Pharmacotherapy for the treatment of osteoporosis in the elderly

The complications of osteoporosis increase with age.

J A Dave, MB ChB, PhD, FCP (SA), Cert Endocrinology & Metabolism (SA)

Endocrinologist in private practice; Part-time senior specialist in the Division of Endocrinology and Diabetic Medicine at Groote Schuur Hospital and the University of Cape Town, Cape Town, South Africa

Corresponding author: J A Dave (joel.dave@uct.ac.za)

Introduction

Osteoporosis is common globally in both women and men. For decades it was thought that osteoporosis was confined to post-menopausal women. However, it is becoming increasingly recognised in pre-menopausal women and in men. In osteoporosis the bone is reduced in mass as well as having microarchitecture that increases the risk of a fragility fracture – defined as a fracture that is sustained with minimal trauma or from a standing height or lower. The prevalence of fractures, especially of the hip, increases with increasing age. The classical osteoporotic fractures in older individuals involve the spine, hip and wrist, but may also involve the ribs, shoulder and pelvis.

In 2000, there were an estimated 9 million osteoporotic fractures globally – 1.6 million at the hip, 1.7 million at the forearm and 1.4 million clinical vertebral fractures. There is at least one report estimating that the global prevalence of hip fractures will increase to 6.26 million by 2050 (1990: 1.3 million; 2000: 1.6 million). Apart from the high cost of treating osteoporotic fractures (£1.7 billion/year in the United Kingdom and $18 billion/year in the USA), fractures are a major cause of morbidity and mortality in the elderly, with a mortality rate of 15 - 35% in the first year following a fracture. In those who survive, there is a high rate of immobility and disability. Therefore, it is essential that once the patient has been diagnosed with osteoporosis and secondary causes for osteoporosis have been excluded, appropriate management is initiated in order to prevent a fracture.

Management of osteoporosis

It is important to recognise that non-pharmacological measures also play an important role in the prevention and management of elderly patients with osteoporosis. These measures include maintaining a healthy diet (adequate amounts of calcium and vitamins D, C, B6 and K), regular weight-bearing exercise, cessation of smoking, reducing alcohol intake (<3 units/day) and avoiding bone toxic drugs such as glucocorticoids. Since a previous fracture and falling are two factors consistently shown to increase the risk for a future fracture, a fall assessment is a critical part of the assessment of an elderly patient with osteoporosis. This assessment includes a history, physical examination, assessment of gait and balance problems using the ‘get-up-and-go’ test and an assessment for intrinsic and extrinsic risk factors for falling.

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Pharmacotherapy

Pharmacotherapy for the treatment of osteoporosis can be classified as inhibitors of bone turnover such as calcium, vitamin D, hormone replacement therapy, selective oestrogen receptor modulators, bisphosphonates, calcitonin and denosumab or stimulators of bone formation such as strontium ranelate and recombinant parathyroid hormone.

Inhibitors of bone formation/turnover

Calcium. The data from the many studies assessing the contribution of calcium to the prevention and treatment of osteoporosis are difficult to interpret due to heterogeneity between the studies, the high drop-out rate, a lack of uniformity in outcome measures, and different formulations and doses used. A meta-analysis of these studies revealed a small but positive improvement in bone mineral density (BMD) as well as a non-significant decrease in vertebral (23%) and non-vertebral (14%) fractures. A meta-analysis of 15 studies showed that calcium supplementation increased the risk of myocardial infarction in the 5 trials with patient-level data (hazard ratio (HR) 1.31; 95% confidence interval (CI) 1.02 - 1.67; p=0.035) and in the 10 studies with trial-level data (pooled relative risk (RR) 1.27; 95% CI 1.01 - 1.59, p=0.038). The average dose of calcium in these studies was 1 200 mg/day with some patients taking as much as 2 000 mg/day. The National Osteoporosis Foundation of South Africa (NOFSA) recommends 500 mg of elemental calcium daily for the prevention and treatment of osteoporosis. There is no convincing evidence to support a specific formulation.

Vitamin D. Vitamin D stores are maintained by diet and adequate sun exposure. Despite this, the prevalence of vitamin D insufficiency/deficiency is common, even in areas with high sun exposure. Many studies report a prevalence between 30 - 50% and it has been estimated that 1 billion people globally have vitamin D deficiency. The elderly are especially prone to vitamin D deficiency as the ability of their skin to convert vitamin D diminishes over the age of 70 years and many elderly people (especially those in institutions) have limited sun exposure. Although vitamin D deficiency has been shown to affect proximal muscle power and increase the risk of falling, a recent meta-analysis suggests that supplementing vitamin D in elderly patients with vitamin D deficiency will prevent falls, but will not in patients with normal levels of vitamin D. Studies assessing the efficacy of vitamin D for the prevention and treatment of osteoporosis have yielded inconsistent results due to study design differing significantly, differing methods of supplementation and varied use of calcium. Various meta-analyses show a significant reduction or a trend to a
reduction in vertebral and non-vertebral fractures. A recent meta-analysis showed that high-dose (≥800 IU) supplementation of vitamin D in patients aged ≥65 years reduced the risk of hip fracture by 30% (HR 0.70; 95% CI 0.58 - 0.86) and the risk of any non-vertebral fracture by 14% (HR 0.86; 95% CI 0.76 - 0.96).[7]

The recommended dosage of vitamin D is 800 - 1 000 IU/day. A serum 25 hydroxyvitamin D level should be obtained in those at risk for vitamin D deficiency and the level should be maintained >30 ng/mL.[8] There is no consistent evidence supporting a specific formulation.[9]

**Bisphosphonates.** For the past two decades these drugs have been extensively prescribed for the treatment of established osteoporosis. Their ability to adsorb to bone in areas of high osteoclastic activity and to inhibit osteoclast function as well as their ability to inhibit osteoblast apoptosis results in a significant increase in BMD.

In addition, there are many studies proving their anti-fracture efficacy for reducing vertebral and non-vertebral fractures in high risk post-menopausal women (patients with osteoporosis or those with a previous fracture), men with osteoporosis, and in steroid-induced osteoporosis. There is no robust evidence for the efficacy of alendronate in those aged >80 years. In contrast, in a pooled analysis of data from three pivotal risedronate randomised controlled trials (RCTs) (n=1 400 over the age of 80 years), risedronate was shown to decrease the risk of a new vertebral fracture by 81% (n=1 392; RR 0.19, 95% CI 0.60 - 0.90) at 1 year and by 44% at 3 years (RR 0.56; CI 0.19 - 0.61), but there was no significant reduction of non-vertebral fractures.[10] In the Hip Intervention Program (HIP) trial, risedronate reduced the risk of hip fracture (n=5 445; RR 0.60; 95% CI 0.40 - 0.90) in women aged 70 - 79 years, but not in those who aged ≥80 years.[11] In the HORIZON-Recurrent Fracture Trial, in which more than half of the participants were aged >75 years (range 50 - 85), an annual infusion of zoledronic acid in women and men who had undergone a recent surgical repair of a hip fracture reduced the risk of any new clinical fracture by 35% (n=2 127; RR 0.65; CI 0.50 - 0.84) and reduced all-cause mortality by 28% (RR 0.72; CI 0.56 - 0.93).[12] After decades of use, the side-effects of the bisphosphonates are now well known: hypocalcaemia, increased parathyroid hormone, skin rash (with all bisphosphonates); osteonecrosis of the jaw (more common in patients with an underlying malignancy receiving intravenous bisphosphonate), oesophageal ulceration and gastrointestinal irritation (with intravenous forms); and fever, acute-phase reaction, bone pain, transient leucopenia and eye inflammation (with intravenous forms).

Potential risk factors for atypical fractures include hypocalcaemia, obesity, younger age (<70 years) and early menopause. There is now widespread consensus that alendronate should be stopped in patients after 5 years and use of a ‘drug-holiday’ or a change to another agent should be based on their current BMD and risk for a future fracture.[13] In the PROOF study showed a 36% reduction in vertebral fractures, but no reduction in hip fractures. Furthermore, there was a significant drop-out rate and the lack of a dose response for osteogenic or anti-osteogenic effects by binding to the oestrogen receptor in various oestrogen-dependent target tissues. They are anti-osteogenic at the breast and oestrogenic at the uterus and bone. Raloxifene has been shown to decrease vertebral fractures by 38 - 52% in patients with osteopenia or osteoporosis but, more importantly in the elderly, SERMs do not reduce the risk of non-vertebral fractures.[14] This, therefore, probably limits their use in the elderly. The effect on bone was accompanied by a 90% reduced risk of oestrogen-receptor positive breast cancer and no increased risk of cardiovascular or central nervous system events, but was associated with an increased risk of DVT.[15]

**Calcitonin.** There are conflicting data regarding the efficacy of calcitonin in increasing BMD and reducing fractures. The PROOF study showed a 36% reduction in vertebral fractures, but no reduction in hip fractures. Furthermore, there was a significant drop-out rate and the lack of a dose response for...
has led to some questioning the validity of these data. More recently, calcitomin has been shown to increase the prevalence of certain malignancies. There is generally no indication for its use as there are other more effective agents. According to the NOFSA guidelines, calcitomin can be considered for use in patients who cannot tolerate more effective therapies (e.g. those with a creatinine clearance <30 ml/min).\textsuperscript{xviii}

**Denosumab.** Denosumab is a human monoclonal antibody that decreases bone resorption by inhibiting receptor activator of nuclear factor kB ligand (RANKL) thereby affecting the differentiation and activation of osteoclasts. The Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months (FREEDOM) trial showed a 68% reduction in the risk of new vertebral fractures (r=7 808; RR=0.32, CI 0.26 - 0.41), a 40% risk reduction of hip fractures (RR 0.60; CI 0.37 - 0.97) and a 20% risk reduction of non-vertebral fractures (RR 0.80; CI 0.67 - 0.95) in postmenopausal women using denosumab (60 mg subcutaneously every 6 months for 36 months) compared with those receiving placebo.\textsuperscript{xix} In addition, this reduction has been maintained for the first 2 years of the FREEDOM extension trial. Of note is that almost 33% of patients in the treatment arm were aged >75 years, thereby proving its efficacy in the elderly.

**Stimulators of bone formation**

**Strontium ranelate**

Strontium ranelate enhances osteoblastogenesis and osteoblast activity while at the same time decreasing osteoclast differentiation and function. Since it therefore decreases bone resorption while enhancing bone formation, the net effect is an increase in bone mineral density that has been confirmed in RCTs. These RCTs (Spinal Osteoporosis Therapeutic Intervention (SOTI) trial, and Treatment of Peripheral Osteoporosis (TROPOS) trial) have also proven the efficacy of strontium ranelate in reducing the risk of vertebral fractures (SOTI trial: 49% at 1 year and 4 1% at 3 years) and non-vertebral fractures (TROPOS trial: 16% at 3 years) in patients with postmenopausal osteoporosis.\textsuperscript{x} An open-label extension study including patients from the SOTI and TROPS trials showed a maintenance of fracture efficacy over 10 years with RR reductions for vertebral fractures of 35% and of non-vertebral fractures of 38% after 10 years, without an increase in any adverse events.\textsuperscript{x} Furthermore, data from the SOTI and TROPS trials were also used to assess the efficacy of strontium ranelate in patients aged >80 years.\textsuperscript{xii} In this analysis, strontium ranelate was shown to decrease the risk of vertebral fractures by 59% and non-vertebral fractures by 41 % at 1 year. In the RCTs, strontium ranelate was shown to be safe. However, post-marketing analyses have shown a few worrying potential adverse events:

- **Venous thromboembolism (VTE).** A post-marketing analysis of data from the SOTI and TROPOS trials revealed an increased annual incidence of VTE in the strontium ranelate group v. the placebo group (0.9% v. 0.6%, respectively), largely confined to those with a previous history of VTE. It has therefore been advised that strontium ranelate should not be used in individuals with a previous history of VTE, those who are immobilised or those with other risk factors for VTE.

- **DRESS syndrome (drug rash with eosinophilia and systemic symptoms).** This syndrome has been shown to occur rarely in patients 3 - 6 weeks after taking strontium ranelate and has a mortality rate up to 8 - 10%. Therefore, strontium ranelate should be stopped in patients who develop a rash and should not be re-started.

- **Myocardial infarction.** Pooled data from randomised placebo-controlled studies of patients with postmenopausal osteoporosis demonstrated a significant increase of myocardial infarction in patients treated with PROTOS v. placebo (1.7% v. 1.1%, respectively) (odds ratio (OR) 1.6; 95% CI 1.07 - 2.38). Therefore, the following have been added as contra-indications:

  - prior history of ischaemic heart disease, peripheral arterial disease or cerebrovascular disease
  - systolic blood pressure (SBP) ≥160 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg.

In addition, it has been suggested that the cardiovascular risk of the patient is assessed prior to starting treatment and also while on treatment.

**Parathyroid hormone (PTH).** Intermittent low-dose administration of PTH or its 1-34 fragment is anabolic thereby stimulating bone formation. In contrast, prolonged high-dose administration of PTH or its 1-34 fragment will stimulate bone resorption. A meta-analysis of 8 RCTs showed that treatment with teriparatide (the 1-34 fragment of PTH) increased bone mass in the spine by 8.14% (95% CI 6.72 - 9.55; 8 trials; n=2 206) and at the hip by 2.48% (95% CI 1.67 - 3.29%; 7 trials; n=1 303), and decreased the risk of a vertebral fracture by 70% (RR 0.30; 95% CI 0.21 - 0.44; 3 trials; n=1 452) and the risk of a non-vertebral fracture by 38% (RR 0.62; 95% CI 0.44 - 0.87; 3 trials; n=1 842).\textsuperscript{x} The use of teriparatide is largely limited by its cost and need for daily injections, so NOFSA has recommended specific clinical indications for its use.

**Conclusions**

Osteoporosis and its complications are common in the general population but especially in the elderly. With proper education and management, both osteoporosis and falls are preventable, thereby preventing fractures. It is essential that once low BMD (either osteopaenia or osteoporosis) is diagnosed, all patients should start supplementation with calcium and vitamin D, they should start weight-bearing exercise, they should undergo an assessment for falls and they should be encouraged to stop smoking and reduce their alcohol intake. The specific pharmacotherapy for osteoporosis to reduce fractures should be individualised, as each treatment has its associated benefits and potential risks.
References