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OSTEOPOROSIS IN MEN- A REVIEW

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INTRODUCTION

Osteoporosis is a musculoskeletal disease characterized by decreased bone mineral density (BMD) and increased risk of fragility fractures. Osteoporosis is a silent disease with no symptoms until a fracture occurs. While osteoporosis has been traditionally considered a female disease, it is becoming an increasingly important male health problem, result in significant mortality and morbidity in men and lead to considerable societal costs, including direct medical costs and indirect costs resulting from reduced quality of life, disability, and death (Becker DJ 2010). It is estimated that the lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 (in Sweden) is 30%, which is similar to the risk of developing prostate cancer (Merrill RM 1997). In the same line, osteoporotic fractures in men account for more hospital bed days than those due to prostate cancer (Kanis JA 2004). Moreover, one in three fragility fractures after the age of 50 years occurring in men (Johnell o 2006). Although at least 15-30% of men (Randell A 1995) will sustain one or more fragility fractures in their lifetime, the consequences of osteoporosis are underestimated, and the condition is often unrecognized and untreated in most men (Curtis JR 2009).

Eitiology and pathogenesis

Osteoporosis in men occurs from a complex interplay of different factors, including age-related sex hormone deficiency, genetics, and lifestyle choices (e.g., physical inactivity, tobacco and excessive alcohol use), as well as specific risk factors (e.g., corticosteroid excess) that cause bone loss and microarchitectural disruption (Rao SS 2010).

Osteoporosis in men has been classified, classically, into three types: (1) Age-related or senile osteoporosis; (2) Idiopathic in middle aged males; and (3) Secondary osteoporosis (Khosla S 2004).
Up to 50%-65% of the diagnoses in male patients are secondary to metabolic diseases, toxic substances or iatrogenic side effects (Orwoll ES 1998). (Table -1)

Age-related osteoporosis in men, like in women, is more likely to occur as age increases, and is typically seen in males over the age of 70 years (Wilson T 2015). As men get older, production of estradiol and testosterone decreases. Unlike in women, who experience an abrupt decline in estrogen levels at menopause that leads to accelerated bone loss, men have slower bone loss with a smaller overall decrease in BMD (Rao SS 2010).

Idiopathic osteoporosis can be present in any age group, but it is more prevalent in younger individuals. Genetic factors linked with gene polymorphisms such as collagen specific proteins (COLIA 1 and COLIA 2), in vitamin D receptors; and in lipoprotein receptor-related protein (Eisman JA 2006), are the supposed etiology for this type of osteoporosis ((Eisman JA 2006). A recent study showed that men whose fathers had osteoporosis tended to also have reduced bone size and reduced volumetric BMD (Van Pottelbergh I 2003).

Table-1 Causes of secondary osteoporosis (Gielen E 2011, Mosekilde L 2013)

Medications	Glucocorticoids Anticonvulsants Chemotherapeutics Thyroid hormone GnRH-analogues Anticoagulants
Chronic diseases	COPD Gastrointestinal disorders: malabsorption syndromes, inflammatory bowel disease, celiac sprue, primary

	biliary cirrhosis, postgastrectomy, etc Hypercalciuria Hyperthyroidism Hyperparathyroidism Hypogonadism Neuromuscular disorders Systemic illnesses: mastocytosis, malignancies Rheumatoid arthritis Ankylosing spondylitis D.M type 1&2 Systemic mastocytosis Neoplasms e.g Multiple myeloma Renal failure SCA , Homozygous B- Thalassemia Homocystinuia Osteogenesis imperfecta
Poor nutrition	Low serum levels of vitamin D Low calcium
Other	Alcohol abuse Post-transplant osteoporosis Sedentary lifestyle Tobacco abuse

Diagnostic criteria

The World Health Organization (WHO 2007) established diagnostic criteria for osteoporosis using bone mineral density (BMD) measurements. It classifies patients into three diagnostic categories: normal BMD, low bone mass (i.e., osteopenia), or osteoporosis (Ebeling PR 2008) **Table -2**.

Although the validity of defining osteoporosis in men using BMD is unclear, it is generally agreed (including ISCD 2013) that a T-score of −2.5 or less, is useful to define osteoporosis.

Table-2 WHO Diagnostic categories of osteoporosis (Ebeling PR 2008)

Diagnostic category	Criterion
Normal bone mass	BMD within 1 standard deviation of the reference mean for young adults (T-score ≥ −1.0)
Low bone mass (osteopenia)	BMD of > 1.0 to < 2.5 standard deviations below the mean for young adults (T-score < −1.0 and > −2.5)
Osteoporosis	BMD ≥ 2.5 standard deviations below the mean for young adults (T-score ≤ −2.5)
Severe or established osteoporosis	BMD ≥ 2.5 standard deviations below the mean for young adults in the presence of one or more fractures

Laboratory blood and urine tests are mainly used in men with low BMD or fragility fractures in order to identify possible causes of secondary osteoporosis and help to differentiate osteoporosis from other osteopenic conditions such as osteomalacia. Table 3

Table-3 Biochemical work-up of osteoporosis in men (Cianferotti L 2012)

First line diagnostic tests include: [are essential in the initial evaluation of an osteoporotic patient, which can reasonably exclude with 90% probability secondary forms of osteoporosis] -CBC&ESR -Se.Ca (corrected for albumin) -Se.PO -Alkaline phosphatase -Se. Cr -Protien electrophoresis, -24 hr urinary calcium.
Second-line diagnostic tests are advisable according to clinical judgment. The second line tests are should not routinely proposed in initial assessment which include:

-TSH -PTH -Se.25(OH) vitD -Ionized calcium -Low dose dexa suppression test -Se. testosterone,Se. SHBG -Urine and serum immunofixation electrophoresis -Anti-Transglutaminase Ab -Se PSA -Other disease specific tests such as urine N-methylhistamine, tryptase, Se.ferritin -Biochemical markers of bone metabolism

Screening Guidelines& Absolute risk assessment
Although screening guidelines vary by organizations, most rely on age and the identification of other clinical risk factors to identify males at risk for fracture. **Table-4**

However, low BMD alone is a poor predictor of fracture in men, with one study finding that only 21% of elderly men who went on to have a nonvertebral fracture and 39% of men who went on to have a hip fracture had a T-score below −2.5. This indicates a need for tools that predict fracture risk independently of, or in addition to, BMD (Schuit SC 2004).

The use of risk assessment tools that include clinically relevant risk factors to predict fracture risk such as FRAX, are being increasingly incorporated into osteoporosis screening and treating guidelines (Willson T 2015).

Table-4 Screening Guidelines of osteoporosis in men

Organization	Screening Recommendations
National Osteoporosis Foundation (NOF)	BMD testing using DXA for men age 70+ and in those age 50–69 with risk factors for fracture. In those with a prior fracture, BMD testing and vertebral imaging are recommended to assess disease severity. Vertebral imaging is recommended - in men aged 80 years and older, - in men aged 75–79 years with a T-score of −1.5 or less -in men aged 50–69 years with low trauma fracture -long-term glucocorticoid treatment, -historical height loss of at least 1.5 inches, or prospective height loss of 0.8 inches or more.
International Society for Clinical Densitometry (ISCD)	BMD testing for men aged 70 years and older and in men under the age of 70 years with clinical risk factors including prior fracture or disease or medication associated with bone loss or low BMD.
National Osteoporosis Guideline Group (NOGG)	Assess 10-year major osteoporotic fracture probability in men aged 50 years and older using UK FRAX. BMD testing is recommended based on age and fracture probability using predetermined assessment thresholds.
The Endocrine Society (ENDO)	BMD testing using DXA in men aged 70 years and older and in men aged 50–69 years who have risk factors such as low body weight, prior fracture as an adult, and smoking. Laboratory testing should be done to detect secondary causes.

Management
The decision regarding osteoporosis treatment should be based on clinical evaluation, diagnostic workup, fracture risk assessments, and BMD measurements. **Figure 1**

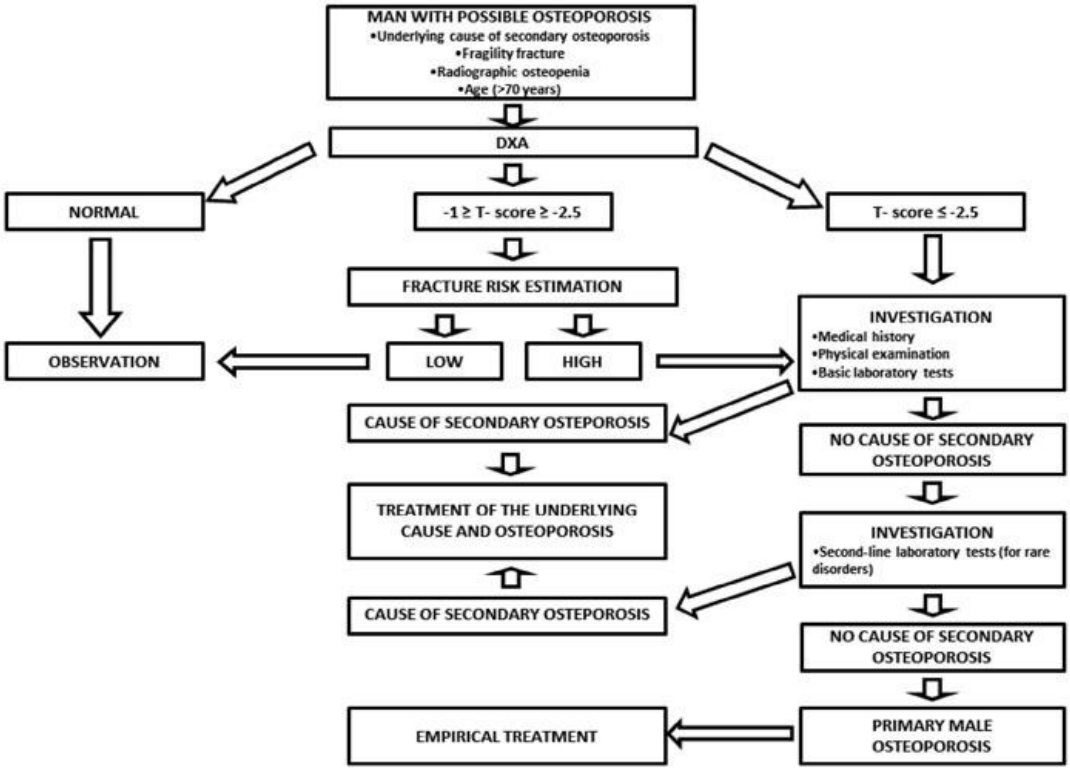

Figure.1 Management algorithm for men with possible osteoporosis. Adapted from: Ioannis P. Stathopoulos et al. HORMONES 2014, 13(4):441-457

Recent guidelines recommend treatment for men 50 years and older who present with any of the following: hip or vertebral fracture; T-score of −2.5 or less at the femoral neck or spine after appropriate evaluation to exclude secondary causes; or low bone mass (T-score between −1.0 and −2.5 at the femoral neck or spine) and a 10-year hip fracture risk of at least 3 percent or a 10-year major fracture risk of at least 20 percent (as calculated using the FRAX) (Dawson-Hughes B 2008).

The US Food and Drug Administration (FDA)-approved pharmacologic therapies for osteoporosis treatment in men include bisphosphonates (alendronate, risedronate, and zoledronic acid), teriparatide, and denosumab. All of these agents inhibit bone resorption, except teriparatide, which promotes new bone growth (WillsonT 2015). Denosumab and teriparatide are currently considered options for patients who are intolerant of or have contraindications to bisphosphonate therapy (Miller 2004, Cummings 2009).

Testosterone treatments for osteoporosis in eugonadal men are not usually recommended in the clinical practice guidelines. On the other hand, in hypogonadal men long-term treatment with testosterone replacement therapy has been shown to be well tolerated and effective in men with osteoporosis (Snyder PJ1999).

It is imperative to be aware that adequate calcium and vitamin D stores must be present to allow pharmacologic treatments for osteoporosis to be effective (Sunyecz JA 2008).

The calcium intake in men older than 50 years is 1,200 mg. However, the recommended vitamin D intake for preventing osteoporotic fractures is at least 800 IU per day (Tang BM 2007).

All men should be counseled on lifestyle measures, such as smoking cessation and limiting alcohol consumption to less than two drinks per day. Weight-bearing exercise can increase BMD in older men (Kukuljan S 2009).

CONCLUSION

While the rate of osteoporosis in men is lower than in women, the consequences are possibly more devastating. Many organizations now provide clinical guidelines to address osteoporosis screening and treatment in men. Evaluation of secondary causes, especially hypogonadism, is important, as they can play a significant role in the development of osteoporosis in men. All men should be educated to improve modifiable risk factors and maintain recommended daily intakes of calcium and vitamin D. The recently revised evidence-based recommendations focused on the management of male osteoporosis, hopefully open door for further researches.

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