ABSTRACT

Population aging is a reality that is being faced worldwide, and Brazil is no different. Osteoporosis was considered to be a postmenopausal women’s disease for many years. Men have many development and hormonal factors that differentiate their skeletal maturation, which affects the incidence of osteoporosis and fractures. An up-to-date review of the specific literature within the Medline system is presented.

Keywords – Osteoporosis; Bone Density; Male

INTRODUCTION

Osteoporosis was for a long time considered to be a women’s disease. Today, it is being recognized that osteoporosis is also a public health issue for men, given the significance incidence of osteoporotic fractures that they present\(^1\).

Postmenopausal osteoporosis is a characteristic of hormone loss, i.e. of estrogen in postmenopausal women. In men, testosterone levels remain functional until the seventh decade of life. For this reason, it was thought that men would not have osteoporosis and would not need hormone replacement. The existence of risk factors within modern life and the aging of the population have brought male osteoporosis into view.

Definition, risk factors and classification

Osteoporosis is a systemic disease of the skeleton characterized by compromised bone resistance that predisposes towards an increased risk of fractures. Hip fractures are the most severe of these, and they occur at later stages of life\(^2\). Bone resistance is provided by the combination of bone mass (as assessed using densitometry) and bone quality (in terms of bone macro and microarchitecture and metabolic activity), with their interactions with local and systemic factors. Sexual hormones, systemic bone metabolism factors and, especially, testosterone in men have important roles in determining the bone mass\(^3\). Bone densitometry provides measurements of bone mineral density (BMD), and this directly assesses the bone mineral content. There has been much discussion regarding whether the fracture risk gradient, according to BMD values, differs between men and women\(^4\). From an analysis on 12 cohorts, Johnell et al\(^5\) concluded that the risk of hip fractures according to age and BMD among men was similar to that of women of the same age and BMD\(^5\). They found that the incidence of fractures and mortality among women at more advanced ages was greater than among men because of women's greater longevity, and they also concluded that hip BMD values were an important risk factor for fractures, independent of sex\(^5\).

In Brazil, through statistics from the Brazilian Institute for Geography and Statistics (IBGE), it can be seen that the population is aging. For example, the population pyramid has become inverted, comparing the male and female populations over the age of 80 years for 1980 with the projection for 2050 (Figure 1). The Brazilian population over the age of 50 years is remaining very active and is increasing in numbers, thereby leading to increased incidence of the diseases that progress with aging, notably osteoporosis.

A variety of factors contribute towards the fact that...
women are affected more than men are: men attain a higher peak bone mass than women do and do not have the losses consequent to the menopause\(^6\). Different patterns of bone loss over the course of time contribute towards a biomechanical advantage with aging. Histories of fracture due to mild trauma are an important risk factor for the occurrence of new fractures, and such patients are candidates for treatment after they have been correctly diagnosed with osteoporosis. The treatment consists of calcium supplementation and administration of the most appropriate medication\(^7\).

Male osteoporosis is classified as primary or secondary. Primary osteoporosis may be idiopathic or because of aging, and this form is also called senile osteoporosis in both sexes.

In diagnosing male osteoporosis, it is important to investigate the risk factors. Kanis et al\(^8\) validated risk factors in several cohorts and created models integrated with BMD to predict the risk of fractures. The most important of these risk factors, both for men and for women are low body mass index (BMI), body BMD, family history, use of glucocorticoids, previous fractures, smoking, alcohol use and rheumatoid arthritis\(^8\). Senile or primary osteoporosis in men tends to occur over the age of 70 years, through a combination of factors: diminished calcium absorption in the intestine, reduced vitamin D activation, diminished osteoblast lifetime and lowered sexual hormone levels\(^9,10\).

**Secondary osteoporosis**

Causes of osteoporosis can be identified in around 40% to 60% of men, especially those with osteoporotic fractures\(^11,12\). The commonest causes are hypogonadism and prolonged corticoid therapy, followed by gastrointestinal diseases, vitamin D deficiency, alcoholism and chronic use of anticonvulsants, which also appear in significant proportions\(^10\). Corticoids induce bone loss directly, and indirectly through hypogonadism, through suppression of the secretion of hypothalamic gonadotropic hormone and the direct effect of diminished testicular production of testosterone\(^10\). Men using corticoids are at increased risk of vertebral and non-vertebral fractures\(^10-12\). Androgens influence the proliferation of osteoblasts and the production of cytokines, growth factors and bone matrix proteins, through the androgen receptors of osteoblasts\(^13\). Hypogonadism before puberty has a notable effect on the development of the cortical skeleton, which can be alleviated with testosterone\(^13\).
In adults, it leads to diminished metabolism, bone formation and vitamin D levels, and can be reversed through adequate hormone replacement\(^{(13)}\).

Although there have been reports that moderate alcohol consumption may be associated with gains in bone mass, particularly in the great trochanter\(^{(13)}\), many studies have demonstrated that excessive alcohol consumption is associated with osteoporosis and increased risk of fractures\(^{(13)}\). Stopping the addiction results in gains in bone mineral density, and this was demonstrated in a study on 30 men who presented a gain of 3%, two years after stopping their alcoholism\(^{(12,13)}\). The use of immunosuppressants during organ transplantation is an important factor for triggering osteoporosis, and this has been seen in relation to heart, kidney and liver transplantation\(^{(13)}\). The cause of osteoporosis in men is commonly heterogenous, and there may be several factors contributing towards the existence of the disease. Underlying diseases and risk factors should always be investigated in the clinical assessment, as indicated in Table 1.

### Table 1 – Causes of male osteoporosis and risk factors for osteoporosis and osteoporotic fractures, adapted from references 5, 9, 10, 11 e 12.

<table>
<thead>
<tr>
<th>Causes of male osteoporosis</th>
<th>Risk factors</th>
</tr>
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<tbody>
<tr>
<td>• Corticoid use</td>
<td>• Age ≥ 70 years</td>
</tr>
<tr>
<td>• Immunosuppressant use</td>
<td>• Fractures before the age of 40 years</td>
</tr>
<tr>
<td>• Hypogonadism</td>
<td>• Maternal history of fractures</td>
</tr>
<tr>
<td>• Alcoholism</td>
<td>• Low body mass index</td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Low calcium intake</td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease</td>
<td>• Unstable balance</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>• Quadriceps weakness</td>
</tr>
<tr>
<td>• Anticonvulsant medication</td>
<td>• Falls over the last 12 months</td>
</tr>
<tr>
<td>• Gastrointestinal diseases</td>
<td>• Caucasian ethnicity</td>
</tr>
<tr>
<td>• Ankylosing spondylitis</td>
<td>• Poor visual acuity</td>
</tr>
<tr>
<td>• Thyrotoxicosis</td>
<td>• Lumbar pain</td>
</tr>
<tr>
<td>• Hyperparathyroidism</td>
<td>• Sedentarism</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>• Use of androgen inhibitors</td>
</tr>
</tbody>
</table>

**Epidemiology**

Fractures occur frequently among men. Fractures in men resulting from osteoporosis are a public health problem. Hip fractures are the most important type, and these present high morbidity and mortality\(^{(14)}\), with the highest medical costs relating to osteoporosis.

In the United States in 1995, the expenditure on osteoporotic fractures was estimated to be US$ 13.8 billion. Since the worldwide population is aging, it is expected that there will be around 6.3 million hip fractures annually by around 2050\(^{(14)}\). In the United States, the risk of hip fractures over women’s lifespan beyond the age of 50 years is around 17.5%, while for men, the risk is 6%\(^{(14)}\). The risk of spinal fracture is 5% for men and 16% for women\(^{(13)}\).

**Physiopathology**

Sexual hormones are responsible for the maturation and sexual dimorphism of the skeleton. Boys have an additional two years of prepubertal growth because of their later puberty, at the age of 14 years. Puberty among girls is earlier, at the age of 12 years. The pubertal growth spurt among boys lasts for four years, while it lasts for three years among girls\(^{(15)}\). Thus, males reach a height that is 10% greater than seen among females, and a peak bone mass that is 25% greater\(^{(15)}\). Some of the testosterone is transformed into estrogens, which are responsible for closure of the epiphyses at the end of the growth stage. Aromatase deficiency causes deficient skeletal growth, and this is reversible through estrogen therapy for men\(^{(15,16)}\). Men and women lose similar quantities of trabecular bone during the aging process; however, thinning of the trabeculae predominates in men, while loss of connectivity predominates in women. The resistance of the vertebrae diminishes more through loss of connectivity than through thinning of the trabeculae\(^{(17)}\). Loss of connectivity results from accelerated bone loss, with the estrogen deficiency of the menopause\(^{(15,17)}\). In patients undergoing treatment for prostate cancer with androgen inhibitors, the treatment results in a fall in bone densitometry values due to the fall in testosterone values\(^{(18)}\). The importance of sexual hormones in men has been established with regard to gaining and maintaining bone mass, but there is no well-defined correlation in relation to testosterone and fracture rates in cases of primary osteoporosis\(^{(19)}\).

Adequate calcium intake in the diet and maintenance of constant adequate physical activity are important for maintaining quality of life during the aging process\(^{(20)}\).

**DIAGNOSIS**

The best means for diagnosing osteoporosis is clinical, with correct assessment of the underlying diseases that
may cause secondary osteoporosis, and the risk factors, as laid out in Table 1. BMD is as effective among men as it is among women for predicting fractures in situations of low BMD\(^{21,22}\). Because of the lower incidence of fractures in men, bone densitometry examinations are requested less often for men than for women.

BMD evaluations should be requested for the following:

- Men aged 50 years and over who suffer fractures caused by mild trauma, including those with spinal deformities; younger men with fractures due to mild trauma should be included in this.
- Men presenting conditions that are known to cause secondary osteoporosis, such as hypogonadism, corticoid use, alcoholism and other diseases and risk factors, as shown in Table 1.
- BMD should be measured routinely among men aged 70 years and over\(^{23}\).

Currently, BMD values are quantified as T scores, which provide a relationship with the mean peak value for skeletal maturation, using a grading system parallel to the one used for women: T scores from –1 to –2.5 signify “low bone mass”, which was previously called osteopenia\(^{5}\); T scores less than or equal to –2.5 signify densitometric osteoporosis. The scale for men (male values) should always be used; there are no adjustments for ethnicity. These values are valid for bone densitometry examinations performed on apparatus for dual-energy x-ray absorptiometry (DXA). Z score values provide a relationship with the mean BMD for the age group, less than or equal to –2, and a cause for secondary osteoporosis should always be investigated\(^{1,2,21,22}\). Laboratory tests are indicated for evaluating diseases and causes of secondary osteoporosis, which should be corrected when detected. Box 1 provides a suggestion for a routine that can be increased or diminished according to clinical needs.

In addition to these examinations, biological markers for bone metabolism, reabsorption and formation can be used, according to the local facilities available for medical laboratory services, as shown in Box 2.

Calcium metabolism should be assessed with regard to situations of hypo and hypercalcaemia. Electrophoresis on serum proteins among patients over 50 years of age is important particularly for the diagnosis of multiple myeloma. Bone scintigraphy should not be a routine examination, and should just be used in cases of suspected bone neoplasia, metastasis or Paget’s disease.

**Box 1 - Suggested examinations for investigating male osteoporosis\(^{1,2,21}\).**

- Bone densitometry
- 24-hour urine: CA, P and creatinine
- Total and ionic calcium
- Serum protein electrophoresis
- Intact PTH
- Thyroid profile
- Alkaline phosphatase
- Radiographs
- Bone scintigraphy
- 25 OH D

**Box 2 - Biochemical markers for bone metabolism\(^{11}\).**

<table>
<thead>
<tr>
<th>Formation markers</th>
<th>Reabsorption markers</th>
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<tbody>
<tr>
<td>Osteocalcin</td>
<td>Hydroxyproline</td>
</tr>
<tr>
<td>Bone alkaline phosphatase</td>
<td>Hydroxylysine</td>
</tr>
<tr>
<td>Type 1 procollagen</td>
<td>Pyridinoline</td>
</tr>
<tr>
<td>N-propeptide</td>
<td>Deoxypyridinoline</td>
</tr>
<tr>
<td>Type 1 procollagen</td>
<td>Bone sialoprotein</td>
</tr>
<tr>
<td>C-propeptide</td>
<td>Acid phosphatase</td>
</tr>
<tr>
<td></td>
<td>Tartrate-resistant acid phosphatase</td>
</tr>
<tr>
<td></td>
<td>Telopeptides of type 1 collagen (CTX, NTX)</td>
</tr>
</tbody>
</table>

**TREATMENT**

The treatment should start with elimination of risk factors that can be removed, such as smoking, alcohol use and sedentarism. The calcium intake in the diet should be brought to adequate levels and physical activity advice should be given\(^{20}\). Treatments for diseases that could be causes of secondary osteoporosis should be updated. Corticoid use should be withdrawn or adjusted in consultation with the attending physician, to the lowest dose possible. Vitamin D levels should be evaluated and corrected to normal values, through supplementation.

Use of testosterone in men with hypogonadism has shown beneficial effects regarding increased BMD in the lumbar spine, but the side effects need to be evaluated\(^{13}\). Indications for testosterone use should be preceded by an evaluation by a urologist.
The medications of choice for treating male osteoporosis are bisphosphonates, especially alendronate and risedronate, which also act on osteoporosis induced by corticoids\(^{(13,24)}\). Ibandronate\(^{(25)}\) and annual intravenous zolendronate may be used. Although strontium ranelate has bone-forming properties, no protocol for use in men has yet been defined.

Teriparatide is effective in cases of severe osteoporosis with fractures, and also in cases of osteoporosis induced by corticoids\(^{(2,13)}\).

REFERENCES