Bisphosphonate medicine use in the management of osteoporosis

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Abstract

Osteoporosis is a common systemic progressive skeletal disease that remains a significant problem worldwide. It is important to understand the pathogenesis and the possible mechanism of action of anti-osteoporotic drugs. Treatment of osteoporosis is strictly related to severity of pathology and consists of prevention of fragility fractures with the correct lifestyle and adequate nutritional supplements. Bisphosphonates are the agents most extensively studied and prescribed in clinical practice for more than 20 years. They give the most effective protection from various fractures including vertebral, hip and other non-vertebral fractures. Bisphosphonates are generally well tolerated and have a favourable safety profile when used in the treatment of osteoporosis. This review aims to provide an overview of the management of osteoporosis with the use of bisphosphonate medicines. The purpose of this review is to focus on the main current pharmacological products available for the treatment of osteoporotic patients.

Keywords: osteoporosis, bisphosphonates

Introduction

Osteoporosis, from the Greek term “porous bone”, is a systemic progressive skeletal disease which remains a significant problem worldwide.1 This metabolic bone disorder is an asymptomatic condition that is characterised by low bone mass and bone structure deterioration that leads to bone fragility and bone fractures in both men and women.1 Osteoporosis often goes untreated and unrecognised owing to the fact that it is clinically silent until fractures develop. The increase in the incidence of osteoporotic fractures in an individual is accompanied by fear of disability and mortality.2 Osteoporotic-related fractures also cause pain, an increase in total healthcare costs and nursing home placement, thereby affecting the economy.3 According to the National Osteoporosis Foundation of South Africa, 1.6 million women and 0.8 million men above the age of 50 years were suffering from osteoporosis in 2017, almost 30% of hip-fracture patients die within a year and more than 50% of them never function independently again.4 Early diagnosis and management of osteoporosis is therefore crucial for the improvement of the quality of life of patients and bisphosphonates are the drugs most commonly used to suppress osteoclast-mediated bone resorption.3

Bone homeostasis and pathogenesis

Bone is composed of mineral organ matrix, cells and water. Bones provide structure for the body, protect internal organs and store minerals essential for bone development and stability e.g. calcium and phosphorous. The four major types of bone cells are osteoblasts (bone-forming), osteoclasts (bone-resorbing), osteocytes and bone-lining cells. Osteoblasts, as well as many other cell types such as adipocytes, chondrocytes, fibroblasts and myoblasts, differentiate from mesenchymal stem cells, whereas osteoclasts are derived from the haematopoietic mononuclear lineage. Two cytokines, which are mainly produced by bone marrow stromal cells and osteoblasts, are essential for osteoclastogenesis: macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL), which belongs to the tumour necrosis factor (TNF) superfamily. RANK is the receptor for RANKL and is expressed on mononuclear osteoclast precursors. Osteoprotegerin (OPG), which is also produced by stromal cells and osteoblasts, is a natural decoy receptor for RANKL and thus antagonises the osteoclastogenic action of RANKL.6 From birth until the age of 30 years, bone formation reaches its peak and thereafter, bone mass decreases steadily. Bone remodelling occurs throughout life to maintain mechanical strength and repair. This means that bone is continuously resorbed by osteoclasts and replaced with new bone by osteoblasts.1

Parathyroid hormone (PTH) and calcitonin (CT) are two peptide hormones that play important roles in calcium homeostasis through their actions on osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells), respectively.2 One of the hormones considered to influence bone remodelling is CT, which was discovered more than 50 years ago as a calcium-lowering factor produced by thyroidal C cells. As stated in the sections above, osteoporosis is explained at a cellular level by imbalanced
bone remodelling, a physiologically relevant homeostatic process mediated through bone-resorbing osteoclasts and bone-forming osteoblasts. On the basis of their cellular differences, there are two distinct therapeutic options to treat osteoporosis, either by osteoclast inhibition (antiresorptive) or osteoblast activation (osteo-anabolic). Currently, the vast majority of patients are medicated by antiresorptive means, and there is only one osteo-anabolic treatment option so far, i.e., daily injection of PTH or a PTH fragment. Based on the pathophysiology and since a long-term blockade of bone remodelling may have adverse effects on skeletal integrity, one of the major goals of research is to identify novel target proteins for osteo-anabolic medication.³

Oestrogens also have multiple effects on bone cells and mineral homeostasis by exhibiting both skeletal and extraskeletal activities. Therefore, oestrogen deficiency contributes to the pathogenesis of osteoporosis. Skeletal activities by oestrogen are direct or indirect. Direct skeletal activities are based upon oestrogen receptors on osteoblasts and osteoclasts; indirect activities of oestrogens are mediated by oestrogen receptors on various other cell types including stromal cells, which upregulate OPG on exposure to oestrogen, and the cells of the immune system that influence bone homeostasis.⁷

In postmenopausal women an oestrogen deficiency leads to an upregulation of RANKL on bone marrow cells, which is an important determinant of increased bone resorption. Oestrogen itself stimulates OPG production in osteoblasts and therefore exerts antiresorptive effects on bone. The effects of extraskeletal oestrogen deficiency are mainly based upon increased renal calcium excretion and decreased intestinal calcium absorption.⁷

Oestrogen deficiency may also lead to a continuous increase in serum PTH levels. Secondary to this the hyperparathyroidism is a compensatory mechanism for net calcium losses in the aging body on the one hand, while oestrogen also seems to have a direct depressive action on the parathyroid gland. Additionally, oestrogen deficiency increases the sensitivity of bone to PTH. The other mechanisms responsible for inadequate intestinal calcium absorption in the elderly are vitamin D deficiency, the impaired metabolism of vitamin D to its active form and a decrease in intestinal vitamin D receptors.⁷

Therefore, oestrogen treatment was found to increase both serum vitamin D levels and calcium absorption in postmenopausal osteoporotic women.⁷

The production of many different cytokines and other inflammatory mediators, such as interleukin (IL)-1, IL-6, TNF-α, and prostaglandin E2, are involved in the pathogenesis of osteoporosis.⁷

Oestrogen treatment increases the production of insulin-like growth factor-1 (IGF-1) and transforming growth factor (TGF)-β by osteoblastic cells. It has been illustrated that the pathophysiology of osteoporosis is complex and multifactorial. An imbalance in bone remodelling where bone resorption exceeds bone formation may result in the pathological changes seen in osteoporosis.⁷

To summarise, the following are basic pathogenic mechanisms⁶:

- Failure to produce optimal bone mass and strength during growth.
- Excessive bone resorption resulting in a decrease in bone mass and deterioration of bone.
- Inadequate formation response to increased resorption during bone remodelling.

Risk factors

A variety of risk factors and causes are associated with the development of osteoporosis.⁴,⁵,⁹-¹¹

- Advanced age
  Old age and oestrogen deficiency are the two most critical factors for the development of osteoporosis in both women and men. As age progresses, bone mass decreases due to mitochondrial dysfunction, oxidative stress, DNA damage and lipid peroxidation which cause cortical porosity. Therefore, the balance between bone formation and resorption becomes progressively negative with advancing age.¹⁰

- Oestrogen deficiency
  Oestrogen is critical for bone maintenance. It decreases bone resorption by inhibiting the generation and activation of osteoclasts. In women, cortical bone loss is mostly caused by oestrogen deficiency. Postmenopausal women, whose oestrogen levels naturally decline, are at the highest risk for developing osteoporosis although older men are also affected.⁹

- Calcium, vitamin D and parathyroid hormone
  A decrease in calcium intake, and impaired intestinal absorption of vitamin D cause an increase in PTH resulting in bone resorption. PTH enhances bone resorption by promoting recruitment and activation of osteoclasts.¹¹

- Cytokines, prostaglandins and leukotrienes
  Locally produced cytokines, prostaglandins and leukotrienes during chronic inflammation can stimulate bone resorption or inhibit bone formation or both.¹¹

- Other factors
  Other factors that lead to the development of osteoporosis include smoking, alcohol use, inadequate physical exercise, immobilisation, malnutrition, low body mass index, falling, high caffeine intake, excessive exercise, excess vitamin A, anorexia, diabetes, hyperthyroidism, glucocorticoid use and gastrointestinal disorders such as inflammatory bowel disease, chronic liver disease and pancreatitis.⁴

Managing osteoporosis

Non-pharmacological therapy

Literature categorises non-pharmacological measures in the management of osteoporosis into three aspects: 1) nutrition, 2) lifestyle, and 3) fall prevention.¹²-¹⁵ Nutrition entails adopting a balanced diet with adequate dietary intake and/ or supplementation of protein, calcium and vitamin D. The recommended daily intake of calcium and vitamin D for different
age groups appears in Table I. A reasonable intake should help maintain bone health, reducing the risk of reduction in bone mass later in life.16,17 The supplementation with calcium and vitamin D has a significant role in osteoporosis management, but is not sufficient to reduce fracture risk.18

Some dietary restrictions include limiting intake of alcohol, caffeine and carbonated beverage. Excessive alcohol consumption has been linked to the increased risk of falling due to compromised balance, as well as poor absorption of nutrients. Excessive caffeine is associated with increased calcium loss, while carbonated beverages may increase risk of fracture by lowering bone mass density.13-15 Lifestyle modifying measures such as smoking cessation are also essential to prevent loss of bone mass. Adding moderate weight-bearing exercises to one's routine reduces fracture risk by strengthening the musculoskeletal system and improving bone mass density. Physiotherapy has been successfully used as rehabilitation following a fracture.12,16

Fall prevention has been hailed as a popular strategy to avoid osteoporosis-related fractures. Balance training, weight-bearing exercises and physiotherapy go a long way as preventative measures to preserve muscle strength and coordination. Additional measures include limiting medication that affects mental alertness, modifying aspects of one's immediate environment (e.g. slippery floors, removing objects one could trip over), acquiring appropriate footwear, and improving visual acuity.12,14,16,19

Although non-pharmacological treatments, such as weight bearing activity for at least 30 minutes daily, smoking cessation, and avoidance of heavy alcohol consumption, have important roles in maintaining bone health, pharmacological products play a key role in the treatment of osteoporosis and fracture prevention.18

**Treatment**

The approach in the management of osteoporosis is strictly related to the severity of pathology. As stated in the sections above, it is important to prevent fragility fractures with an active lifestyle and adequate nutritional supplements, including daily calcium and vitamin D intake, performing weight-bearing activities, avoiding or stopping smoking, and avoiding heavy alcohol consumption.18

The main aim involved in the treatment of osteoporosis involves increasing bone mass and strength by inhibiting bone resorption or promoting bone formation.18

**Pharmacological therapy with bisphosphonates**

The bisphosphonates are pyrophosphate analogues in which the phosphorous-oxygen-phosphorus structure (P-O-P) has been replaced with a phosphorus-carbon-phosphorus (P-C-P) bond, making it resistant to hydrolysis.16,17,20

In postmenopausal women at high risk for fractures, oral bisphosphonates are considered first-line pharmacological therapy. Bisphosphonates act by interfering with specific intracellular pathways in osteoclasts, resulting in cellular toxicity. Specifically, they bind to hydroxyapatite and are thus absorbed by bone, inhibiting osteoclastic bone resorption via several modalities: cytotoxic or metabolic injury of mature osteoclasts, inhibition of osteoclast attachment to bone, inhibition of osteoclast differentiation or recruitment, and interference with osteoclast structural features necessary for bone resorption (i.e. components of the cytoskeleton).18

There are two subclasses of bisphosphonates: nitrogen-containing bisphosphonates (NBPs e.g. alendronate, ibandronate, pamidronate, risedronate, and zoledronate), which are the most common, and non-nitrogen-containing bisphosphonates (NNBPs e.g. etidronate). NBPs inhibit the mevalonate pathway, a fundamental metabolic pathway involved in osteoclast formation and function; NNBPs act through the formation of metabolites that form toxic ATP analogues that induce osteoclast apoptosis. However, before initiating therapy, it is important to treat any comorbid conditions, such as hypocalcaemia, vitamin D deficiency, and renal impairment. These conditions can be identified by measuring serum calcium, 25-hydroxyvitamin D (25[OH]D), and creatinine, respectively.18

The most common adverse events, particularly for oral bisphosphonates, are Barrett’s oesophagus and gastrointestinal disturbances such as dyspepsia, oesophagitis, and oesophageal varices. Rarely, atrial fibrillation and renal failure may occur. Therefore, intravascular bisphosphonates should not be used in patients with chronic kidney disease and an estimated glomerular filtration rate < 30–35 mL/min. Moreover, atypical femur fractures, especially sub-trochanteric and diaphyseal fractures, have been linked to bisphosphonate use, likely due to over-suppression of bone turnover. Lastly, NBPs, but not NNBPs, have been associated with bisphosphonate-related osteonecrosis of the jaw, an oral complication that could arise in patients, especially those with recent maxillo-facial or oral surgery.18

**Table I. Dosages of calcium and vitamin D for different age groups**

<table>
<thead>
<tr>
<th>Group and ages</th>
<th>Elemental Calcium (mg)</th>
<th>Vitamin D (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>Birth to 6 months</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td>6–12 months</td>
<td>270</td>
</tr>
<tr>
<td>Children/Adolescents</td>
<td>1–3 years</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>4–8 years</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>9–18 years</td>
<td>1 300</td>
</tr>
<tr>
<td>Adults</td>
<td>19–49 years</td>
<td>1 000</td>
</tr>
<tr>
<td></td>
<td>≥ 50 years</td>
<td>1 200</td>
</tr>
</tbody>
</table>
Bisphosphonates adsorb to hydroxyapatite forming a permanent part of bone structure, following which they are released gradually during bone remodelling. This affords them a half-life of approximately 10 years. The antiresorptive properties of bisphosphonates result from blocking prenylation and inhibiting guanosine triphosphatase-signalling proteins, leading to reduced osteoclast maturation, number, recruitment, bone adhesion, and life span. Table II gives the summarised drug profiles for bisphosphonates.

**Special prescriber’s points**

Before use, patients’ serum calcium concentration levels must be normal. Patients should be advised to take bisphosphonates with a full glass of water, at least 30 minutes before ingesting anything else in the morning (this includes supplements containing calcium and vitamin D). This should minimise gastrointestinal side-effects. Patients are advised to remain in a sitting or standing position (upright) for a minimum of 30 minutes after a dose of alendronate or risedronate, and one hour after ibandronate to prevent oesophageal erosion. In this way, assimilation and potential gastrointestinal adverse events are minimised. Intravenous administration of zoledronic acid (infused at least for 15 min yearly) or ibandronate (every three months as a 15- to 30-s intravascular injection) is suggested for patients in whom bisphosphonate use is contraindicated, such as those with low tolerance, gastrointestinal disease, or assimilation problems.

**Table II. Individual bisphosphonate drug profiles**

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Dosage</th>
<th>Pharmacokinetics</th>
<th>Adverse effects</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronate</strong></td>
<td>5 mg daily, 35 mg weekly (prevention) 10 mg daily or 70 mg tablet, 70 mg tablet with vitamin D 2800 or 5600 units, or 75 mL liquid weekly (treatment).</td>
<td>Poorly absorbed (&lt; 5–10%) less with food or beverage other than water; long bone t1/2 (2–10 years); renal elimination (of absorbed) and faecal elimination (unabsorbed).</td>
<td>Common: nausea/dyspepsia (oral); transient flu-like illness (injectables). Rare: GI perforation, ulceration, and/or bleeding (oral); musculoskeletal pain; osteonecrosis of the jaw; atypical fractures.</td>
<td>Do not co-administer with any other medication or supplements (including calcium and vitamin D). Wait 30 minutes to 1 hour.</td>
</tr>
<tr>
<td><strong>Risedronate</strong></td>
<td>5 mg daily, 35 mg weekly, 75 mg for 2 days monthly, 150 mg monthly.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ibandronate</strong></td>
<td>150 mg monthly, 3 mg intravenous. Quarterly.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pamidronate</strong></td>
<td>60–90 mg weekly, infusion over 2–4 hours.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Zoledronate</strong></td>
<td>4 mg weekly, infusion over minimum 15 minutes.</td>
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</tbody>
</table>

**Missed doses**
A missed weekly dose may be taken the next day. If more than one day elapses, that dose is to be skipped until the next scheduled one. A missed monthly dose may be taken up to seven days before the next.

**Table III. Available formulations of bisphosphonate medicines in South Africa**

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Indication</th>
<th>Dosage</th>
<th>Available trade names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronic acid</strong></td>
<td>Postmenopausal osteoporosis. Osteoporosis in men.</td>
<td>10 mg daily, or 70 mg once weekly</td>
<td>Fosamax Alendronate Unicorn Femax Fosagen Osteobon-70 Osteonate SANDOZ Alendronate</td>
</tr>
<tr>
<td><strong>Clodronic acid</strong></td>
<td>Malignant hyperglycaemia. Osteolysis from solid tumours. Osteolysis due to hematological neoplasms.</td>
<td>1.6 g daily or twice daily in divided doses</td>
<td>Bonephos</td>
</tr>
<tr>
<td><strong>Ibandronic acid</strong></td>
<td>Tumour-induced hyperglycaemia. Metastatic bone disease.</td>
<td>IV infusion, according to corrected plasma calcium concentration: 1 to 4 mg</td>
<td>Bonordonat Boniva</td>
</tr>
<tr>
<td><strong>Pamidronic acid</strong></td>
<td>Tumour-induced hyperglycaemia.</td>
<td>Not to be administered as bolus injection.</td>
<td>Aredia</td>
</tr>
<tr>
<td><strong>Risedronic Acid</strong></td>
<td>Postmenopausal osteoporosis</td>
<td>35 mg once weekly</td>
<td>Actonel</td>
</tr>
<tr>
<td><strong>Zoledronic Acid</strong></td>
<td>Postmenopausal osteoporosis. Osteoporosis in men. Tumour-induced hyperglycaemia. Metastatic bone disease. Malignant hyperglycaemia.</td>
<td>IV Infusion over at least 15 min, 4 mg every 3 to 4 weeks</td>
<td>Aclasta Zometa Zomabon Zobone Zomedron</td>
</tr>
</tbody>
</table>
Bisphosphonates should be initiated 4–6 weeks after a fracture and should not be discontinued in patients with an osteopathic fragility fracture who have been receiving the drug for less than five years, due to the potential for delayed healing time. Available formulations of bisphosphonate medicines in South Africa are listed in Table III.

For patients at high risk for fracture, initial therapy should include alendronate, risedronate, zoledronic acid, and denosumab, which are approved agents with efficacy in reducing hip, other non-vertebral, and spine fractures. Intravenous administration of teriparatide, denosumab, or zoledronic acid may be an appropriate initial therapy for patients unable to use oral therapy. Raloxifene or ibandronate should be considered in special cases where patients require drugs with spine-specific efficacy.

In the management of osteoporosis combination therapy is not generally recommended, but may be considered if a patient with high risk for fractures is already under treatment with oestrogen for menopausal symptoms or raloxifene to reduce the risk of breast cancer; in these cases, an additional agent such as a bisphosphonate, denosumab, or teriparatide may be appropriate.

Conclusion

In older patients, pharmacological treatment of osteoporosis is necessary to reduce the risk of fractures. The choice of safe and effective anti-osteoporosis agents is guided by early diagnosis and characterisation of the pathology aids in the choice of safe and effective anti-osteoporosis agents.

Oral bisphosphonates, with adequate supplementation of calcium and vitamin D, are considered the first choice for pharmacological therapy. Since their introduction to clinical practice, bisphosphonates have improved the clinical care of skeletal disorders characterised by excessive osteoclast-mediated bone resorption. The informed and judicious use of bisphosphonates relays a clear clinical benefit for carefully selected patients that outweighs the risks associated with bisphosphonate use. Maintenance of adequate calcium and vitamin D intake is crucial for all patients receiving bisphosphonate therapy. Second- or third-line treatments may include newer pharmacological agents, such as teriparatide, denosumab and raloxifene, to increase bone mineral density, suppress bone remodelling, and prevent possible atypical fractures. With further study and the identification of the primary genes and signalling pathways responsible for bone loss in individual patients, new treatment options will become available, allowing for the use of personalised therapy based on genetic risk and environmental factors.

References