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EDITORIAL

Choosing the approach treatment strategy for osteoporosis in men

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1. Introduction

Osteoporosis is a musculoskeletal disorder characterized by reduced bone mineral density (BMD) and a higher risk of fragility fractures [1]. It is a major health problem, affecting mainly the female population [1]. However, osteoporosis increasingly affects men demonstrating an exponential increase in the incidence of fractures a decade later compared with women [1]. The lifetime risk of fracture for a man with osteoporosis has been estimated to be higher than the chance of developing prostate cancer. Nowadays, one in four hip fractures occur in men. Furthermore, the incidence of hip fractures in men is expected to increase by 310% until 2050 [2].

Although osteoporosis is associated with a significant degree of disability, morbidity and mortality, the disease is still underdiagnosed and undertreated in men. A man is less likely to be evaluated and treated following a hip fracture or glucocorticoid treatment compared with a woman in the same situations [3].

With regard to etiology, male osteoporosis is more frequently (compared with female osteoporosis) attributed to secondary causes. Except for hypogonadism due to the gradual decline in testosterone concentrations with age or other causes, risk factors for male osteoporosis include hypercalciuria, type 1 diabetes mellitus (DM), primary or secondary hyperparathyroidism, thyrotoxicosis, chronic obstructive pulmonary disease, Parkinson's disease, rheumatoid arthritis, endogenous hypercortisolaemia, medications such as glucocorticoids, anti-androgens or tricyclic anti-depressants [4–6]. According to a systematic review and meta-analysis, the strongest risk factors associated with almost a three-fold increased risk of fractures in men are dementia, history of stroke and non-pharmacological hypogonadism. Other risk factors associated with a two-fold increased risk are a history of prior fracture and history of >1 falls within the last year [6]. Type 2 DM is also associated with increased fracture risk, independently of bone mineral density (BMD), which may be normal or even higher. Accumulation of glycosylation products in bone which distort bone architecture and increase fragility, as well as the coexistence of micro- and macro-angiopathy, constitute the main mechanisms [5]. Other risk factors include alcohol abuse, smoking and low dietary protein intake [4–6].

Several international scientific organizations have provided guidelines for the management of male osteoporosis [4,7]. They do not recommend population-based screening by dual-energy x-ray absorptiometry (DXA) in men at any age [4,7]. Risk assessment should be made on a case finding basis, with DXA restricted to those who have clinical risk factors and increased fracture probability as assessed by Fracture Risk Assessment Tool (FRAX) or other risk algorithms [8].

A detailed medical history and clinical examination of the patient should be performed in order to identify risk factors for secondary osteoporosis [4]. Baseline laboratory examination is recommended in order to exclude secondary causes and evaluate the safety of the treatment: Complete blood count, serum glucose, calcium, phosphorus, creatinine (with estimated glomerular filtration rate), albumin, alkaline phosphatase, liver function tests, 25-hydroxyvitamin D [25(OH)D], total testosterone and 24-h urinary calcium [4]. Depending on the findings of the history and physical examination, further testing should be performed including free or bioavailable testosterone, serum protein electrophoresis with free κ and λ light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (to exclude celiac disease), thyroid stimulating (TSH) and parathyroid hormone (PTH) levels [4].

Both lumbar spine (LS) and hip BMD assessed by DXA scan are recommended. Forearm DXA (1/3 or 33% radius) is suggested for those patients in which spine or hip BMD cannot be interpreted or for men with hyperparathyroidism or those receiving androgen deprivation therapy for prostate cancer [4].

There is no current, universally validated strategy for therapeutic decision-making in men. Dietary and lifestyle modifications are recommended to reduce fracture risk, including 1000–1200 mg/day calcium intake (either from dietary sources or supplements) and adequate vitamin D intake to achieve 25 (OH)D concentrations >30 ng/ml [4]. Regular weight-bearing and muscle-strengthening physical activity, as well as smoking

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cessation and reduction of alcohol intake in men with high consumption are also recommended [4].

The recommendations for treatment, as well as reference values for treatment using either normal young male or premenopausal women, vary across the world. The following indications for treatment are examples of such recommendations: men with a history of non-traumatic hip or vertebral fracture or those with a spine, FN and/or TH BMD ≤-2.5 SD (compared with the mean of normal young white males) [4]. Therapy is also suggested for men with osteopenia (T score <-1.0 and >-2.5) in the spine, FN or TH plus an estimated 10-year risk ≥20% or ≥ 3% for major osteoporotic and hip fracture, respectively, by using the FRAX model, although this may vary according to national fracture data. Long-term glucocorticoid therapy in pharmacological doses (e.g. prednisone or equivalent ≥7.5 mg/d) is another indication for therapy [4,7].

Food and Drug Administration (FDA) or European Union (EU) European Medicines Agency (EMA)-approved therapies for male osteoporosis include bisphosphonates (alendronate, risedronate and zoledronic acid), teriparatide and denosumab [4]. Two large randomized-controlled trials evaluated zoledronic acid [9] or denosumab [10] for the treatment of osteoporosis in men, having fracture as a primary or secondary endpoint. Intravenous administration of zoledronic acid for two years in men significantly reduced the risk of new vertebral fractures compared with placebo [9]. Treatment with denosumab also reduced the incidence of new vertebral fractures in patients receiving androgen deprivation therapy for nonmetastatic prostate cancer compared to placebo [10]. Other studies in men primarily evaluated BMD and changes in bone turnover markers. One-year denosumab therapy significantly increased the BMD in the LS, total hip (TH), femoral neck (FN), trochanter and radius in men compared with placebo [11].

A recent meta-analysis supported that alendronate exerts a beneficial effect on LS, FN and TH BMD, as well as on the incidence of new vertebral fractures [12]. Furthermore, treatment with risedronate for two years showed a significant increase in LS BMD compared with placebo in men with osteoporosis with no differences in new vertebral and non-vertebral fractures between groups [13]; however, this study was not powered to show fracture reduction. The safety and efficacy profile of risedronate was similar for those men that continued risedronate therapy for four years [14]. On the other hand, 18-month teriparatide therapy resulted in significantly higher LS BMD, greater improvement in bone microstructure and finite element-derived strength than risedronate in men with glucocorticoid-induced osteoporosis [15]. Post-hoc analyzes of most of the clinical studies in men demonstrated that the treatments were equally efficient irrespectively of testosterone levels. Testosterone treatment is suggested for men with serum testosterone levels <200 ng/dl (6.9 nmol/l) on more than one determination, and signs or symptoms of androgen deficiency or those at high fracture risk and low testosterone who cannot receive the aforementioned approved anti-osteoporotic medication [4].

There is no evidence to support a specific timetable of BMD measurement to monitor therapy. Measurement of a bone resorption or formation marker at 3–6 months after initiation of anti-resorptive or osteo-anabolic therapy can be helpful [6] to provide data on therapy response and monitoring, although more robust evidence is necessary.

2. Expert opinion

A higher degree of suspicion is needed to identify men who have osteoporosis compared with women. Except for advanced age, several diseases and conditions have been identified as risk factors for male osteoporosis. DXA screening should be performed in all men aged ≥70 years or in younger individuals with a history of non-traumatic fracture or other risk factors, such as hypogonadism, hyperparathyroidism, thyrotoxicosis, endogenous hypercortisolaemia or medication-induced bone loss. A detailed medical history, clinical and basal laboratory examination (liver and kidney function tests, glucose, calcium, phosphorus and calciotropic hormones) or a more specialized disease-oriented biochemical assessment, are necessary to recognize risk factors for secondary osteoporosis. Modifications in dietary habits, such as adequate calcium and vitamin D3 intake, as well as lifestyle changes including regular physical activity, smoking cessation and reduction of alcohol consumption are recommended to decrease the risk of osteoporosis. Pharmacological treatment is recommended in men with a history of non-traumatic hip or vertebral fracture, those with a LS, FN, TH BMD ≤ −2.5 SD or in men with osteopenia at the same skeletal sites plus a 10-year risk of major osteoporotic or hip fracture of ≥20% or ≥3%, respectively. Men following long-term glucocorticoid therapy in pharmacological doses should also be treated for osteoporosis. Alendronate, risedronate, zoledronic acid, denosumab and teriparatide are approved treatments for male osteoporosis. Testosterone is suggested in hypogonadal men at high risk of fracture.

Areas of controversy include the superiority of one therapy versus another, with regard to fracture risk, the use of male reference data in all DXA machineries for more representative results, as well as the exact laboratory diagnostic work-up (i.e. the cost-effectiveness of screening for less common diseases, such as endogenous hypercortisolemia and hypercalciuria, needs to be proven in prospective studies). Further imaging data, such as from spine X-ray or vertebral fracture assessment (VFA), may contribute in a more precise fracture risk assessment, such as in cases with height loss (>4 cm). Finally, the supplementary role of sarcopenia in augmenting fracture risk in older men needs to be further assessed and validated in future studies.

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