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Review article

Guidelines of the Brazilian Society of Rheumatology for the diagnosis and treatment of osteoporosis in men



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ABSTRACT

Osteoporosis, a metabolic disease characterized by low bone mass, deterioration of the bone tissue microarchitecture and increased susceptibility to fractures, is commonly regarded as a women's health problem. This point of view is based on the fact that compared with men, women have lower bone mineral density and longer lifespans and lose bone mass faster, especially after menopause, due to a marked decrease in serum estrogen levels. However, in the last 20 years, osteoporosis in men has become recognized as a public health problem

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due to the occurrence of an increasingly higher number of fragility fractures. Approximately 30% of all hip fractures occur in men. Recent studies show that the probability of fracture due to hip, vertebral or wrist fragility in Caucasian men older than fifty years, for the rest of their lives, is approximately 13% versus a 40% probability of fragility fractures in women. Men show bone mass loss and fractures later than women. Although older men have a higher risk of fracture, approximately half of all hip fractures occur before the age of 80. Life expectancy is increasing for both sexes in Brazil and worldwide, albeit at a higher rate for men than for women. This Guideline was based on a systematic review of the literature on the prevalence, etiology, diagnosis and treatment of osteoporosis in men.

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Diretrizes da Sociedade Brasileira de Reumatologia para diagnóstico e tratamento da osteoporse em homens

R E S U M O

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Osteoporose, uma doença metabólica caracterizada por baixa massa óssea, deterioração da microarquitetura do tecido ósseo e aumento da suscetibilidade a fraturas, é comumente vista como um problema de saúde feminino. Essa visão tem fundamentos: em comparação com os homens as mulheres têm densidade mineral óssea menor, têm vida mais longa e perdem massa óssea mais rapidamente, principalmente após a menopausa, devido à diminuição acentuada dos níveis séricos de estrógeno. Entretanto, nos últimos 20 anos a osteoporose no homem tem sido reconhecida como um problema de saúde pública devido à ocorrência cada vez maior de fraturas por fragilidade. Cerca de 30% de todas as fraturas de quadril ocorrem em homens. Estudos recentes mostram que a probabilidade de fratura por fragilidade do quadril, vértebra ou punho em homens brancos após os 50 anos, pelo resto de suas vidas, situa-se em torno de 13%, 40% nas mulheres. Os homens apresentam perda de massa óssea e fraturas mais tardiamente do que as mulheres. Embora os homens mais idosos tenham maior risco de fratura, cerca de metade das fraturas de quadril ocorre antes dos 80 anos. A expectativa de vida tem aumentado para ambos os sexos no Brasil e em todo o mundo, porém em uma velocidade maior para homens do que para mulheres. Esta Diretriz foi baseada em uma revisão sistemática da literatura com relação a prevalência, etiologia, diagnóstico e tratamento da osteoporose em homens.

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Introduction

Pathophysiology of bone loss in men

Osteoporosis is a metabolic disease characterized by low bone mass, deterioration of the bone tissue microarchitecture and increased susceptibility to fractures. Osteoporosis is commonly regarded as a women's health problem. This point of view is based on the fact that compared with men, women have lower bone mineral density (BMD) measured by area (g/cm^2) and a longer lifespan and lose bone mass faster, especially after menopause, due to the marked decrease in serum estrogen concentrations. However, in the last 20 years, male osteoporosis has become recognized as a public health problem due to the increasingly common occurrence of fragility fractures. Approximately 30% of all hip fractures occur in men.¹

Skeletal development shows some differences between men and women. Men have longer and wider appendicular bones with thicker cortices than women. After birth, the bone

growth patterns of appendicular (arms and legs) and axial (spine) bones differ between men and women. The accelerated growth of the skeleton before puberty is due much more to the development of the legs than of the spine for both sexes. Thus, the onset of puberty, usually later in boys than in girls, results in longer bones in men than women.² Furthermore, cortical thickness increases during the peripubertal period due to the increased formation of periosteal bone in boys. In this period, the female bone has reduced periosteal formation but with increased endocortical apposition. In other words, the male bone grows more "on the outside" and the female bone more "on the inside".

Androgens, growth hormone (GH) and insulin-like growth factor (IGF-1) stimulate periosteal apposition in men, whereas estrogens inhibit this apposition in women, making the long bones narrower in women than in men.³ Endosteal apposition in women most likely depends on estrogenic action. Due to the greater muscle development in men, there is subsequent apposition of cortical bone in long bones, increasing even more their torsional strength. Men reach a

peak bone mass that is 8–10% higher than that in women, which is a further determinant of male protection against fractures.⁴

The losses of trabecular and cortical bone mass, which progress with aging, begin at different stages for men. The loss of trabecular bone mass begins in the young adult, whereas the loss of cortical bone mass is delayed and occurs more frequently after 50 years of age.⁵ Male bone loss associated with the onset of fractures occurs after 70 years of age.⁶

The decreases in trabecular bone mass in men and women are similar in number but different in pattern. Although trabeculae become thinner in men, their connectivity is better preserved, whereas resorption cavities with losses in the number of trabeculae and their connectivity predominate in women.⁷ The final result is a smaller decrease in total trabecular surface in men than in women. The thinning of trabeculae in men is associated with a decrease in bone formation, whereas the loss of trabeculae and connectivity in women is apparently related to the acceleration of bone resorption resulting from decreased plasma estrogen concentrations.⁸ The preservation of the number of trabeculae partly explains the lower risk of fractures in men than in women. Men with osteoporosis and fractures have greater loss of trabecular connectivity than men with osteoporosis without fractures.⁹ In cortical bone, periosteal apposition is greater with age in men than in women, whereas endosteal loss in the medullary cavity is similar for both sexes. Periosteal bone formation in men increases bone diameter and compensates for endosteal loss. The end result is better maintenance of the cortical area, conferring greater bone strength to male bones.¹⁰

Androgens and estrogens are important for the development and maintenance of bone mass in men. As mentioned previously, androgens play key roles in bone mass acquisition, particularly in periosteal expansion, bone diameter increase and muscle mass development with consequent bone mass increase. The description of (1) longitudinal skeletal growth abnormalities and low bone mass in a young man with an inactivating mutation of the estrogen receptor gene,¹¹ (2) aromatase-deficient men and (3) experimental genetic models of enzymatic and hormonal deficiency clarified the participation of estrogens in male skeleton development. Aromatase-deficient individuals lacked epiphyseal fusion and had higher values of bone remodeling markers and low bone mass, despite the higher testosterone plasma concentrations. These individuals responded to estrogen therapy with increased bone mass, highlighting the role of the female hormone in the regulation of male bone remodeling.¹² In men, the serum concentrations of estradiol depend on the activity of aromatase on testosterone. Only a small fraction of circulating estradiol derives directly from the testis; therefore, the peripheral aromatization of testicular and adrenal androgens plays a key role in defining male estrogenic concentrations, especially in elderly men. The role of estrogen and its predominance over androgen became evident for peak bone mass acquisition, longitudinal bone development, growth spurt initiation, epiphyseal growth plate fusion at puberty and bone remodeling rate in young men.¹³ Thus, serum estrogen concentrations also play an important role in

maintaining bone mass in men. Cross-sectional studies show that BMD is more directly related to estrogen than to circulating androgens. Men with higher concentrations of circulating estradiol have lower rates of bone loss over time in prospective studies.¹⁴ The serum estradiol threshold of 40 pmol/L seems to be the level below which male bone loss is more intense.¹⁵ It has been suggested that significant differences in aromatase activity, which is genetically determined, may be present among men, mediating differences in circulating estradiol concentrations and, therefore, playing a relevant role in the differences in BMD among elderly individuals.¹⁶ The understanding of the pathophysiology of male osteoporosis is closely associated with its classification, as shown ahead.

Question: What is the prevalence of male osteoporosis?

Discussion

The prevalence rates of male osteoporosis range from 2% to 8% at ages older than 50 years, and 33% to 47% of men meet the diagnostic criteria of osteopenia.^{17,18} Evidence has shown that the likelihood of hip, vertebral or wrist fragility fractures among Caucasian men after the age of 50, for the rest of their lives, is approximately 13% (*versus* 40% in women).¹⁹ Men show bone mass loss and fractures approximately 10 years later than women.^{20,21}

One study analyzed measurements of BMD in a sample of men aged 60–74 years, showing the prevalence of osteoporosis in 10.2% of the sample.²²

The Osteoporotic Fractures in Men Study (MrOs) followed more than 6000 men, with a mean age of 73.7 years, for 4.5 years. At the beginning of the study, only 2% of the mean were identified as having osteoporosis and, at the end, approximately 7% of men were diagnosed with osteoporosis. Progressive bone loss was associated with a 3.2-fold increase in fracture risk for each standard deviation of the T-score.^{23–25} The BMD/fractures association in elderly men was also observed in the Study of Osteoporotic Fractures (SOF).²⁶ In the Canadian Multicentre Osteoporosis Study (CaMos),²⁷ only hip fracture was related to age, as observed in the MrOs.

A study conducted in Minnesota determined an incidence of clinical vertebral fracture of approximately 0.7/1000 person-years.²⁸ Another longitudinal study conducted in Australia and lasting 3.2 years determined an incidence of hip and vertebral fractures of 2.4/1000 and 0.8/1000 person-years, respectively.²⁹

A prospective observational study showed that the relative risk (RR) of fracture following a low-impact fracture was higher in men than in women aged 60 years and older (RR = 3.47 and RR = 1.95).³⁰

In Brazil, a study of bone mass in men aged 50 years and older showed that bone mass loss of the femoral neck was significantly higher in patients aged 70–79 years.³¹ After 50 years of age, osteoporotic fractures are 2–3 times more common in women than in men. Hip fractures become more frequent with age, with similar incidence rates between sexes. From

85 to 89 years of age, these fractures account for approximately 33% of all fragility fractures in men and 36% in women.

Although older men have a higher risk of fracture, approximately half of all hip fractures occur before age 80.³² Life expectancy is increasing for both sexes in Brazil and worldwide, albeit at a higher rate for men than for women. Recent data have shown that Brazil has 11,422 elderly people older than 100 years of age. Of this total, 7950 are women and 3472 are men.³³ In 2000, an occurrence of 424,000 hip fractures in men was estimated worldwide and, by 2025, an occurrence of 800,000 fractures is projected, representing an 89% increase in 25 years.¹ The morbidity and mortality associated with hip and vertebral fractures are apparently higher in men than in women, which may be associated with greater presence of comorbidities and lower life expectancy in men. More men die after the first year of hip fracture than women.³⁴

Recommendation

The incidence and prevalence of osteoporosis and fractures due to bone fragility vary among countries and are mainly related to population differences. In Brazil, a study on the bone mass of men aged 50 or older showed that bone mass loss in the femoral neck was significantly higher in the 70- to 79-year decade of life.

Question: What are the main causes of male osteoporosis?

Discussion

Osteoporosis in men can be divided into three categories: (1) involuntional osteoporosis (age-related), (2) idiopathic osteoporosis (in young and middle-aged men) and (3) secondary osteoporosis (caused by other diseases, drugs and external factors). Models of association between classification and pathophysiology were proposed for the first two categories.³⁵

Involuntional osteoporosis is defined as osteoporosis occurring in men older than 60 years of age. Although elderly men show no marked decrease in sex hormones as occurs in women after menopause, male aging is associated with an increase in the serum concentration of sex hormone-binding globulin (SHBG), which decreases the availability of free and active testosterone and estradiol (not bound to SHBG). As previously discussed, free estradiol is associated with the maintenance of BMD and the bone remodeling rate in elderly men. Conversely, free testosterone plays a role in periosteal apposition, promoting bones with larger diameters and better biomechanical properties. Although the cause of the serum SHBG increase in the elderly is not well known, the decrease in IGF-1 concentration may play an important role, as it is inversely correlated with SHBG (IGF-1 inhibits SHBG production by hepatocytes). The decrease in IGF-1 is also associated with the decrease in GH, and the decrease of both impairs periosteal apposition and compensatory bone formation.

Table 1 – Secondary causes of osteoporosis in men.

More frequent	Glucocorticoids ^a Alcoholism Hypogonadism
Less frequent	Low body mass index (BMI) Sedentary lifestyle Smoking Hyperthyroidism Hyperparathyroidism Malabsorption syndromes Chronic liver disease Hypercalciuria Use of anticonvulsants Use of immunosuppressants Organ transplantation Rheumatoid arthritis Multiple myeloma Mastocytosis

^a Therapeutic use or Cushing's syndrome.

Idiopathic osteoporosis occurs in young men and middle-aged adults younger than 60 years. Although uncommon, some individuals develop osteoporosis and fractures before age 60, that is, before the onset of age-specific musculoskeletal changes. In these individuals, the inadequate peak in bone mass, associated with genetic problems, unfavorable lifestyle or concomitant diseases difficult to diagnose, such as incomplete forms of imperfect osteogenesis, may be associated with decreased bone mass and fractures. Even considering the possibility of these associations, hormonal changes occur in younger men that are very similar to the hormonal abnormalities observed in elderly men. SHBG also increases in men with idiopathic osteoporosis, which decreases free estradiol and testosterone. In these patients, there is also a decrease in IGF-1, although GH secretion is normal. In this context, the drop in IGF-1 has a genetic cause and is associated with the presence of a peculiar simple sequence (192/192) in the IGF-1 gene. The decreases in free estradiol and testosterone are associated with the same changes in bone resorption and formation observed in the pathophysiology of involuntional osteoporosis. In this scenario, circulating estradiol may also be decreased due to a mild defect in aromatization, even with a normal plasma testosterone level.

Secondary osteoporosis is defined when there is an underlying cause associated with bone mass loss. The main causes of secondary osteoporosis in men are outlined in [Table 1](#). The secondary causes of osteoporosis can be determined in only 50% of men with osteoporosis. The most frequent secondary causes, responsible for up to 40% of the cases, include use of glucocorticoids, excessive alcohol intake and hypogonadism, both idiopathic and related to androgenic deprivation due to prostate cancer treatment.³⁶⁻⁵² Other causes should be investigated during the medical consultation, such as primary hyperparathyroidism, hyperthyroidism (primary or treatment-induced), gastrointestinal problems limiting calcium absorption, chronic obstructive pulmonary disease, use of anticonvulsants, hyperparathyroidism, inflammatory rheumatic diseases, diabetes mellitus, renal failure,

HIV infection, chemotherapy, multiple myeloma and other neoplasms.⁵³⁻⁵⁸

Vitamin D deficiency should be considered in all cases. Low vitamin D concentrations are associated with osteomalacia and the risk of hip fractures in both men and women older than 65 years. In a study conducted in the city of São Paulo, 25-hydroxyvitamin D concentrations were evaluated in 382 elderly individuals of both sexes, showing that 40.7% of the elderly living in nursing homes and 15.3% of patients living in their own homes had vitamin D deficiency (less than 25 nmol/L). Approximately 30.5% of nursing home patients and 40.9% of patients living in their own homes had vitamin D insufficiency (>25 and <50 nmol/L).⁵⁹

Other risk factors associated with the development of osteoporosis and fractures in men are similar to those described for women. In addition to alcohol abuse, excessive smoking, sedentary lifestyle and low body mass index (BMI), the use of glucocorticosteroids, hypogonadism and conditions or diseases that can alter bone metabolism and calcium absorption should be considered. A study analyzed the prevalence and risk factors for osteoporosis in 325 Brazilian men aged 50 years or older⁴⁴ and showed that 44.6% of them had osteopenia and that 15.4% had osteoporosis. Furthermore, the main independent risk factors for low BMD were: (a) low BMI, (b) reduced practice of physical exercise in the last 12 months, (c) older age, (d) past or present history of smoking, (e) no use of thiazide diuretics, (f) white ethnicity and (g) history of maternal fracture after age 50. Other epidemiological studies⁶⁰ also showed that history of maternal or paternal fracture is an important risk factor for osteoporosis in men. This information should be collected during the clinical evaluation of all patients. Another study conducted with Brazilian men older than 50 years using total body densitometry to evaluate body composition showed that, although a higher BMI protects bone mass, the main weight component associated with bone protection is lean mass (i.e., muscle mass).⁶¹

Recommendation

The most frequent causes of secondary male osteoporosis are use of glucocorticoids, excessive alcohol consumption and primary or secondary hypogonadism, most often related to the use of androgen deprivation therapy for prostate cancer treatment. Other causes should be researched, including endocrine and gastrointestinal causes, use of medications, multiple myeloma and other neoplasms.

Question: What are the signs and symptoms of male osteoporosis?

Discussion

Osteoporosis in both men and women is a silent disease, i.e., usually asymptomatic. Pain, when present, is caused by fractures that occur more frequently in the vertebrae, humerus, wrist and femur and may be associated with other manifestations (Table 2).⁶²

Table 2 – Signs and symptoms of osteoporosis.

After vertebral fracture	Decreased height (after vertebral fracture) Chronic pain in the lumbar and/or thoracic region (due to post-fracture deformity) Wrist pain due to fracture of the distal third of the forearm (Colles fracture) Bent or kyphotic posture – dorsal hyperkyphosis Abdominal prominence Diaphragmatic breathing
Lower limb in external rotation due to fracture of the femoral neck.	

The diagnosis of osteoporosis in men is based on the same fundamental principles that govern the diagnosis of other diseases: anamnesis, physical examination and complementary tests, which, in addition to aiding in reaching the correct diagnosis, help to identify possible causes of secondary osteoporosis and to evaluate the risk of fracture, contributing to the treatment decision-making process.⁶³

In individuals under evaluation for osteoporosis, anamnesis and physical examination should be meticulous, investigating the existence of chronic diseases, medication use, smoking and excessive alcohol consumption, balance impairment rendering the individual prone to falls, history of fractures and family history of osteoporosis. The assessment of risk factors for reduced BMD may help to identify patients who should be screened with bone densitometry. In the presence of risk factors for osteoporosis or findings suggesting fracture, physicians should ensure that anamnesis and initial physical examinations cover the various aspects related to the occurrence of fractures in men (Table 1).⁶³ The physical examination offers little information to aid diagnosis, and the occurrence of fragility fractures may be the first clinical manifestation. Kyphotic deformities of the spine, such as thoracic hyperkyphosis, may result from vertebral fractures, along with decreased height with a loss greater than 3.0 cm relative to the height when young and localized pain during palpation of the vertebral column. In all cases, height, weight and BMI should be measured. Assessments of mobility, balance during walking, risk of falls, loss of muscle mass and signs of fragility are important. Evidence of secondary causes of osteoporosis, such as testicular atrophy, hyperthyroidism, chronic obstructive pulmonary disease and chronic diseases, such as autoimmune, rheumatologic, endocrine and other diseases, should be carefully assessed. Considering that only one-third of vertebral fractures are accompanied by symptoms (clinical fractures), chest and lumbar spine radiography should be performed in all patients at the first consultation and repeated annually.

Recommendation

Osteoporosis is usually an asymptomatic disease and difficult to diagnose. Detailed anamnesis may identify possible concurrent risk factors for bone mass loss or signs and symptoms suggesting fracture, such as back pain, height loss or findings indicating diseases that can cause osteoporosis (secondary

causes). The occurrence of fractures due to bone fragility is often the first manifestation of the disease and also alerts to investigating its causes. Obtaining a thorough anamnesis, with access to family history, history of previous fractures, medications used, lifestyle, chronic diseases and history of falls, is strongly recommended.

Question: Which groups of men benefit from bone densitometry?

Discussion

The bone densitometry test should be used to diagnose bone mass loss. The assessment of BMD is an important predictor of fractures. Studies show that the decrease in each standard deviation of hip BMD is associated with a 2.6-fold increase in the RR of hip fracture. Epidemiological data have shown that BMD values of the spine or hip indicate similar fracture risks for men and women of the same age.⁶⁴ Men with fragility fractures can be diagnosed with osteoporosis even without using densitometry. In these cases, densitometry will be used only in the follow-up of the post-treatment progression. The following studies have reported evidence:

The **European Prospective Osteoporosis Study** showed that the risk of fractures in men was similar to that observed in women when considering the same BMD values. In this study, although the BMD measurement was higher in men than in women, no sex differences in the occurrence of vertebral fractures could be identified when performing the analysis adjusted for the same BMD values.⁶⁵ Another observational study conducted in the Netherlands found that the occurrence of hip fractures, when adjusted for age and BMD values, also showed a similar risk between sexes, as discussed above.⁶⁶ Therefore, using the criteria proposed by the World Health Organization originally suggested for the diagnosis of osteoporosis in postmenopausal women, based on T-score values, for the diagnosis of osteoporosis in men seems reasonable.⁶⁷

A prospective study involving more than 5900 men aged 65 years or older found in the follow-up period of approximately five years that the fracture rate increased with age (approximately 0.7% for men aged 65–69 years, increasing to 5% for men aged ≥ 85 years). Individuals with fractures also had lower BMD values in both the lumbar spine and the femoral neck and were more likely to have falls. These fractures were almost invariably associated with minimal trauma.⁶⁸ A cross-sectional study using a random sample of 600 men aged between 60 and 74 years, subjected to dual X-ray densitometry (DXA) and vertebral fracture evaluation, found that the BMD values were significantly lower among individuals with vertebral deformities, and 24% of them had osteoporosis.²²

An analysis conducted in more than 50,000 men between 1992 and 1997 diagnosed with prostate cancer and subjected to androgen deprivation therapy found an increased risk for the occurrence of osteoporotic fracture. This study showed that men receiving nine or more gonadotropin-releasing hormone (GnRH) agonist doses or subjected to orchiectomy had

RRs of 1.45 and 1.54 for the occurrence of bone fractures, respectively.⁵¹

A systematic review with meta-analysis of 167 studies conducted to determine which population of men should undergo bone densitometry showed that age over 70 years, low BMI values (20–25 kg/m²), body weight loss (>10%), sedentary lifestyle, prolonged glucocorticoid use and previous osteoporotic fracture were associated with an increased risk of fractures.⁶⁹

The indication of bone densitometry in men follows the norms published by the Brazilian Society of Clinical Densitometry (Sociedade Brasileira de Densitometria Clínica – SBDens),⁷⁰ currently the Brazilian Association of Bone Evaluation and Osteometabolism (Associação Brasileira de Avaliação Óssea e Osteometabolismo – ABRASSO): (a) men aged 70 years or older, (b) men with a history of fragility fractures, (c) men with a disease or condition associated with low bone mass, (d) men taking medication associated with low bone mass or bone loss, (e) men in whom pharmacological interventions for osteoporosis are considered, (f) men undergoing treatment for osteoporosis, to monitor treatment efficacy and (g) men not undergoing treatment, in whom the identification of bone mass loss can determine treatment indication. To determine the relative bone density value (T-score), the normality database for Caucasian men should be used as a reference for all ethnic groups (without adjustment for ethnicity). Osteoporosis can be diagnosed in men aged 50 years or older if the T-score for the lumbar spine, total femur or femoral neck is ≤ -2.5 . The Z-score should be used for men aged 20–50 years. In this age group, a Z-score ≤ -2.0 is defined as “below the range expected for age”, and a Z-score > -2.0 should be classified as “within the limits expected for age”. The ethnicity defined by the patients themselves should be used to calculate the Z-score.

Recommendation

Men aged 70 years or older should undergo bone densitometry examination for the diagnosis of osteoporosis in the absence of fragility fracture. For men younger than 70 years, the indication for bone densitometry should be based on the presence of risk factors (cited above) according to the norms published by ABRASSO.

Question: Which laboratory tests should be performed to evaluate osteoporosis in men?

Discussion

The guidelines of the Endocrine Society (ES) (2012) and the National Osteoporosis Foundation (NOF) (2014) recommend that elderly men diagnosed with osteoporosis should undergo laboratory tests, including serum measurement of calcium and phosphorus, creatinine and alkaline phosphatase, liver function tests, thyroid function tests (TSH and free T4), vitamin D [25(OH)D] and total testosterone measurements, complete blood count and 24-h urinary calcium determination.^{71,72} These tests aim to detect secondary conditions associated with bone loss and osteoporotic fractures.⁷³

Further examination may be conducted according to the clinical symptoms, including suspected multiple myeloma (protein electrophoresis), Cushing's syndrome (urinary cortisol measurement), celiac disease (anti-tissue transglutaminase antibodies – tTG) or according to the severity of osteoporosis, especially when unusual for age or sex.⁷⁴

An interesting point that should be considered in this analysis refers to the finding of a laboratory evaluation conducted in 1572 men aged 65 years or older in the MrOs,⁷⁵ which showed that approximately 60% of individuals had one or more laboratory tests with abnormal results. Among the altered tests, only vitamin D deficiency and high alkaline phosphatase levels were worsened in individuals with a diagnosis of osteoporosis.⁷⁵

Recommendation

Laboratory tests are useful to identify or exclude secondary causes of osteoporosis. Complete blood count, calcium, phosphorus and creatinine measurement or assessment of glomerular filtration rate, 25(OH)D and 24-h urinary calcium determination should be requested when assessing osteoporosis in men. In elderly men, the positive predictive value of laboratory tests for secondary causes of osteoporosis is apparently low, except for 25(OH)D and alkaline phosphatase determination. Depending on the history and physical examination, laboratory evaluation of the gonadal state and thyroid function may be helpful, and in some cases, specific tests for the diagnosis of multiple myeloma or celiac disease may be necessary.

Question: Which lifestyle recommendations contribute to preserving bone mass in men?

Discussion

Guidelines aimed at bone mass preservation in men are similar to those recommended for women and include the indication of a balanced diet with adequate calcium intake, practice of physical activity and abstention from harmful factors, such as excessive alcohol consumption and smoking. Because bone tissue is dynamic and changes throughout life, it requires normal serum levels of hormones; adequate caloric intake, particularly of protein, calcium and vitamin D; and strength exercise.⁷⁶⁻⁷⁸ Recognizing that the bone mass peak, which is determined by sex, heredity, family history, ethnicity, diet and physical exercise, occurs during the first decades of life and has a protective effect against reduced BMD and consequent establishment of osteoporosis is crucial to achieving a better understanding of the importance of lifestyle in preserving bone mass and of factors affecting bone health.⁷⁹

The serum concentration of 25-hydroxyvitamin D should be carefully monitored because of its critical role in regulating intestinal calcium absorption, renal tubular reabsorption of urinary calcium and stimulation of bone resorption intrinsically related to the maintenance of serum calcium levels, which are important for bone health, structure and strength.⁸⁰

In patients susceptible to falls, measures aimed at reducing them should be implemented because they account for 90% of the number of hip fractures.⁸¹ This incidence is due to the fact that in comparative terms, while the reduction of one standard deviation of BMD is related to an approximately 2.5-fold increase in the risk of hip fracture, this risk can increase approximately 3- to 5-fold when a sideways fall occurs.⁸² Important preventive measures of falls include anti-gravity exercises, moderate-impact training and resistance training, which were able to increase muscle strength and flexibility, improving motor coordination and balance.

A systematic review that included 159 studies with a total of 79,193 participants in which the most commonly tested interventions were physical exercise as the sole intervention (59 trials) found that exercise programs and home interventions, aimed at preventing falls, reduced both the occurrence and risk of falls.⁸³ Thus, in addition to being highly recommended to reduce the risk of falls, the practice of physical exercise has also been indicated as non-pharmacological therapy for bone mass maintenance, as the necessary stimulus for the bone to maintain its structural and functional strength is directly related to the load imposed on it.⁸⁴ In recent years, numerous studies have been conducted to define the magnitude of physical activity indicated during adulthood and to identify its relationship with bone health.⁸⁵⁻⁸⁸ A randomized clinical trial analyzing the effect of impact exercise on elderly subjects found a significant increase in femoral neck BMD after 12 months of follow-up.⁸⁵ Evidence has shown that the practice of physical exercise during adulthood, more specifically when indicated for individuals older than 60 years, as assessed in a systematic review of randomized clinical trials, seems to both enable maintenance of the bone mass acquired during childhood and adolescence and to increase BMD.^{89,90} However, a secondary study with the same level of evidence showed the absence of sufficiently strong evidence to justify the practice of gravity or strength exercises to increase the BMD of the spine and femoral neck in men.⁹¹

Recommendation

Eating a balanced diet with adequate intake of carbohydrates, fats, proteins and minerals is essential for bone formation. Good dietary intake levels of calcium and vitamin D are extremely important not only in adolescence, when bone mass peaks, but also throughout life. The regular practice of strength exercises, an important factor for reaching the bone mass peak allowed by an individual's genetic potential, and a healthy lifestyle should be maintained throughout life, thereby minimizing bone mass loss.

Physical exercise programs not only directly affect bone health but are equally important for maintaining muscle mass and improving balance and, consequently, for reducing the risk of falls and fractures.

It should be noted that most physical activities are preferable to a sedentary lifestyle and should be encouraged, although the indication of any physical activity must necessarily consider the age, health status, physical condition and functional ability of the patient.

Question: What are the roles of vitamin D and calcium in the treatment of male osteoporosis?**Discussion**

The main constituents of hydroxyapatite crystals $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ of mineralized bone are calcium and phosphorus. Calcium is an essential element involved in numerous metabolic processes. Therefore, factors related to calcium absorption, deposition and removal from bone tissue determine bone health, structure and strength. Calcium needs vary according to age, sex and ethnicity and, during the growth phase, adolescence, pregnancy and lactation.

In turn, vitamin D is a key nutrient for systemic homeostasis, and its active metabolite, 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] or calcitriol, acts on the regulation of intestinal calcium absorption, renal tubular reabsorption of urinary calcium and stimulation of bone resorption to maintain its adequate serum levels.

Despite the importance of calcium as a constituent of the bone mineral matrix, the effects of its supplementation on the reduction of osteoporotic fractures lack uniformity.⁹²⁻⁹⁴ The study titled Vitamin D Individual Patient Analysis of Randomized Trials (DIPART), with a 14.4% male population, showed no reduction in the occurrence of pelvic fractures (hazard ratio (HR)=0.84 with 95% confidence interval (CI): 0.70-1.01).⁹⁵ Studies analyzing changes in BMD specifically related to calcium and vitamin D supplementation in the male population diagnosed with osteoporosis are scarce, although some evidence stands out.

A clinical trial conducted by Daly et al., which included men with lumbar spine Z-scores within ± 2.0 SD and who were randomized for dietary supplementation with calcium- and vitamin D-fortified milk (1000 mg calcium + 800 IU cholecalciferol) found that men who received dietary supplementation with fortified milk showed positive effects on BMD after follow-up periods of 12 and 18 months.⁹⁶ There were significant increases in the lumbar spine BMD of approximately 0.8% in the 12th month and 1.0% in the 18th month of follow-up. Corroborating these findings, another randomized clinical trial, conducted by Dawson-Hughes et al., also found that men subjected to dietary supplementation with calcium and vitamin D showed a significant increase in femoral neck BMD compared with those from the placebo group (0.95 ± 4.07 versus -1.35 ± 4.70 , respectively).⁹⁷

Conversely, conflicting results are reported when using these components alone (calcium or vitamin D), such as those found by Ebeling et al., where no differences in lumbar spine and femoral neck BMDs were observed among men diagnosed with primary osteoporosis and with at least one fragility fracture treated with calcitriol or calcium (1.9 ± 5.7 g/cm² versus 1.6 ± 10.1 g/cm² and 2.0 ± 6.0 g/cm² versus -0.05 ± 4.3 g/cm² for calcium and calcitriol, respectively) after a two-year follow-up.⁹⁸

Recommendation

Calcium and vitamin D are considered essential for the treatment of osteoporosis. Evidence shows that supplementation

with calcium and vitamin D is related to reduced bone mass loss.

Question: What is the role of androgen replacement (testosterone) in the treatment of male osteoporosis?**Discussion**

Changes in sex hormones observed in men diagnosed with primary or secondary hypogonadism or with aging are, at least partly, important factors for the reduction in BMD.⁹⁹ Men show a gradual decline in circulating testosterone production with age,¹⁰⁰ with an increase in SHBG, accentuating the decrease in the bioavailable fraction of testosterone.⁹⁹ *In vitro* and *in vivo* studies indicate that estrogens and androgens act through distinct cellular mechanisms in bone mass gain and maintenance. Estrogens show anti-resorptive activity through osteoclast inhibition, whereas androgens apparently stimulate osteoblast proliferation and differentiation and inhibit apoptosis.¹⁰¹⁻¹⁰³

Evidence suggests that bone mass loss in men over time is more closely related to a decrease in estrogen than in androgens.¹⁰⁴⁻¹⁰⁶ A prospective observational study that analyzed the relationship between hypogonadism (serum testosterone concentration lower than 300 ng/dL), serum estradiol concentration and BMD in 405 elderly men (with ages ranging from 68 to 96 years) found that the femoral neck, lumbar spine and distal radius BMD did not differ significantly between individuals considered eugonadal and diagnosed with hypogonadism.¹⁰⁴ However, when individuals were analyzed according to the mean estradiol concentration, a significant linear association between estradiol concentration and BMD was established. Thus, men who had lower estradiol values had lower BMD.¹⁰⁴

In contrast to fragility fractures, which show no defined correlation between androgenic hormone therapy and the incidence of fractures in involutional osteoporosis (because fracture is not an outcome analyzed in the studies), various clinical trials, controlled or uncontrolled, have shown that testosterone administration is associated with an increase in BMD in both individuals diagnosed with primary or secondary hypogonadism and those with osteoporosis.¹⁰⁷⁻¹¹¹ In turn, when analyzing the effects of androgen hormone therapy on BMD in eugonadal men, the results are controversial. Anderson et al., in a clinical trial, found that six-month androgen supplementation of eugonadal men diagnosed with established osteoporosis was associated with an increase in lumbar spine BMD.¹⁰⁷ Conversely, a study that also included eugonadal men subjected to transdermal patch testosterone treatment was unable to find the same results.¹¹²

A three-year study analyzing a population of elderly men (older than 65 years) diagnosed with hypogonadism and treated with androgen (testosterone enanthate) showed an increase of more than 8.9% in BMD compared with those receiving placebo.¹¹³ Corroborating these findings, another randomized clinical trial conducted by Basurto et al. assessed the effect of androgenic hormone therapy with testosterone

enanthate at a dose of 250 mg given every three weeks for a 12-month period on the BMD of men older than 60 years and plasma testosterone values lower than 320 ng/dL.¹¹⁰ This study showed a significant increase in lumbar spine BMD (from 1.198 ± 0.153 g/cm² to 1.240 ± 0.141 g/cm²).¹¹⁰ Another study, also randomized, including elderly patients (mean age 68.2 ± 5.2 years) diagnosed with osteoporosis found that administering hormonal therapy in the form of testosterone undecanoate was associated with significant increases in lumbar spine and femur BMD after six and 12 months.¹⁰⁸ It should be noted that a complete evaluation of the prostate should be performed before introducing androgenic hormone therapy to avoid undesirable treatment side effects that may compromise the glandular function or even stimulate a proliferative process.

Recommendation

The administration of testosterone in men with primary or secondary hypogonadism and/or diagnosed with osteoporosis has limited evidence of increases in BMD, especially in the lumbar spine. There is still no evidence relating the use of testosterone to a reduction in the risk of fragility fractures.¹¹⁴

Question: What is the role of bisphosphonates in the treatment of male osteoporosis?

Discussion

Bisphosphonates are non-hydrolysable synthetic analogs of inorganic pyrophosphate and are characterized by two carbon-phosphorus bonds (P–C–P). These compounds are deposited in the bone matrix due to their affinity to hydroxyapatite crystals, acting in bone formation and resorption sites. The mechanisms by which these compounds prevent resorption are not yet fully identified, although they apparently act in resorption processes by reducing osteoclast activity. The efficacy of this class of drugs has been shown in numerous studies in both women and men, and they are considered first-line drugs for the treatment of osteoporosis.

Alendronate

Clinical trials have shown that the use of alendronate by men diagnosed with osteoporosis is related to a significant increase in BMD. Orwoll et al. found that men randomized for treatment with alendronate at a dose of 10 mg/day showed a significant increase in lumbar spine BMD ($7.1 \pm 0.3\%$) at the end of the 24th month of follow-up.¹¹⁵ Another clinical trial conducted by Ringe et al. randomized men diagnosed with osteoporosis into treatment with alendronate (10 mg/day) or 1-alfacalcidol (1.0 µg/day). This study showed significant increases in lumbar spine and femoral neck BMD among individuals treated with alendronate after 24 months of follow-up.¹¹⁶ Similar results were found in another randomized clinical trial, wherein men with a mean age of 56.9 ± 11 years and diagnosed with osteoporosis were treated with either alendronate (10 mg/day) combined with calcium or treated with calcium alone.¹¹⁷ After a 36-month follow up,

there were significant increases in lumbar spine BMD (4.2% in the 1st year and 6.3% and 8.8% for the 2nd and 3rd years, respectively).

Risedronate

Favorable effects of risedronate on increased BMD have been shown in several clinical trials with different follow-up periods, ranging from six months to four years.^{118–122} A two-year multicenter clinical trial conducted by Boonen et al. showed that men diagnosed with osteoporosis showed a significant increase in lumbar spine BMD when randomized for treatment with risedronate (35 mg/week) compared with those who received the placebo (4.5% increase in BMD with 95% CI: 3.5–5.6%).¹²¹ In 2012, the same authors published data on the continuation of the aforementioned study with an additional 24-month follow-up, totaling four years of study.¹²² In this follow-up, now an open study, the individuals who had been randomized for treatment with risedronate continued using this drug, and those who had received the placebo began treatment with bisphosphonate. The study showed that individuals treated with risedronate in the first two years of the study and who received the same drug in the second phase for another two years showed a significant increase in lumbar spine BMD; the same effect was observed among the individuals who received the placebo in the first phase of the study and began the drug treatment in the second phase. The beneficial effects of risedronate on the decrease in bone fractures were evaluated in another open-label clinical trial, designed by Ringe et al., whose primary objective was to assess the occurrence of new vertebral fractures.¹²⁰ For 24 months, 316 men with a mean age of 57 years and diagnosed with osteoporosis were randomized for treatment with risedronate (5.0 mg/day) or placebo. This study showed a significant decrease in the number of vertebral fractures among individuals treated with the bisphosphonate (relative risk aversion (RRA) = 0.144; 95% CI: 0.055–0.217 and number needed to treat (NNT) = 7 [4–18]) at the end of the follow-up.

Zoledronic acid

Clinical trials have shown the beneficial effect of zoledronic acid on BMD gain and the decreased occurrence of bone fractures. At the end of the 24th month of follow-up in a multicenter, non-inferiority clinical trial, Boonen et al. showed that men randomized for treatment with zoledronic acid (5.0 mg/year) had increased lumbar spine and femur BMD.¹²³ Another multicenter, placebo-controlled, randomized clinical trial including more than 1000 individuals identified a lower occurrence of vertebral fractures after 24 months (RRA = 0.030; 95% CI: 0.009–0.045 and NNT = 32 [22–105]).¹²⁴

Recommendation

Use of oral (alendronate, risedronate) or parenteral (zoledronic acid) bisphosphonates for the treatment of osteoporosis in men significantly increases BMD. Evidence shows that the use of risedronate and zoledronic acid is related to a decrease in the risk for fragility fractures.

Question: What is the role of denosumab in the treatment of male osteoporosis?**Discussion**

Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL binds with high affinity, preventing the ligand from activating its sole receptor, the receptor activator of nuclear factor-kappa B (RANK), on the surfaces of osteoclasts and their precursors.¹²⁵ Therefore, this antibody reduces the differentiation, activity and survival of osteoclasts, thereby decreasing bone resorption. The approval of its use for the treatment of osteoporosis in men was based on data from a randomized controlled clinical trial titled *A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of denosumab vs placebo in males with osteoporosis (ADAMO)*, which showed increases in BMD of the lumbar spine, femur and distal third of the radius^{126,127} in 242 men during 12 months of follow-up.¹²⁷ All individuals met the following inclusion criteria: T-scores ≤ -2.0 and ≥ -3.5 in the lumbar spine or femoral neck or T-scores ≤ -1.0 and ≥ -3.5 in the lumbar spine or femoral neck associated with the presence of previous osteoporotic fracture. The most commonly reported adverse events were back pain, arthralgia, nasopharyngitis and constipation. No cases of atypical femoral fracture, hypocalcemia, mandibular osteonecrosis or complications in fracture consolidation were reported.

Similar results were also found in a multicenter study including patients undergoing non-metastatic prostate cancer treatment using anti-androgenic drugs who had been randomized for administration of denosumab or placebo.¹²⁸ In this study, patients received subcutaneous injections of denosumab ($n = 734$) or placebo ($n = 734$) every six months and daily calcium and vitamin D supplements. Significant increases in lumbar spine and femur BMD were observed in the first month after the initial dose. During the three-year follow-up, the use of denosumab was related to increases in the BMD of the lumbar spine (8.0%), the femoral neck (4.9%) and the distal third of the radius (6.9%).¹²⁸ Furthermore, the results showed a 45% decrease in the risk of any new fracture and a reduction in the incidence of new vertebral fractures at the 12th, 24th and 36th months of follow-up.

Recommendation

The use of denosumab in men diagnosed with osteopenia or osteoporosis, with previous osteoporotic fracture or undergoing treatment with androgen deprivation for non-metastatic prostate cancer promotes significant increases in vertebral and femoral BMD, with few adverse events.

Question: What is the role of teriparatide in the treatment of male osteoporosis?**Discussion**

Teriparatide (recombinant human parathyroid hormone 1-34 (PTH [1-34]rh)), obtained through recombinant DNA

technology, is a synthetic polypeptide with a sequence similar to amino acids 1-34 of the amino-terminal region of the endogenous human parathyroid hormone, which is the sequence responsible for its biological action. Teriparatide e mambas as versões binds with similar affinity to the G protein-coupled receptor because it is identical to the biologically active fraction of endogenous PTH (PTH [1-84]),¹²⁹ thereby stimulating new bone formation and allowing bone microarchitecture restoration and attenuation of the process of severe osteoporosis. The strongest available evidence on the efficacy of teriparatide in increasing BMD and reducing vertebral and non-vertebral fractures was obtained in studies that analyzed postmenopausal women diagnosed with osteoporosis.¹³⁰⁻¹³²

Kurland et al. published the first clinical trial analyzing the use of recombinant PTH in individuals diagnosed with idiopathic osteoporosis.¹³³ In this study, 23 men were randomized for subcutaneous treatment with 400 IU of PTH [1-34]rh or placebo. At the end of the 18-month follow-up period, the results showed a gain in vertebral column BMD among patients treated with teriparatide. In another randomized clinical trial, Orwoll et al. analyzed the efficacy and safety of teriparatide in men diagnosed with idiopathic osteoporosis or osteoporosis secondary to hypogonadism.¹³⁴ In this study, 437 individuals were randomized for treatment with teriparatide at doses of 20 μg , 40 μg or placebo. After an average treatment time of 11 months, the results showed significant increases in vertebral column and femoral neck BMD. The response to teriparatide occurred regardless of the presence or absence of hypogonadism. Extending the follow-up time of these patients, Kaufman et al. observed significantly higher BMD values in both the femoral neck and vertebral column in the 18th and 30th months of follow-up compared with the values observed for patients randomized for treatment with placebo.¹³⁵ No significant difference in the occurrence of new vertebral fractures was found between patients treated with teriparatide and patients treated with placebo at the end of the 30-month follow-up (RRA = -0.062 , 95%CI: -0.125 to 0.027 ; RRA = -0.057 , 95% CI: -0.123 to 0.037 for 20 μg and 40 μg teriparatide, respectively).

Recommendation

The use of teriparatide in men with or without hypogonadism showed a significant increase in BMD; however, there is still no robust evidence that its use is related to reduced risk of fragility fractures.

Question: What is the role of strontium ranelate in the treatment of male osteoporosis?**Discussion**

Strontium ranelate is a substance that apparently has a double effect on bone metabolism: it reduces bone resorption and increases the formation of bone mass and, thus, is an alternative for the treatment of osteoporosis.¹³⁶ *In vitro* studies have shown its capacity to reduce bone resorption via osteoclast

inactivation and to increase bone formation via osteoblast activation.^{137,138}

Two clinical trials examined the effects of strontium ranelate administration compared with placebo or alendronate on bone mass in males diagnosed with established primary osteoporosis.^{139,140} This first study, published in 2010, analyzed the effects of strontium ranelate and alendronate on BMD.¹⁴⁰ A total of 228 men diagnosed with primary osteoporosis were randomized for treatment with strontium ranelate (2.0 g/day) and alendronate (70 mg/week). In this open-label study, individuals treated with strontium ranelate showed mean BMD increases of approximately $5.8 \pm 3.7\%$ in the lumbar spine and $3.5 \pm 2.8\%$ in the total hip compared with $4.5 \pm 3.4\%$ and $2.7 \pm 3.2\%$ in the lumbar spine and total hip, respectively, of individuals who had been randomized for treatment with alendronate after 12 months of follow-up. Another clinical trial, conducted by Kaufman et al., which analyzed data from 54 centers, showed that patients who had been randomized for treatment with strontium ranelate at the dose of 2.0 g/day showed a significant increase in lumbar spine BMD after two years of follow-up (12%; 95% CI: 10.6–13.2% versus 2.1%; 95% CI: 0.6–3.6% in the placebo group),¹³⁹ along with an increase in femur BMD.

The adverse effects of strontium ranelate were re-evaluated in 2014 by the European Medicines Agency, which issued a statement (EMA/139813/2014) restricting the use of this drug to the treatment of adults with severe osteoporosis and at high risk for fracture, for whom treatment with other drugs is not available. Patients with clinical symptoms or history of ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease or uncontrolled hypertension should not be treated with strontium ranelate.

Recommendation

The use of strontium ranelate by men with a diagnosis of primary osteoporosis or reduced BMD associated with risk factors during a two-year period is well tolerated and contributes to increase the lumbar spine BMD, although there are no robust data on its antifracture efficacy. We endorse the EMA recommendation to restrict the use of strontium ranelate to adults with severe osteoporosis and high risk of fracture without the possibility of treatment with other medications and to counter-indicate its use in patients with clinical symptoms or history of ischemic heart disease, arterial disease and/or cerebrovascular disease or uncontrolled hypertension.

Question: What is the role of combined or sequential regimens in the treatment of male osteoporosis?

Discussion

The different mechanisms of action suggest that the sequential or simultaneous use of drugs with anabolic and anti-resorptive actions has an excellent potential to increase BMD more than any agent used alone.

Studies analyzing the performance of combined therapeutic regimens in postmenopausal women diagnosed with osteoporosis showed significant increases in vertebral column and femoral neck BMD compared with the use of monotherapy drugs. However, a clinical trial with the same population found that the use of teriparatide alone was associated with higher BMD gains in both the lumbar spine and the femoral neck compared with the combined regimen with alendronate.^{141–144}

A few clinical trials involving a small number of male patients were designed to assess the impact of combination therapy in the treatment of osteoporosis. Walker et al. randomized 29 men diagnosed with osteopenia (T-score < -2.0 SD) for treatment with risedronate (35 mg/week), teriparatide (20 µg/day) or the combination of the two.¹⁴⁵ This placebo-controlled study showed that at the end of the 18th month of follow-up, all therapies increased the BMD of the lumbar spine, with no significant differences between groups. Conversely, another clinical trial, also randomized, conducted by Finkelstein et al. showed that patients who had been treated with teriparatide monotherapy showed a higher increase in BMD compared with those who had been treated with alendronate or the combination of both drugs.¹⁴⁶ The same researchers, after observing changes in bone remodeling markers, concluded that the treatment with alendronate impairs the capacity of teriparatide to increase BMD because it attenuates the stimulation induced by this drug in bone formation.¹⁴⁶

Recommendation

Similar to postmenopausal women, prior or concomitant administration of bisphosphonates for the treatment of osteoporosis in men is associated with increased suppression of bone remodeling, delaying the effects of the administration of anabolic drugs, such as teriparatide.^{147,148}

Question: Can the Frax[®] algorithm model for Brazil be used for the clinical diagnosis of male osteoporosis?

Discussion

In 2008, the World Health Organization (WHO) introduced a fracture risk assessment algorithm termed the **Fracture Risk Assessment Tool (FRAX[®])**, which incorporated individual risk factors with the values obtained in bone mineral densitometry. This tool, available in 57 countries, covering 79% of the world population older than 50 years, was developed based on analyses of epidemiological studies conducted in Europe, the United States and Asia. The aim of this tool is to quantify the absolute risk, in the next ten years in patients between 40 and 90 years of age, of the occurrence of hip fracture (proximal femur) or of another major fracture due to bone fragility (forearm, proximal femur, humerus or vertebral column) based on easily obtained clinical risk factors, such as age, history of previous fractures, family history of osteoporotic fracture, use of glucocorticoids, low BMI, smoking and excessive alcohol consumption.¹⁴⁹ The BMD of the femoral neck may or may not

Table 3 – FRAX study in men in Brazil.

Age	Population Men	Incidence/100,000 Men
40-49	68,196	21
50-59	126,376	24
60-69	79,423	66
70-79	34,592	138
80-89	3424	618
90+	297	1144

be included to improve fracture risk stratification. It should be noted that only variables with established clinical evidence are considered in the interpretation of this instrument. Some variables, such as physical activity, vitamin D deficiency, diabetes, bone mass loss observed between sequential BMD measurements and falls, although important, still lack sufficient clinical evidence on their association with fractures to be considered in the FRAX[®] instrument. To design this algorithm, a meta-analysis of data from large epidemiological studies, including more than 59,000 individuals, of whom 74% were women, was conducted to identify fracture risk factors independent of BMD.¹⁴⁹ Thus, because of the method used to evaluate the possible relevance associated with each risk factor, generalizing the results in a population without specific epidemiological studies is improper. Therefore, the probability of fracture differs widely in different parts of the world, and the FRAX[®] instrument should be calibrated individually in each country where the hip fracture epidemiology and mortality are known. The inclusion of the risk of death is important because individuals with near-death probability are less likely to experience fractures than those with long life expectancy, and some risk factors affect both the likelihood of death and the probability of fracture. Examples include increased age, prolonged use of corticosteroids and smoking.

The Brazilian FRAX[®] model has been available since May 1, 2013. Data from four epidemiological studies conducted in the Northeast, South and Southeast regions were collected and analyzed to obtain national data on the incidence of hip fracture and mortality.¹⁵⁰ The results showed that in the Brazilian population, the incidence of fractures increases with age and that hip fracture is predominant in women over 50. The absolute risk of hip fracture or major fracture was increased in individuals with a clinical risk factor, low BMI, female gender, advanced age and low T-score on hip densitometry. Of the clinical risk factors, history of fracture due to bone fragility was responsible for the highest increase in the risk of fracture in the next 10 years in the less advanced age groups, and family history of hip fracture (paternal or maternal) was the most relevant risk factor between the ages of 80 and 90.¹⁵⁰ In total, 146 hip fractures in men over 40 years were identified in the four Brazilian studies used in the construction of the Brazilian FRAX[®] model. The results in Table 3 were obtained when calculating the incidence of hip fractures in men per 100,000 people.

Based on the 2015 Census of the Brazilian population, the occurrence of 23,422 hip fractures in men was estimated.

FRAX calculations for men

The 10-year probability of hip fracture gradually increased in the male population. As expected, the likelihood of a major fracture (clinical spine, forearm, humeral and hip fracture) was greater than the probability of a hip fracture for all ages. Each risk factor contributed independently to the probability of fracture. A parental history of hip fracture (father or mother) was the most important fracture risk. Other factors associated with increased fracture risk were low BMI, prolonged use of corticosteroids, rheumatoid arthritis and previous fragility fracture. When densitometry was used in the FRAX[®] calculation, for all ages, the probability of fracture increased with the decrease in the T-score. Thus, the T-score for any probability of fracture decreased with age.¹⁵⁰ However, limitations of these data are reported and should be considered as analyses of fracture rates based on regional estimates, not necessarily representing the country as a whole and the multiethnicity found in Brazil.

Recommendation

The FRAX[®] instrument was validated in a Brazilian population of men and women and can be used to evaluate the absolute risk of major fracture and isolated hip fracture in the next 10 years in men aged between 40 and 90 years.

Conflicts of interest

The authors declare no conflicts of interest.

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