, aids, and the implementation of individually tailored exercise programmes, which have been proved to reduce falls and fall-related injuries. In addition, strengthening of the paraspinal muscles may not only maintain bone density but also reduce the risk of vertebral fractures. Given the strong interaction between osteoporosis and falls, the selection of patients for prevention of fracture should be based on bone-related factors and on risk factors for falls.

Rehabilitation after vertebral fracture includes proprioceptive dynamic posture training, which decreases kyphotic posturing through recruitment of back extensors and thus reduces pain, improves mobility and leads to a better quality of life. A newly

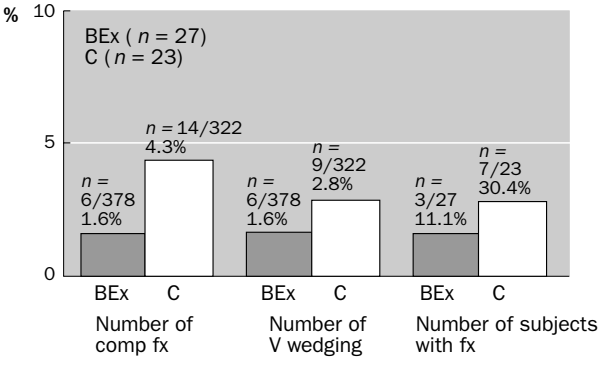

Fig. 17.3 Effect of back muscle strengthening on the rate of vertebral fractures in post-menopausal women. A total of 378 vertebrae were examined in the back exercise group, and a total of 322 vertebrae were examined in the control group (14 vertebrae, T_4–L_5, were examined in each patient). BEx, back exercise group; C, control group; comp fx, compression fracture; fx, fractures; V, vertebral. Source: Pfeifer *et al.* (2004).

developed orthosis increases back extensor strength and decreases body sway as a risk factor for falls and fall-related fractures. Exercise programmes can improve strength and mobility in patients with hip fracture.

Comment

In the management of patients with increased risk of fracture due to osteoporosis or extraskeletal risk factors, measures of musculoskeletal rehabilitation should be considered as a prelude to, or even in conjunction with, pharmacotherapy to optimize musculoskeletal health, improve quality of life and reduce the risks of fracture and fracture recurrence. In this review paper by the founding members of the American Society for Bone and Mineral Research (ASBMR) Working Group on Musculoskeletal Rehabilitation, Pfeifer and colleagues emphasize the role of elements of muscle function, such as strength and coordination, in the prevention of fracture and post-fracture rehabilitation in patients with osteoporosis.

Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women 80 years of age or older: implications for the use of antiresorptive agents in the oldest old

Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P. *J Am Geriatr Soc* 2004; **52**: 1832–9.

BACKGROUND. Despite the debilitating effects of vertebral fractures and the availability of therapies to reduce fracture occurrence, only a small percentage of women with osteoporotic fractures receive treatment, and this percentage decreases with age. One explanation for this decrease is that clinicians presume that it is too late to alter the course of disease in its late stage. Treatment of very elderly women with combined calcium and vitamin D supplements has been shown to reduce the risk of fracture. However, there is no published evidence in persons over 80 years of age that further reducing bone turnover by adding an antiresorptive agent provides protection against osteoporotic fractures in addition to that provided by calcium and vitamin D.

INTERPRETATION. In this study in elderly women (up to 100 years of age) with osteoporosis, risedronate 5 mg significantly reduced the risk of new vertebral fractures over 1 and 3 years. The reductions in fracture risk in the risedronate-treated women were seen within 1 year of treatment and were in addition to any benefit experienced as a result of calcium and, if needed, vitamin D supplementation, which has been shown to significantly decrease the risk of osteoporotic fractures in older individuals.

Comment

This study is the first to document a benefit of antiresorptive treatment in addition to that afforded by calcium and vitamin D in a population of women 80 years of age or older with osteoporosis. These findings support the concept that reducing the rate of bone remodelling remains an effective osteoporosis treatment strategy even

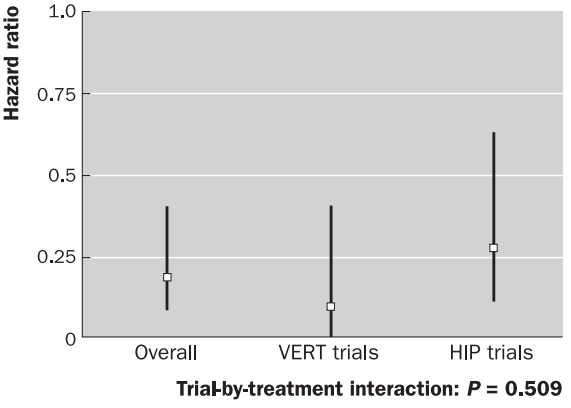

Fig. 17.4 Risk of new vertebral fracture during 1 year of treatment with risedronate 5 mg relative to the risk during treatment with placebo in patients with osteoporosis (aged ≥80) in the overall analysis population and in the Vertebral Efficacy with Risedronate Therapy (VERT) and Hip Intervention Program (HIP) trials. Bars represent 95% confidence intervals. Source: Boonen *et al.* (2004).

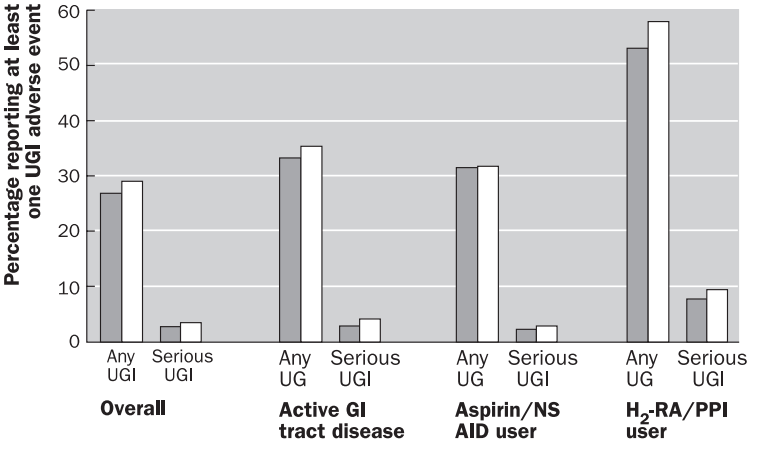

Fig. 17.5 Incidence of any upper gastrointestinal (UGI) adverse events and serious UGI adverse events associated with placebo (*black bars*) or risedronate 5 mg (*white bars*) treatment in all patients aged 80 and older (overall) and in subgroups of patients aged 80 and older who had active gastrointestinal (GI) disease, who were using aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), or who were using histamine2 receptor antagonists (H2-RAs) or proton pump inhibitors (PPIs). Source: Boonen *et al.* (2004).

in the oldest patients, although it remains to be determined whether similar results would be seen for other antiresorptives.

Compared with patients under 80 years of age, patients over 80 had significantly lower femoral neck BMD and body mass index values and a greater frequency of prevalent fractures at baseline and were therefore at greater risk of fracture than their younger counterparts, supporting the concept that the risk of fracture continues to increase with age, even in the very old. These findings underscore the need to arrest bone loss and prevent fracture in elderly patients and the importance of a rapid treatment effect.

One of the limitations of this study was that it was unable to document a treatment effect on non-vertebral fractures in patients 80 years of age or older, despite the fact that the patients 80 years of age or older included in the analyses met the criteria for osteoporosis and, as noted previously, had an even more severe degree of osteoporosis than the younger patients in the analyses. Thus, the failure to demonstrate an effect of treatment on the risk of non-vertebral fracture cannot be attributed to the selection of very old patients with less skeletal fragility. Nor can it be explained by a greater effect of calcium and vitamin D in patients 80 years of age or older since the calcium- and vitamin-D-associated changes in bone turnover markers in the placebo groups were similar in patients 80 years of age or older and patients less than 80 years of age. The robust effect of risedronate treatment on vertebral fractures in patients 80 years of age or older suggests that risedronate treatment addressed the skeletal fragility component of fracture risk, even in these very old patients. It is possible, therefore, that the reduced effect of treatment on non-vertebral fractures in patients 80 years of age or older may reflect the increasing influence of non-skeletal risk factors for these types of fractures, such as falling, with increasing age.

Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in Caucasian men

Haentjens P, Johnell O, Kanis J, *et al. J Bone Miner Res* 2004; **19**: 1933–44

BACKGROUND. Various studies have identified a history of a fragility fracture as one of the main risk factors for subsequent hip fracture, even after adjusting for BMD. Prospective associations have been documented between hip fracture occurrence and spine or Colles' fracture, both in women and in men. However, the occurrence of Colles' fracture has been largely ignored in public health approaches to identifying target populations at risk of hip fracture.

INTERPRETATION. This study is the first to estimate the effects of Colles' and spine fracture on absolute risks of hip fracture in post-menopausal women and ageing men. As expected, estimates indicated that, in post-menopausal women, the risk of sustaining a hip fracture is higher after a spine fracture than after a Colles' fracture. In ageing men,

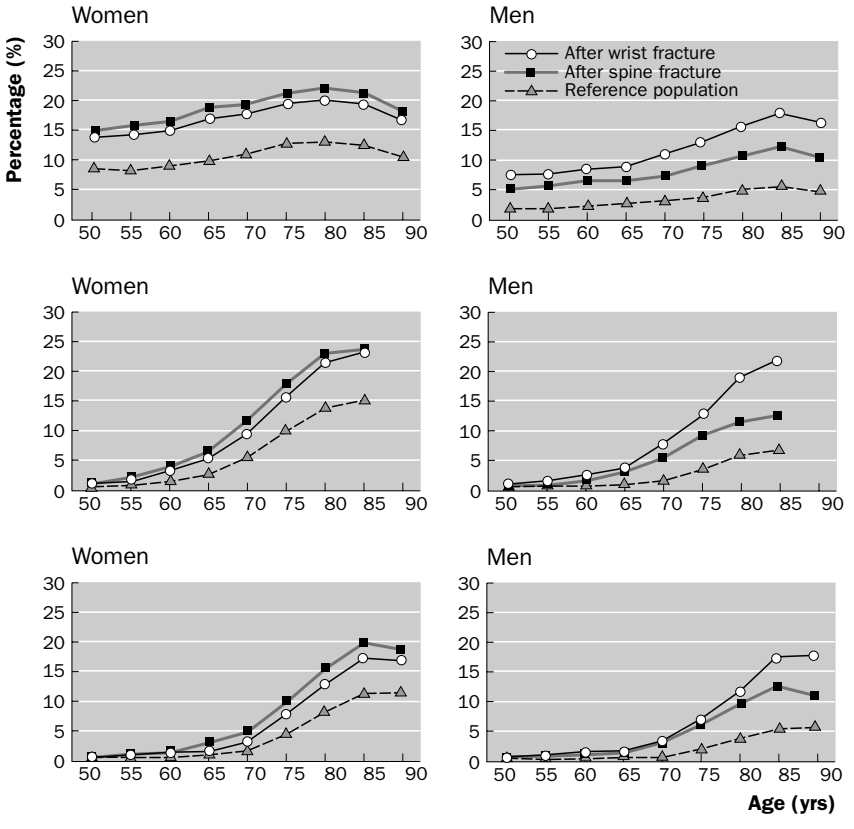

Fig. 17.6 Remaining lifetime and 10- and 5-year risk of hip fracture in post-menopausal women and ageing men at a given baseline age reached free of fracture. Individual curves are shown for a history of a Colles' fracture (*bullets*), a spine fracture (*squares*) or neither of these fracture types (*open triangles*) at a given baseline age.
Source: Haentjens *et al.* (2004).

on the other hand, the prospective association between fracture history and the subsequent risk of hip fracture appeared to be strongest for Colles' fracture. Similar trends were observed when calculating remaining lifetime and 10- and 5-year risks. These data provide strong evidence for gender-related differences in the relationship between fracture history and the future occurrence of hip fracture.

Comment

The findings presented in this study have important clinical implications. They highlight the predictive risk of Colles' fracture for future hip fracture in men, and

also the presence of substantial gender-related differences in the association between subsequent osteoporotic fractures. From a public health perspective, the results support the need for targeting interventions at men with Colles' fracture to potentially reduce the burden of morbidity and mortality due to hip fracture in old age. The data are consistent with gender-related differences in the pathogenesis of hip fractures. They support the concept that Colles' fracture is an early and sensitive marker of skeletal fragility in men.

The incidence of distal forearm fractures is markedly lower in men than in women, with a male-to-female ratio of only about 1:6 at age 55 and decreasing even further to 1:10 above 75 years. This low incidence of Colles' fracture in men is partly explained by differences in bone size and cortical thickness as a result of differences in the degree of periosteal bone formation and endocortical bone resorption between the sexes, providing a mechanical advantage to the male appendicular skeleton. In those who do suffer a Colles' fracture, impaired skeletal strength (low bone density and/or a deterioration of bone architecture) is likely to be present. Vertebral fractures, on the other hand, are less important risk factors for hip fracture in men than a history of Colles' fracture. These findings suggest that, at least in a subset of men, the occurrence of vertebral fracture may be a marker of trauma rather than a marker of bone fragility. This assumption is supported by prevalence data, which demonstrate little difference in the rates of radiographically detected vertebral deformities among men and women (around 5–10%) at younger ages.

Low BMD less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Study (EPOS)

Kaptoge S, Benevolenskaya L, Bhalla A, *et al. Bone* 2005; **36**: 387–98

BACKGROUND. Aside from major trauma, the occurrence of nearly all limb fractures in those over age 50 is explained by a fall. In those with pre-existing bone loss, a fracture as a result of a fall is more likely. Anticipated risk factors for limb fractures would thus include those associated with both falling and low bone density, including some, such as frailty, that might be common to both. Although there is evidence that BMD is important in determining limb fractures, little is known about its relative importance if adjusted for the risk of falling and other implicated risk factors, especially with data from diverse populations in which large variations in BMD and fall risk are to be expected.

INTERPRETATION. This paper reports results from a multicentre multinational prospective study of fractures and falls, the European Prospective Osteoporosis Study, in which non-spine fractures were identified prospectively over a mean of 3 years and spine fractures over a mean of 3.8 years. The authors present the results of modelling the risk of limb fracture as a function of BMD after adjusting for the other significant risk factors for fracture that have been described. The main result is that BMD appeared to be less

important in explaining variations in the incidence of upper limb fractures in women across diverse populations in Europe compared with the effect of at least some of these other factors. These include variation in the location-specific risk of falling, a personal or family history of fracture, or factors that may be associated with the likelihood of falling, such as amount of time spent walking/cycling.

Comment

This study has demonstrated important limitations in the role of BMD in predicting the risk of non-spine fractures across populations. These results have important implications for developing prevention strategies. In particular, for upper limb fractures the risk of falling had a much more significant effect than BMD on the risk of fracture. This suggests that models for fracture risk based on BMD and other data obtained in comparatively homogeneous populations should be treated with caution if it is desired to extrapolate to different populations. From a clinical perspective, these findings emphasize the increasingly recognized need to develop risk models that include non-BMD-related risk indicators alongside BMD. Interestingly, for any non-spine fracture, there was still a residual centre effect that was not entirely accounted for by adjustment of person-specific covariates, centre-level BMD and centre fall rates.

Conclusion

Osteoporotic fractures are an extremely common health problem in the elderly and the incidence is projected to rise as longevity increases unless preventive policies are initiated. The prevalence of vertebral deformities in women increases markedly between the ages of 50 and 90, and epidemiological data suggest that half or more of women 80 years of age or older have vertebral fractures. However, from a geriatric perspective non-vertebral fractures are also particularly important, because the incidence of non-vertebral osteoporotic fractures (e.g. fractures at the hip, clavicle, wrist and humerus) increases dramatically with age as a result of factors in addition to BMD, such as the risk of falling.

Both an increased propensity to falls and a loss of bone mass due to secondary hyperparathyroidism have been recognized as main risk factors for osteoporotic fractures in the elderly. In fact, recent evidence from the European Prospective Osteoporosis Study suggests that BMD may be less important than the risk of falling as a predictor of non-vertebral fracture in elderly women. Supplementation with calcium and vitamin D addresses both of these risk factors. Calcium and vitamin D reverse secondary hyperparathyroidism, with beneficial effects on BMD. Additionally, calcium and vitamin D supplementation significantly improves body sway and lower extremity strength, reducing the risk of falls. Randomized studies in both institutionalized and community-dwelling elderly people demonstrate that calcium and vitamin D reduce the risk of osteoporotic fracture in both populations,

particularly in the presence of dietary deficiencies. Although most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive agent, calcium and vitamin D should be a first-line strategy for the prevention and treatment of osteoporosis.

Recent analyses of pooled data from different risedronate trials in osteoporotic post-menopausal women support the concept that bisphosphonate treatment can reduce the incidence of osteoporosis-related vertebral and non-vertebral fractures within 6 months of the start of treatment, and that the benefit continues for at least 3 years. This early onset of action is clinically important for older patients with a high risk of osteoporotic fractures in the near term. In patients 80 years of age or older, risedronate was recently found to provide a statistically significant and clinically relevant antivertebral fracture effect over 3 years. These findings provided the first evidence that, even in patients 80 years of age or older, reducing bone resorption rate remains an effective strategy for the treatment of osteoporosis and provides an additional benefit on top of the benefit already provided by the calcium and vitamin D supplementation. However, a treatment effect on non-vertebral fractures was not seen in patients 80 years of age or older. Although alendronate and risedronate have been shown to effectively reduce the risk of non-vertebral fractures across a wide range of ages, little evidence currently exists to support the efficacy of bisphosphonates in reducing the risk of non-vertebral fractures in women 80 years of age or older. Most studies have not enrolled such elderly subjects. The Hip Intervention Program (HIP) with risedronate enrolled two groups of patients: group 1 consisted of women 70–79 years of age with osteoporosis, and group 2 consisted of women 80 years of age or older who had at least one non-skeletal risk factor for hip fracture or low BMD. In the HIP trial, no effect of risedronate on the risk of non-vertebral fracture was observed in group-2 patients, but these patients were not selected on the basis of low BMD and may not have been osteoporotic.

Secondary prevention of hip fractures should be an integral part of the management of individuals who sustain hip fractures. One option is the prescription of medications that lower the risk of hip fracture. Such therapies that are currently available include calcium and vitamin D supplementation, alendronate and risedronate. The bisphosphonates and calcium reduce the risk of hip fracture by improving bone mass and bone quality, and vitamin D supplementation affects the risk of falling not only by increasing bone mass but also by improving muscle function. However, the rate of use of these therapies among patients with hip fractures is low. Despite the fact that proven, efficacious drugs are now available for the treatment of osteoporosis, osteoporosis continues to be underdiagnosed and undertreated in the elderly, even after hip fracture. One of the many reasons why clinicians do not consistently initiate treatment for osteoporosis even after a hip fracture might be the fact that all of these drugs have been tested for primary prevention of hip fractures. There is an urgent need for studies to evaluate either pharmacological or non-pharmacological measures aimed at the secondary prevention of hip fractures.

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Abbreviations

$1,25(OH)_2D_3$	1,25di-hydroxyvitamin D
$25(OH)D_3$	25-hydroxycholecalciferol
$25OH_2D_3$	25-hydroxyvitamin D
AD-SOS	amplitude-dependent speed of sound
ADT	androgen deprivation therapy
ALP	alkaline phospatase
AMG 162	human monoclonal antibody to RANKL
Alox15	arachidonate 15-lipoxygenase
ALP	alkaline phosphatase
ANOVA	analysis of variance
APOSS	Aberdeen Prospective Osteoporosis Screening Study
AR	androgen receptor
ASBMR	American Society for Bone and Mineral Research
ATAC	Arimidex, Tamoxifen, Alone or in Combination
AUC	area under the receiver operating characteristic curve
AUC	area under the receiver operating control
BMC	bone mineral content
BMD	bone mineral density
BMP	bone morphogenetic protein
BSALP	bone-specific ALP
BSAP	bone-specific phosphatase
BUA	broadband ultrasound attenuation
CA	cortical area
CB1	cannabinoid type 1
CEE	conjugated equine oestrogen
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CORE	Continuing Outcomes Relevant to EVISTA
CSA	cross-sectional area
CSM	Committee on the Safety of Medicines
CT	calcitonin
CT	computed tomography
CTx	C-terminal cross-linking telopeptide of bone collagen
CTX	C-terminal telopeptide fragments of collagen
CTX	C-terminal teleopeptide of type 1 collagen
DASH	Dietary Approaches to Stopping Hypertension
dB/Mhz	decibel per megahertz
DMPA	depot medroxyprogesterone acetate
DOPS	Danish Osteoporosis Prevention Study
DPD	deoxypyridinoline
DXA	dual energy X-ray absorptiometry
ELISA	enzyme-linked immunoassay
ELISA	enzyme-linked immunosorbent assay
EMA	endomysial antibodies
EMEA	European Medical Evaluation Agency
EPIC	Early Post-menopausal Intervention Cohort
ERα	oestrogen receptor α
ERM	oestrogen receptor modulator
FDA	Food and Drug Administration
FEA	finite element analysis
FEV1	forced expiratory volume in 1 second

FSH	follicle-stimulating ormone
FIT	Fracture Intervention Trial
FPP	farnesyl diphosphate
Gab2	Grb2-associated binding protein
GIOP	glucocorticoid-induced osteoporosis
GnRH	gonadotropin-releasing hormone
GPRD	General Practitioner Research Database
HERS	Heart and Estrogen/ Progestin Replacement Study
HR	hazard ratio
HR-MRI	high-resolution magnetic resonance imaging
HR-pQCT	high-resolution peripheral quantitative computed tomography
HRT	hormone replacement therapy
HSA	hip structure analysis
ICTP	C-terminal telopeptide of type I collagen
ICTP	pyridinoline cross-linked C-terminal teloteptide of type 1 collagen
IGF-1	insulin-like growth factor-1
IL-6	interleukin-6
lod	log of the odds
LASA	Longitudinal Aging Study Amsterdam
LS-spine	lumbosacral spine
MCT	micro-computed tomography
μCT	micro-computed tomography
MMP	matrix metalloproteinase
MORE	Multiple Outcomes of Raloxifene Evaluation
MSC	marrow stromal cell
MTHFR	methylenetetrahydrofolate reductase
MWS	Million Women Study
NDNS	National Diet and Nutrition Survey
NEAP	non-carbonic acid production
NEAP	net endogenous non-carbonic acid production
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Clinical Excellence
NNT	number needed to treat
NORA	National Osteoporosis Risk Assessment
NSAID	non-steroidal anti-inflammatory drug
NTX	collagen-type I N-telopeptides
NTX	N-teleopeptide of type 1 collagen
NTx	N-terminal cross-linking telopeptide of bone collagen
OPPG	osteoporosis–pseudoglioma syndrome
OR	odds ratio
PAD	peripheral arterial disease
PBR	pre-treatment bone resorption
PEPI	Post-Menopausal Oestrogen/Progestin Interventions
PET	positron emission tomography
PHPT	primary hyperparathyroidism
PICP	carboxy-terminal extension peptide of procollagen type 1
PINP	amino-terminal extension peptide of procollagen type 1
PINP	N-terminal propeptide of type 1 collagen
PPAR-γ	proliferator-activated receptor-γ
PRAL	Potential Renal Acid Load
PTH	parathyroid hormone

QUAL-EFFO	Quality of Life Questionnaire of the European Foundation for Osteoporosis
QUS	quantitative ultrasound
RANKL	receptor activator of nuclear factor-κ ligand
RDRS-2	Rapid Disability Rating Scale version 2
RIA	radioimmunoassay
RH	relative hazard
RNI	Reference Nutrient Intake
ROC	receiver operating characteristic
RR	relative risk
SAXS	small-angle X-ray scattering
sCTX	serum CTX
SD	standard deviation
SERM	selective oestrogen receptor modulator
SF-36	Medical Outcomes Study Short Form 36 (questionnaire)
sFRP	secreted frizzled-related protein
SI	stiffness index
Smurf	Smad ubiquitin regulatory factor
sOC	serum osteocalcin
SOS	speed of sound
SOTI	Spinal Osteoporosis Therapeutic Intervention
sTRACP5b	serum TRACP isoform 5b
TA	total area
TGF-β	transforming growth factor-β
TNF-α	tumour necrosis factor α
TRACP	tartrate-resistant acid phosphatase
TRAP	tartrate-resistant acid phosphatase
TROPOS	Treatment of Peripheral Osteoporosis
TTG	transglutaminase
ucOC	under-carboxylated osteocalcin
uCTX	urine CTX
uDPD	urinary excretion of deoxypyridinoline
uNTX	urine NTX
uOC	osteocalcin fragments in urine
VDR	vitamin D receptor
VERT	Vertebral Efficacy with Risedronate Therapy
VERT	vertebral fracture reduction
WHI	Women's Health Initiative
WHO	World Health Organization

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