Review

Bone loss

Epidemiology of bone loss

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Abstract

Bone loss occurs when the cellular events of bone formation are quantitatively larger than bone formation. This manuscript discusses the measurement of bone loss, occurrence in the population, risk factors and consequences of bone loss. Recent developments in bone mass measurement and biomarkers have improved our ability to assess bone loss. This process is a normal concomitant of ageing. There are a number of other risk factors, including sex hormone deficiency, physical inactivity, calcium/vitamin D deficiency, inflammatory arthritis, corticosteroids, smoking and alcohol. The major consequence of bone loss in our ageing society is fracture.

Keywords: bone loss, epidemiology

Introduction

Bone is a highly metabolically active tissue; remodelling continues throughout life. The remodelling process is an active coupling of the processes of bone formation and resorption. An imbalance in this active coupling phenomenon, in which the cellular events of bone resorption are quantitatively larger than bone formation, leads to bone loss.

The epidemiology of osteoporosis is distinct from that of bone loss. Although excessive bone loss during ageing is likely to contribute to the incidence of osteoporosis, patients with fractures do not consistently have more rapid bone loss, greater bone resorption or a lower rate of bone formation. Any unifying hypothesis on the epidemiology of osteoporosis needs to consider the relative contributions of low peak bone density and bone loss to the deficit in bone density in adulthood.

Assessment of bone loss

Bone mass can be determined in the total skeleton or in local parts of the skeleton, such as the spine, hip and forearm. Current methods for evaluating skeletal status, assessing osteoporosis and bone loss and determining fracture risk rely mostly on the non-invasive assessment of bone mineral content and bone mineral density. The diagnostic procedure is complicated by the fact that different body sites contain different ratios of trabecular to cortical bone, which have different rates of loss. Furthermore, the measurement of bone mass at one site (such as the radius) might not accurately estimate the bone mass at another site (such as the spine or hip), although there is clearly correlation between sites.

A repeat bone mass measurement can be used to assess bone loss. It is important to understand the limitations of

these methods. Most studies on involutional bone loss have used absorptiometric techniques such as single photon absorptiometry, dual photon absorptiometry and, more recently, dual X-ray absorptiometry and single X-ray absorptiometry. Most of these techniques adjust the estimate of bone mineral for the errors in accuracy, which arise from variability in fat mass between individuals. It is likely that such errors of accuracy contribute to errors in the estimation of bone mass. Moreover, variable fat content of the spine with age is likely to contribute to errors in the estimation of bone loss [1]. At the spine the problem is compounded by the increasing prevalence of osteoarthritis and vascular calcification at the lumbar spine with age.

A further problem is that neither single nor dual X-ray absorptiometry measures true bone density (g/cm^3). The areal bone density (g/cm or g/cm^2) that they provide yields an overestimate of volumetric bone mineral density. This inaccuracy is negligible in the short term but is more important in longitudinal studies, particularly as the width of many bones can increase with age [2]. A recent study by Grampp *et al* [3] advocated the use of quantitative computed tomography as the most accurate method of assessing bone loss.

Another approach to the estimation of the rate of loss has been the measurement of biochemical markers of bone turnover. Previous reports concerning the association of markers with bone loss have been inconsistent. Some cross-sectional studies have found that there is a weak inverse relationship between biochemical markers and bone density, and that marker levels are elevated during periods of accelerated bone loss, such as early menopause [4,5]. Several algorithms have been developed from longitudinal data to provide an estimate of bone loss and stratify people into categories on the basis of their rate of bone loss [6,7]. The large day-to-day variations in the concentration of biochemical markers, and heterogeneity in biochemical markers of bone turnover in patients with fractures, make the application of these techniques difficult even for longitudinal data. More work is required to stratify further the risk of bone loss, but at present the use of biochemical markers has limited value in predicting bone loss in individuals [8].

Occurrence of bone loss

Bone loss is a normal concomitant of ageing and occurs in both genders after peak bone mass has been attained [9]. Starting from the middle of the third decade, women lose 35% of their cortical bone and 50% of their trabecular bone [10], whereas men lose approximately two thirds of this amount over their respective lifetimes [11].

Type 1 (postmenopausal) osteoporosis generally occurs before the age of 65. It affects 5–25% of women in early menopause [10,12]. Eastell *et al* [13] found that the ratio of trabecular to cortical bone of the vertebral body was 75:25, whereas other investigators found the ratio in the femoral neck to be 30:70 [14]. As trabecular bone loss is accelerated relative to cortical bone loss after menopause, regions with substantial amounts of trabecular bone might become fragile sooner.

Type 2 osteoporosis occurs in both men and women and involves the loss of both trabecular and cortical bone. The prevalence of this type of bone loss is universal after peak bone mass has been attained.

Studies have shown that from age 30–40, bone loss (both trabecular and cortical) begins [10,11] and that menopause is followed by an immediate decrease in bone mass and density within a year at both peripheral and central sites. The increased rate of bone loss reaches equilibrium approximately 10 years after menopause and then merges into a continuous age-related loss of predominantly cortical bone [15].

There is no firm evidence that bone loss is a bimodal process (in other words that there are fast losers and slow losers). Some studies have stratified their analysis of fracture risk into those who are fast, normal and slow bone losers. The results of this analysis indicate that those with a faster rate of bone loss have a higher future risk of fracture [16].

Risk factors for bone loss

In contrast with the total variance in bone density, which is undoubtedly predominantly genetic [17], studies on the genetic determinants of bone loss have yielded conflicting results [18–20]. From these data the view has emerged that environmental factors such as exercise might exert a large influence on bone loss at skeletal sites such as the hip and wrist, whereas genetic factors might be important in determining spinal bone loss. Gene–environment interactions undoubtedly contribute at all sites of bone loss.

Of the many factors that influence bone loss, sex hormone deficiency is by far the most important. Data from several studies have shown that rapid bone loss in women after the menopause can be effectively prevented by hormone replacement therapy [21]. As well as sex hormones, abnormalities of the calciotropic hormones are associated with bone loss [22].

Distinct from the accelerated phase of postmenopausal bone loss is a continuous and more gradual process of age-related bone loss that starts before the menopause in women and continues throughout life in both sexes [11]. This type of loss was previously considered to be a relatively slow and constant process, but longitudinal prospective research has provided evidence for a phase of accelerated

bone loss in old age, affecting mainly the hip [23,24]. It is difficult to differentiate the relative contributions of age and oestrogen deficiency in most patients [25].

There have been few longitudinal studies investigating the effect of physical activity on bone loss. Some studies have shown beneficial effects of exercise on bone mass in postmenopausal women. A recent longitudinal study provided evidence that a physically active lifestyle in the later decades of life can retard proximal femur loss [26]. This suggested an interaction between physical activity, weight, weight change and age-related bone loss. Underlying the idea that physical activity increases muscle strength and hence bone mass, several studies have examined the mechanical influence on bone loss [27].

Calcium intake has a significant effect on bone loss in women although the magnitude of effect seems to be dependent on age and site [28]. There is evidence that calcium supplementation slows the rate of bone loss in postmenopausal women [29], especially in those with a low dietary intake of calcium [30]. Moreover, the supplementation of calcium and vitamin D has been shown to reduce the risk of hip fracture in institutionalized elderly patients, who might be deficient in these nutrients [31].

The osteoporosis associated with inflammatory diseases such as rheumatoid arthritis and neoplastic diseases such as myeloma is due in large part to increased bone loss. This has been extensively documented in rheumatoid arthritis, where there is evidence of systemic and periarticular bone loss at an early phase in the disease [32]. Corticosteroids also cause osteoporosis by inducing accelerated bone loss [33].

Smoking predisposes to osteoporosis by inducing an earlier menopause and by causing an increased metabolic breakdown of oestrogen, both of which tend to accelerate bone loss [34].

High intakes of alcohol are known to have deleterious effects on bone mass, owing to the inhibitory effect of the alcohol on osteoblastic activity and the fact that the individuals who consume large amounts of alcohol are also prone to protein and/or calcium malnutrition, reduced mobility and hypogonadism.

Higher weight is associated with lower rates of bone loss [26]; conversely, older women with a smaller body size are at increased risk of hip fracture [35]. This increased risk is seen predominantly in those with involuntary weight loss [36].

Other risk factors for bone loss include gastrointestinal disorders causing malabsorption, the use of drugs such as anticonvulsants, chronic renal disease and amenorrhoea [37].

Outcome of bone loss: clinical implications

The major consequence of bone loss in our ageing society is fracture. The relative contributions of peak bone mass and bone loss to the development of low bone mass later in life with its attendant fractures requires clarification. Until these factors can be measured and their contributions to fracture development calculated it will be difficult to determine the exact role of bone loss in fracture development, because other factors associated with bone loss such as the development of microarchitectural abnormalities and microdamage could also be contributing.

Bone density decreases with advancing age as a result of bone loss [11]. Prospective epidemiological studies indicate that bone mineral density is the single best predictor of fractures [38,39]. A 1 SD decrease in bone mass can account for a 50–100% increase in the risk of all non-spine fractures, and a 1 SD difference in bone mass in the femoral neck is associated with a relative risk of 2.6 for subsequent hip fracture.

Bone turnover is difficult to interpret on an individual level. Heterogeneity in histomorphometric parameters of bone turnover, and biochemical markers of bone turnover [40], are found in patients with fractures. Eriksen *et al* [41] showed that patients with vertebral fractures had increased bone resorption and decreased bone formation at the cellular level but not at the tissue level. Meunier *et al* [42] found that approximately 50% of patients with vertebral fractures had no evidence of abnormalities in bone resorption or formation, approximately 30% had higher bone resorption surfaces, and approximately 20% had evidence of decreased formation.

Approximately 40 in 100 women will experience one or more fractures after the age of 50 years. At 50 years for women the lifetime risk is 17.5% for hip fracture, 16% for vertebral fracture and 16% for Colles' fracture; for men, the respective lifetime risks are 6%, 5% and 2.5% [43]. The consequences of these fractures, which can include reduced life expectancy, prolonged medical care and loss of independence, have a profound socioeconomic impact in an ageing population [44]. The different fracture risk in men is a result of a number of contributing factors, including less bone loss with ageing [45].

Management of bone loss

The two approaches that can be adopted in bone loss modification are, firstly, to identify those at greatest risk and, secondly, to move the distribution of bone loss for the whole population. From the viewpoint of the individual patient, bone loss is only one of the factors associated with ageing that contributes to fracture risk; management therefore needs to be individualized. Initially addressing their modifiable risk factors remains the gold standard of current medical practice. Following this pharmacological

intervention might be required for those individuals identified as being 'at risk'.

No discussion of epidemiology would be complete without considering the pharmaco-epidemiology of bone loss. In recent years a plethora of antiresorptive agents have become available. Rather than identify their individual strengths on the modification of bone loss, we would encourage readers to consider the various consensus statements available [46].

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