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Recent Advances in the Pathogenesis and Treatment of Osteoporosis

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Introduction

Osteoporosis is characterised by deterioration of bone mass and microarchitecture, resulting in increased bone fragility and propensity to fracture. Worldwide, there are nearly 9 million osteoporotic fractures each year, and the US Surgeon General's report of 2004, consistent with data from the UK, suggested that almost one in two women and one in five men will have experience a fracture in their remaining lifetime from the age of 50 years (1). The cost of osteoporotic fracture in the UK approaches £3 billion annually and, across the EU, the estimated total economic cost of the approximately 3.5 million fragility fractures in 2010 was €7 billion (2). In this article we review the pathogenesis of osteoporosis and approaches to improving bone strength, aimed at reducing the immense burden of osteoporotic fracture.

Pathogenesis

Hierarchical structure

Fractures occur when the force applied to a bone exceeds its strength. A bone needs to be both stiff and flexible to resist fracture, which is achieved through a hierarchical structure. Collagen Type 1 fibrils are wound in a triple helical structure, linked together with non-collagenous proteins, which help to prevent shearing. Hydroxyapatite crystals deposited on the collagen structure add strength, particularly in compression. Cross-linkage between collagen fibrils with non-collagenous proteins is reduced in osteoporotic bone, leading to reduced tensile strength (3). In addition, larger hydroxyapatite crystals are found in osteoporosis, making bone more brittle and prone to fracture (4).

Bone cells

Osteoblasts, osteocytes and osteoclasts are the three main types of bone cells. Osteoblasts are bone-forming and may become embedded within bone mineral as mature osteocytes (comprising 90-95% of the cells within bone) or remain on the surface as bone-lining cells. Osteoclasts are multinucleated cells responsible for bone resorption. Osteoblasts and osteoclasts work together in a coordinated fashion at specific sites on the surface of trabecular or cortical bone, forming “bone multicellular units”. During bone formation, osteoblasts lay down new osteoid collagen matrix and over a period of weeks to months, crystals of calcium hydroxyapatite form on the collagen fibrils. Bone is laid down during growth and repair and through adaptation to mechanical loading in a process known as modelling. Remodelling, in contrast, involves a cycle of resorption and formation of existing bone. Osteocytes play a key role in the regulation of modelling and remodelling. The arrangement of the osteocytes around Haversian canals acts as a mechanosensory system and allows communication both directly between neighbouring osteocytes and through the release of endocrine, paracrine and autocrine signalling factors to other bone cells. The various pathways important to the regulation of osteoblast and osteoclast activity, such as RANK-RANKL and wnt signalling, are increasingly recognised as targets for anti-osteoporosis agents.

Changes in bone structure across the lifecourse

The balance of formation and resorption has a critical influence on bone mass and strength throughout life. There is a positive balance during childhood until achievement of peak bone mass in early adulthood (5), with a subsequent period of stability and then a negative balance in older age, with osteoclast activity greater than osteoblast activity, leading to bone loss. In women, this process is accelerated after the menopause. At the level of the whole bone, the cellular mechanisms and associated influences result in differences in structure between males and females, and alterations with advancing age. Males typically have a larger bone cross sectional area than females, and in addition there is a significant reduction in cortical thickness in females following the menopause, contributing to the well established sex differences in fracture risk. The structure of the trabeculae differs between the sexes, with young women having fewer and thinner trabeculae than young men, and a greater reduction in trabecular number in women as they age (6). In addition, cortical porosity increases at a faster rate in female ageing (7).

Clinical Risk Factors

There are many factors that influence fracture risk, either through bone mineral density or through independent mechanisms. These include age, glucocorticoid therapy, a previous personal history of fracture, a family history of hip fracture, current smoking practice, alcohol abuse and certain diseases associated with osteoporosis e.g. rheumatoid arthritis, diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, malabsorption and chronic liver disease. These are summarised in Table 1, and have, in terms of risk assessment, been incorporated into the FRAX® tool (8), a WHO supported initiative which uses risk factors, with or without BMD measurement, to estimate a 10 year probability of

either hip fracture or major osteoporotic fracture. FRAX® is by far the most commonly used such tool globally, covering 75% of the world's population, and may, as in the UK, be linked to assessment algorithms to define thresholds for intervention with treatment (9).

Treatment of osteoporosis

Vitamin D and Calcium supplementation

The role of vitamin D and calcium supplementation has been much debated in recent years with numerous meta-analyses suggesting conflicting findings. A large UK randomised controlled trial demonstrated that supplementation with either calcium, vitamin D or both for secondary fracture prevention at the population level appeared ineffective (10), although supplementation in high risk settings where deficiencies are expected, for example in nursing homes, may be beneficial (11). A recent individual patient data meta-analysis demonstrated that overall, there appeared to be a modest benefit for combined vitamin D and calcium supplementation for hip fractures, total fractures and probably vertebral fractures, but that there was no benefit for vitamin D alone (12). Although there has been discussion from one research group that excess calcium intake may be associated with increased cardiovascular risk (13), this has not been substantiated across many other studies. Indeed, it is reassuring to note that a recent individual-patient-data meta-analysis of the anti-fracture studies suggests that calcium and vitamin D supplementation in combination is associated with an improvement in mortality, which is not observed with vitamin D supplementation alone (14). Almost all of the randomised control trial evidence for the efficacy of anti-osteoporosis drugs comes from patients who were prescribed commitment calcium and vitamin D supplementation; both should therefore usually be prescribed adjunctively with treatment for osteoporosis.

Bisphosphonates

Bisphosphonates are synthetic analogues of the naturally occurring compound pyrophosphate and bind strongly to hydroxyapatite, inhibiting bone resorption by inactivating osteoclasts. The most commonly prescribed oral bisphosphonate is alendronate. If taken properly (in the morning with a glass of water, 45 minutes before food, drink or other medications and remaining upright for about 30-60 minutes after the dose), upper GI side effects are uncommon. However, for those who are unable to tolerate oral bisphosphonates, or in whom they are contraindicated (for example malabsorption or dysphagia), then an intravenous bisphosphonate, such as zoledronate (given yearly in a dose of 5mg by infusion over a minimum of 15 minutes) is an alternative.

Denosumab

Denosumab, a fully humanised antibody to receptor activator of nuclear factor kappa B ligand (RANKL) is a newer antiresorptive agent. RANKL, secreted by osteoblasts, is a major activator of osteoclastic bone resorption and mimics the action of osteoprotegerin (OPG). It is administered as a subcutaneous injection once every six months and its efficacy has been demonstrated in patients with renal impairment, although due consideration should be given to the possibility of underlying renal bone disease in CKD 4-5. Three year fracture data show a 68% reduction in vertebral fracture and 40% reduction in hip fracture (15). Side

effects are uncommon, but may include skin infections, predominantly cellulitis. This is not typically seen at the injection site and is thought to be secondary to an immunomodulatory effect of the drug. Hypocalcaemia can also be a risk, particularly if the patient is vitamin D deficient, or has renal impairment.

Strontium ranelate

Strontium, an element directly below calcium in group 2 of the periodic table, is combined with ranelic acid as a carrier to form strontium ranelate. It is taken as a single daily oral dose. Its mechanism of action remains a subject of research, but there is evidence that it increases bone strength by altering bone material properties. Administration of strontium ranelate leads to a substantial increase in BMD at the spine and hip, though part of this increase is artefactual, due to incorporation of strontium (which has a greater atomic weight than calcium) into bone. Studies have shown a 36% relative risk reduction in hip fracture over three years in osteoporotic patients (16). In 2013 a MHRA warning on Strontium ranelate was issued due to increased risk of cardiovascular disorders (relative risk for myocardial infarction 1.6), in addition to the previously known risk of VTE. Therefore its use is now restricted to treatment of severe osteoporosis in postmenopausal women with high risk of fracture and in men at increased risk of fracture, but with no cardiovascular or cerebrovascular disease. However, within this selected group of patients, particularly now that many individuals have undergone long-term bisphosphonate treatment, strontium ranelate does still offer a useful alternative (17).

Selective Oestrogen Receptor Modulators (SERMs) – Raloxifene

Raloxifene is a selective oestrogen receptor modulator that has antiresorptive estrogenic effects on the skeleton without the unwanted risks of estrogen in the breast. Its use is also associated with a significant decrease in the risk of breast cancer. It has been shown to be effective in preventing post-menopausal bone loss and in preventing vertebral fractures. However there is no evidence that raloxifene prevents hip or non-vertebral fractures (18). Adverse effects include leg oedema, cramps, hot flushes and a two to threefold increase in the risk of venous thromboembolism.

Teriparatide

Teriparatide (recombinant human 1-34 parathyroid-hormone peptide) is the only agent in current widespread use with truly anabolic effects on bone. It is administered by subcutaneous injection in daily doses of 20 µg. It increases bone formation and produces large increases in BMD, leading to approximately 70% reduction in the incidence of new moderate or severe vertebral fractures over 18 months of treatment, together with reductions in non-vertebral fractures (19). Side effects are uncommon but may include nausea, headache, and dizziness; in addition, transient hypercalcaemia and hypercalciuria may occur. Studies have shown added benefit in combination treatments such as teriparatide plus denosumab or teriparatide plus zoledronate (20), although such approaches are not yet approved clinically in the UK, and use of teriparatide in the UK is currently limited to those older patients at highest fracture risk and who may have failed other therapies.

Adverse effects, and duration of therapy

Atypical femoral fractures of the subtrochanteric region and femoral shaft may also rarely occur in patients taking bisphosphonates or denosumab. These are usually located in the lateral cortex around which endosteal thickening may be observed prior to fracture occurrence. Individuals may have prodromal pain and fractures typically are transverse, sometimes bilateral and occur after minimal trauma. Although these fractures can occur in bisphosphonate/ denosumab naïve individuals, they appear more commonly in patients taking these therapies for a prolonged duration. It is thought that the reason for this increased incidence is related to over-suppression of bone turnover. Overall, the fractures prevented greatly outnumber those atypical events potentially resulting from medication (21). Osteonecrosis of jaw is extremely rarely observed during therapy for osteoporosis (<1/100,000/yr for individuals on oral bisphosphonates (22)), but appears more commonly when higher doses of bisphosphonates are given intravenously for treatment of bone metastases. A causal link to bisphosphonates is unproven but international guidance suggests a prudent approach, encouraging patients to maintain good oral hygiene and have regular dental visits, with invasive dental work performed before commencement of bisphosphonate or denosumab therapy (23).

Current UK guidance has therefore moved towards a reassessment of the need for treatment after 3 years of intravenous bisphosphonate/subcutaneous denosumab, and 5 years of oral bisphosphonate (9). For high-risk patients, continuation of treatment is usually warranted, but where there have been no incident fractures and bone mineral density has improved, a period without treatment may be recommended.

Novel therapies

Cathepsin-K inhibitors

Odanacatib is a once weekly oral treatment for osteoporosis in which phase 3 clinical trials have recently been performed. It inhibits Cathepsin-K, a cysteine protease expressed in osteoclasts which degrades type 1 collagen. In postmenopausal women with low BMD, twenty-four months of treatment with odanacatib was shown to produce increases in lumbar spine and total-hip BMD by 5.5% and 3.2%, respectively, whereas BMD at these sites was essentially unchanged with placebo (-0.2% and -0.9%) (24). However, later trial outcomes also demonstrated a possible increase in cerebrovascular events, which has led to a delay in FDA approval whilst outcomes are further adjudicated.

Anti-sclerostin antibodies

Sclerostin, an osteocyte-secreted protein, negatively regulates osteoblasts and inhibits bone formation through the LRP5 / Wnt signalling pathway. The role of sclerostin in bone mass homeostasis was highlighted by the finding that two rare high bone mass diseases, van Buchem's disease and sclerostosis, have been linked to inactivating mutations in the sclerostin gene. A monoclonal antibody to sclerostin, romosozumab, was administered intravenously to healthy men and postmenopausal women and was shown to increase bone-formation markers, along with a dose-related decrease in bone-resorption markers.

Statistically significant increases in bone mineral density of up to 5.3% at the lumbar spine and 2.8% at the total hip compared with placebo were observed on day 85 of treatment (25).

A randomized, double-blind, placebo-controlled multicentre phase 2 clinical trial of a second agent, blosozumab (a humanized monoclonal antibody targeted against sclerostin) demonstrated statistically significant dose-related increases in spine, femoral neck, and total hip BMD as compared with placebo. In the highest dose group, BMD increases from baseline reached 17.7% at the spine, and 6.2% at the total hip. Biochemical markers of bone formation also increased during blosozumab treatment, whilst resorption markers decreased (26).

These findings present promise for future use of anti-sclerostin antibodies as anabolic osteoporosis therapies. Other potential areas for investigation include new selective oestrogen receptor or androgen receptor modulators, calcilytics (calcium receptor antagonists), the nitric oxide pathway and interventions aimed at sarcopenia in what is an exciting and rapidly changing field of osteoporosis treatment and fracture prevention.

Conclusion

In recent decades, our understanding of the pathogenesis of osteoporosis has dramatically increased, with development of a wide range of effective pharmaceutical approaches to fracture prevention. Given the enormous prevalence of osteoporosis, and frequency and burden of resulting fragility fractures, one of the key concerns going forward remains the optimal identification of those requiring treatment (27). The tools for fracture risk assessment are widely available, in the form of the FRAX® calculator, and new medications are undergoing testing. It is vital that awareness of osteoporosis is promoted amongst all health professionals, in order to ensure closure of the so-called “treatment gap”, and with a consequent reduction in the burden of osteoporotic fracture for individuals, healthcare systems and societies.

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Table 1

Risk factors for Osteoporosis

Risk factors independent of bone mineral density	Risk factors dependent on bone mineral density
Age	Untreated hypogonadism, premature menopause
Previous personal history of fragility fracture	Malabsorption
Maternal history of hip fracture – heritable influences	Endocrine disease e.g. hyperthyroidism
Glucocorticoid therapy	Chronic renal disease
Smoking	Chronic liver disease
Alcohol intake ≥ 3 units/day	Chronic obstructive pulmonary disease
Rheumatoid arthritis	Immobility
Body mass index ≤ 19 kg/m ²	Drugs e.g. androgen deprivation therapy, aromatase inhibitors
Falls	
Caucasian ethnicity	
Geography – latitudes furthest from equator	

Table 2

European guidelines on the spectrum of antifracture efficacy of pharmacological interventions for osteoporosis (*posthoc analysis in a subset of patients).

Intervention	Vertebral	Non-vertebral	Hip
Alendronate	+	+	+
Risedronate	+	+	+
Zoledronic acid	+	+	+
Etidronate	+	-	-
Ibandronate	+	+*	-
Raloxifene	+	-	-
Strontium	+	+	+*
Teriparatide	+	+	-
Denosumab	+	+	+