Disorders of bone metabolism

Nicola Peel

Abstract

Bone remodelling is critical to bone health. Alterations in the normal processes and regulation of remodelling may impact on bone mass and bone strength. Changes may be generalized or focal and underlie many of the common disorders of bone metabolism. This article focuses on the changes in bone remodelling which underlie both the development and treatment of osteoporosis. Osteomalacia, as an example of a mineralization disorder and Paget's disease as an example of a focal disorder of bone remodelling, are also briefly reviewed.

Keywords Bone mineral density; bone remodelling; dual-energy X-ray absorptiometry; fracture risk; osteomalacia; osteoporosis; Paget's disease

Introduction

Bone health depends on the composition and structure of bone and is maintained by a continual process of bone remodelling. Changes in the normal bone remodelling cycle underpin the decreased bone mass and increased bone fragility of osteoporosis. These changes occur with ageing and in response to physiological and pathological causes. Figure 1 illustrates the two predominant mechanisms of bone loss.

Mechanisms of bone loss

Increased bone turnover

There are many causes of increased bone turnover with the most common being the loss of oestrogen at menopause. Increased bone turnover is initiated by increased activation frequency of osteoclasts. The consequent increase in remodelling space leads to bone loss which is, at least in part, reversible. Increased bone turnover is also associated with an increased risk of trabecular perforation with the increased number of remodelling sites acting as stress risers within the trabecular architecture. Bone loss within the trabecular compartment occurs preferentially from the horizontal, non-weightbearing plates resulting in disproportionate loss of bone strength for the reduction in bone mass. Bone loss resulting from increased turnover may be generalized as in the menopausal woman but may also be localized, for example affecting the lower limbs following immobilization.

Remodelling imbalance

Remodelling imbalance typically occurs with ageing and is also the predominant mechanism through which glucocorticoid excess affects bone. Remodelling imbalance refers to a mismatch between the processes of resorption and formation with a net deficit at the completion of each remodelling cycle. The resulting reduction in bone mass is irreversible and is characterized by thinning of trabeculae with relative preservation of the trabecular architecture.

Effects of altered bone turnover acting independently on bone strength

Degree of mineralization

Alterations in bone turnover also have potential to affect bone strength by changing the degree of mineralization. Primary mineral apposition occurs early after production of bone matrix by osteoblasts. After completion of the cycle, secondary mineral apposition occurs over many months. Increased bone turnover leads to reduced mineralization as the time between remodelling cycles reduces. Conversely, decreased bone turnover rates reduce the average time between remodelling at any site and hence lead to a greater degree of mineralization. Biomechanical principles indicate that the yield strength (stiffness) of highly mineralized bone increases but that it will withstand less deformation before fracture and therefore becomes brittle. A reduced degree of mineralization results in greater pliability but a reduction in bone strength.

Bone geometry

Bone strength also relates to the geometric properties of bone, with larger bones generally being stronger. Subtle changes in bone size may result from remodelling even in the context of stable or decreasing bone mass in adults. Redistribution of bone mass in the long bones occurs with ageing as periosteal apposition occurs simultaneously with endosteal resorption. Biomechanically, this redistribution reduces the impact of bone loss on bone strength since an increase in diameter of a cylindrical structure compensates for the simultaneous decrease in cortical thickness. This may explain why some fractures, such as distal forearm fractures, do not continue to increase in frequency with ageing despite continued decrease in bone mass.

Osteoporosis as a consequence of altered bone remodelling

It may be seen, therefore, that alterations in bone remodelling underpin changes in bone mass and bone strength. The impact of these changes is manifest in the development and clinical presentation of osteoporosis.

Definition of osteoporosis

Osteoporosis may be defined as a systemic skeletal disease characterized by reduced bone strength, resulting in an increased risk of fracture. Osteoporosis may also be defined quantitatively using diagnostic thresholds based on measurement of bone mineral density (BMD, Table 1) as defined by the World Health Organization (WHO). These diagnostic criteria may be used for measurements performed at the spine, hip or forearm using photon absortiometry (usually dual-energy X-ray absorptiometry, DXA) in postmenopausal women. The thresholds are inappropriate for other measurement techniques such as quantitative ultrasound or other skeletal sites such as the calcaneus. They should be used with caution in other groups such as men or premenopausal women. The WHO criteria should not be used in children or young

Nicola Peel *DM FRCP is a Consultant Physician and Honorary Senior Lecturer at the Metabolic Bone Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. Conflicts of interest: none declared.*

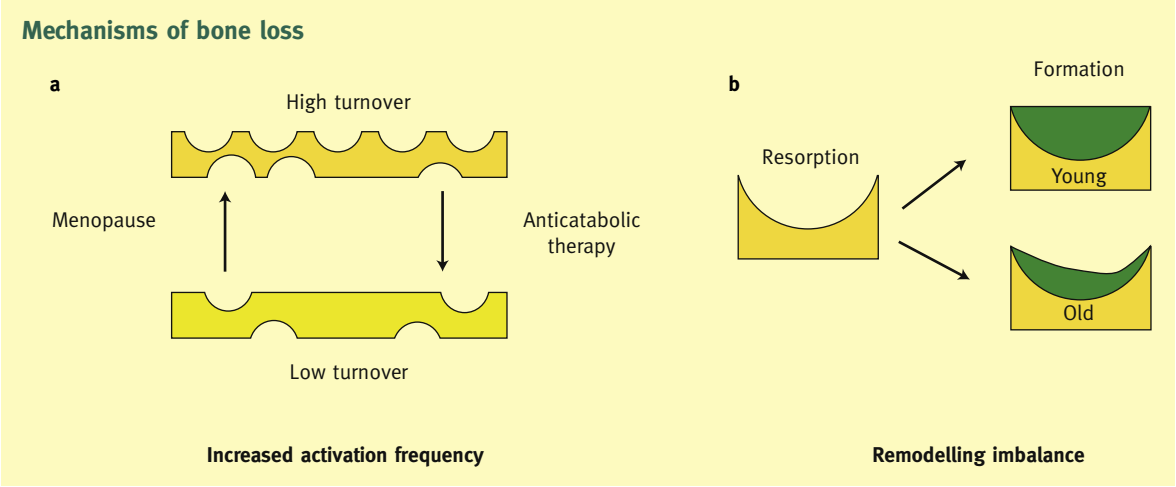

Figure 1 Mechanisms of bone loss — (**a**) increased activation frequency and (**b**) remodelling imbalance.

adults prior to the attainment of skeletal maturity, in whom BMD should be expressed in relation to skeletal size and age.

Epidemiology of osteoporosis

Osteoporotic fractures are common and are associated with considerable morbidity. Fractures of the hip and vertebrae are also associated with an increase in mortality of approximately 20%. In the UK, as an example of a developed nation, it is estimated that beyond age 50, 1 in 2 women and 1 in 5 men will sustain an osteoporosis-related fracture. The financial costs of fracture management and subsequent social care needs are enormous. Health economic modelling demonstrates that case-finding of individuals at high risk and targeting of treatment to reduce fracture risk is cost-effective, although the appropriate intervention thresholds for both diagnosis and treatment vary between different populations.

In general, fracture rates:

- increase with age
- are greater in females than males
- differ between fracture sites both in terms of incidence and in the influence on further fracture risk
- differ between populations
- are increasing over time more than can be explained by ageing of the population alone.

Quantitative definition of osteoporosis. *T* score describes an individual's bone mineral density (BMD) expressed as a standard deviation score in comparison to a young healthy reference population of the same gender and ethnic background (WHO, 1994)

BMD *T* score	Diagnosis
Greater than −1	Normal
Less than −1, greater than −2.5	Osteopenia
Less than −2.5	Osteoporosis
Less than −2.5 plus fragility fracture	Severe osteoporosis

Table 1

Assessment of fracture risk

An individual's risk of sustaining a fracture depends on their risk factor profile. Some risk factors directly affect bone strength by affecting BMD whereas others influence bone strength at least partly through independent mechanisms such as by increasing the risk of falling. Examples of risk factors are shown in Table 2. Several algorithms have been developed to integrate the impact of risk factors, most notably the FRAX® algorithm developed by WHO. FRAX® uses easily obtainable clinical information to estimate the 10-year absolute risk of fracture. The FRAX® algorithm is available for a number of populations worldwide and is increasingly used in clinical practice to aid decisions about the need to assess BMD and whether therapeutic intervention is required.

Measurement of BMD remains a key component of the evaluation of fracture risk and BMD may be reliably quantified using current techniques. The gold standard technique for assessment of BMD is DXA and measurements are usually made at the lumbar spine and proximal femur to capture information about the skeletal regions where fracture is most closely associated with underlying bone fragility.

Examples of factors affecting fracture risk

BMD dependent	BMD independent
Female gender	Age
Premature menopause/amenorrhoea	Prior fragility fracture
Hypogonadism	Glucocorticoid use
Ethnic origin	Family history, particularly hip fracture in first-degree relative
Excess alcohol consumption	Low body mass index
Immobilization	Current smoking
Low dietary calcium intake	Neuromuscular disorders
Vitamin D deficiency	Poor visual acuity

Table 2