Osteoporosis: pathogenesis and clinical intervention

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Abstract
Osteoporosis is a very common disorder and much has been learnt in recent years about the many pathogenic processes that contribute to bone loss and fragility. Drug treatments are now available to prevent bone loss and reduce fracture, and there are prospects for modifying some of the pathogenic processes themselves. In common with other structures, the tissues of the musculoskeletal system undergo many changes with aging, and some of the commonest skeletal disorders are seen in the elderly. The changes in bone lead to osteoporosis and fractures, whereas muscle changes (sarcopenia) contribute to frailty, and changes in cartilage lead to osteoarthritis.

Epidemiology
Osteoporosis is the commonest disorder of bone. The commonly quoted figures state that one in three women and one in twelve men will have a fracture beyond the age of 50, and even these may be underestimates [1–3]. In women, the loss of oestrogen at the menopause is the major change leading to loss of bone. In men the causes are less obvious. However, in both sexes many other factors contribute, and there is a strong interplay between genetic and environmental influences.

Bone mass declines and the risk of fractures increases as people age, especially as women pass through the menopause. Fractures occur at many sites, but wrist fractures (Colles fractures) and vertebral fractures are particularly common. Hip fractures are arguably the most serious outcome of osteoporosis, and are associated with considerable morbidity, as well as loss of independence and increased mortality. In the U.K., the annual costs of osteoporosis to the NHS is estimated to be £1.7 billion, and hip fractures are a major contributor to these costs [4]. Hip fractures are becoming more frequent because the world’s population is aging, and because the frequency of hip fractures is increasing by 1–3% per year in most areas of the world. Rates of hip fracture vary more widely from region to region than does the prevalence of vertebral fractures.

Since prevention of fractures and treatment of osteoporosis with drugs is also costly, it is important to identify individuals at high risk of disabling fractures, thereby allowing careful allocation of expensive treatments to individuals most in need. Low bone density and previous fractures are risk factors for almost all types of fracture, but each type of fracture also has its own unique risk factors. Use of glucocorticosteroids, family history of fracture and smoking are other risk factors.

Key words: aging; bisphosphonates; bone; osteoporosis.
Abbreviations used: PTH, parathyroid hormone; BMD, bone mineral density; SERM, selective oestrogen receptor modulator.

The cellular basis of bone remodelling
The changes that occur in osteoporosis can be understood in terms of subtle but important disturbances in bone remodelling. Bone is metabolically active throughout life. After skeletal growth is complete, remodelling of both cortical and trabecular bone continues. This remodelling requires the co-ordinated actions of osteoclasts to remove bone, and osteoblasts to replace it. Osteoclasts are derived from blood (haematopoietic) stem-cell precursors under the direction of essential genes such as src, of signalling proteins such as nuclear factor κB (NF-κB), and many cell-bound and soluble cytokines and growth factors. The so-called RANK/RANK-ligand (receptor activator of NF-κB) system is now known to be one of the dominant regulators of osteoclast development.

Osteoblasts differentiate from stromal-cell precursors, and manufacture a complex extracellular matrix, which subsequently mineralizes. Bone formation is regulated by master genes, such as cbfa1, and by growth factors such as members of the transforming growth factor β superfamily, which includes the bone morphogenetic proteins.

Apoptosis (programmed cell death) is emerging as a major means of regulating the life span of bone cells of all lineages: osteoclasts, osteoblasts and osteocytes [5]. This may contribute to changes in bone turnover under physiological and pathological conditions. Drugs with adverse effects on bone, such as glucocorticoids, may induce osteocyte apoptosis, whereas therapeutic agents that inhibit bone resorption, including oestrogens and bisphosphonates, may shorten the life span of osteoclasts. Increased apoptosis of osteocytes is a feature seen in fractured femoral necks.

The control of calcium metabolism and of skeletal remodelling is achieved by the systemic calcium regulating hormones, parathyroid hormone (PTH), 1,25-dihydroxy-vitamin D (calcitriol) and calcitonin, acting in concert with local regulatory mediators. There are many ways in which these hormones interact with local mediators and contribute
to the physiological regulation of bone metabolism, to the pathogenesis of skeletal diseases, and to the changes that occur with age. Recently, leptin has been identified as another potential systemic regulatory hormone [6].

With loss of oestrogen, there is an increase in remodelling activity in both cortical and trabecular bone. There is a failure for all the bone removed during bone resorption to be replaced by an equivalent amount of new bone. The gradual loss of trabecular and cortical bone, accompanied by deterioration in their structural integrity, leads to impairment of the ability to resist mechanical loading leading to fracture.

Genetic factors

There are strong genetic contributors to skeletal size and composition. Comparisons of identical and non-identical twins have led to estimates that more than 50% of peak bone mass is determined by genetic factors.

Overall physique affects susceptibility to osteoporosis and may underlie racial differences in incidence [7]. Hip fractures typically occur in the thin and frail rather than the fat and robust, and a low body mass index is a risk factor. Hip axis length is a quantifiable geometric measure related to fracture risk.

Rarely, osteoporosis or unusually high bone mass can occur as the result of mutations in a single gene. Thus inactivating mutations in the lipoprotein-receptor-related protein 5 gene are the cause of the osteoporosis-pseudoglioma syndrome, whereas the high bone mass syndrome is caused by activating mutations of the same gene [8,9]. In the various forms of osteogenesis imperfecta (brittle-bone disease), defects in the synthesis or structure of Type I collagen occur due to a range of different mutations in Type I collagen genes.

In the commoner forms of osteoporosis, genetic factors play an important role in regulating skeletal size and geometry, bone mineral density (BMD), ultrasound properties of bone, and bone turnover, as well as contributing to the pathogenesis of osteoporotic fracture [10]. These phenotypes are determined by the combined effects of several genes and environmental influences. Genome-wide linkage studies in humans have identified several chromosomal loci that show definite or probable linkage to BMD, but so far the causative genes remain to be identified. Linkage studies in mice have similarly identified several loci that regulate BMD.

Most research has so far been done on candidate genes. Among the best studied are the vitamin D receptor and the collagen type I α1 gene. Polymorphisms of vitamin D receptor have been associated with bone mass in several, but not all, studies, and there is evidence to suggest that this association may be modified by dietary calcium and vitamin D intake. A functional polymorphism affecting an Sp1-binding site has been identified in the collagen type I α1 gene that predicts osteoporotic fractures independently of bone mass by influencing collagen synthesis and bone quality. An important problem with studies of most candidate gene studies is small sample size, and this has led to inconsistent results in different populations. This is also complicated by the multiple clinical end points (BMD, fracture, rates of bone loss, etc.) to which genetic factors may contribute in different ways.

Drug treatments

Up until now, all the major drugs used to prevent or treat osteoporosis are inhibitors of bone resorption. This includes oestrogens and oestrogen-related compounds, particularly the SERMs (selective oestrogen receptor modulators), and bisphosphonates and calcitonin. The best evidence for reduction in fractures exists for bisphosphonates, particularly alendronate and risedronate, and for the SERM, raloxifene [11–13].

The bisphosphonates are stable chemical analogues of inorganic pyrophosphate, and are remarkably potent inhibitors of osteoclast activity. The bisphosphonates increase bone mass, and reduce all types of fracture when given in adequate doses. The more potent bisphosphonates all have nitrogen atoms in their side chains, and these compounds appear to inhibit osteoclasts by selectively inhibiting farnesyl diphosphate synthase in the mevalonate pathway of cholesterol biosynthesis. This results in reduced synthesis of isoprenoid lipids and a blockade of prenylation of GTP-binding proteins, which interferes with osteoclast attachment, motility and function [14].

Development of new drugs

Within the next few years, several more new drugs are likely to be licensed for use in osteoporosis. Unfortunately, the process of drug discovery and development is slow. It usually takes at least 10 years from the discovery of a new compound for it to be studied experimentally, for its safety to be established, and for clinical trials to be completed. Even the clinical trial stage for drugs in osteoporosis may require 3 years or more from start to finish, in order to meet the current regulatory requirement for demonstrating a reduction in fractures. As a result, only those drugs already undergoing clinical trials can be expected to be approved in the next few years.

An important step will be the evaluation of additional tissue selective oestrogens or SERMs. The ideal compound of this type would possess all the good properties of oestrogens, but none of the bad. Such an agent would therefore be effective in osteoporosis, heart disease and Alzheimer’s disease, without adverse effects on the breast or uterus in terms of increasing cancer risk. The first compound in this class is raloxifene, which has several of these effects, particularly in reducing fractures and breast cancer. Other SERMs may follow, but the complete assessment of their benefits and profile of action will be a lengthy process.

Among the new drugs under study are the bisphosphonates, ibandronate and zoledronate. An interesting development here is the use of new routes of administration. Zoledronate, for example, produces a sustained inhibition of bone resorption for more than a year after a single injection.
[15]. If this can be shown to reduce fractures, it will offer a very simple and convenient approach to the management of osteoporosis.

Other important advances will come from an increasing emphasis on the development of drugs that stimulate bone formation, as so-called anabolic agents. It would obviously be a significant improvement in therapeutics if anabolic agents could be developed that would enhance the formation of new bone, and therefore produce bigger changes in bone mass and strength than that which can be achieved with current drugs, which only inhibit bone resorption, such as the bisphosphonates and oestrogens.

The first success in developing drugs that enhance bone formation has been with PTH. Although it has been known for many years that PTH given intermittently, rather than continuously, increases bone mass, clinical trials that demonstrate a significant reduction in vertebral and non-vertebral fractures have only recently been completed [16]. The results on bone mass and fracture reduction are impressive when PTH is given by daily injection, and are a probable forerunner of other opportunities in this area.

Thus, various other PTH peptides are being evaluated for their potential anabolic effects, as are strontium salts [17]. Other peptide hormones and growth factors, as well as prostaglandins, might also be used in this way. Statins may also stimulate bone formation, as well as inhibit resorption [18].

Looking further ahead, there are several other ways in which novel agents might be developed based on the increasing knowledge of bone biology and the pathogenesis of osteoporosis. High-throughput screening methods and combinatorial chemistry have vastly increased the rate at which new pharmacological candidates may be identified.

Advances in basic sciences are taking place rapidly on a number of fronts. The role of regulatory factors that determine bone-cell differentiation and function remains at the centre of research. An example of a completely unpredicted regulatory system is the discovery of the ‘high bone mass’ genes responsible for dense bones in certain families, which offers opportunities for developing new types of drugs to improve bone.

Osteoporosis is not yet solved

Much remains to be done, despite the recent and remarkable advances in bringing osteoporosis to public attention, in understanding its pathogenesis, and in improving its diagnosis and treatment.

The challenges in the future will include the problem of translating the increase in knowledge in the basic sciences to the benefit of as many patients as possible in an efficient and cost-effective manner. The increasing emphasis on evidence-based medicine and the political needs to limit costs of health care will have a large part to play in what can be achieved.

We are moving rapidly from an era when only few drugs were available to one in which more and better methods of treatment are likely to exist. Although we can perhaps predict rather well what is likely to happen over the next decade, beyond that, it is probable that the approaches to osteoporosis and its management will differ substantially from those we use now.

References

1 The European prospective osteoporosis study (EPOS) group (2002) J Bone Miner. Res. 17, 716-724

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