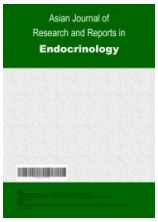

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Male Osteoporosis and a Diagnostic Algorithm for its Investigation

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Osteoporosis is a leading cause of morbidity and mortality in elderly people. Increase understanding of osteoporosis and its complications has been seen in recent years. Osteoporosis and associated fractures are not restricted to postmenopausal women. Considering the rise in life expectancy, the incidence of fractures in men is growing. The main problem at this age is functional impairment and morbidity. Osteoporosis in males, often overlooked problem compared to osteoporosis in females. The number of articles deal only with the patient population of women. Better treatment strategies for this condition can be established by enhancing our knowledge on approach to diagnosis of osteoporosis in men. This review is aimed to provide its diagnostic algorithm for osteoporosis in men.

Keywords: Osteoporosis in men; diagnostic algorithm; risk factors.

1. INTRODUCTION

In 1835, the French pathologist Jean Lobstein coined the term "osteoporosis" to describe deteriorated human bone [1]. In 1941, Fuller Albright reported the cases of women with vertebral fractures and he related it to oestrogen deficiency [2]. Osteoporosis was not officially

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acknowledged and defined as a disease by the WHO until 1994. Although traditionally considered a women's health issue, osteoporosis-related mortality and morbidity rates are higher (2- 3 times) in men [3]. The majority of articles deal only with the population of women patients. This review is aimed to provide its diagnostic algorithm for osteoporosis in men.

1.1 Overview of Osteoporosis

Osteoporosis is a leading cause of morbidity and mortality in elderly people. While less common in men than women, about 1.5 million men over age 65 years in the United States have osteoporosis and another 3.5 million men are at risk [4]. Worldwide, the number of hip fractures is estimated to approximately double to 2.6 million by the year 2025, and 4.5 million by the year 2050. The percentage increase will be greater in men (310%) than in women (240%) [5].

Lifetime risk of any osteoporotic fracture is very high and lies within the range of 40-50% in women and 13-22% for men [6]. The mortality rate associated with hip fractures, as well as other major fractures is higher in men than in women [7]. In addition, few men get evaluated and receive antiresorptive treatment [8].

Osteoporosis has no symptoms until there is a fracture and it ends up making it under recognised and undertreated. A 60-year-old man has an approximately 25% chance of having an osteoporotic fracture during his lifetime, and at 90 years of age, one in every six men will have a hip fracture [9]. While the prevalence of vertebral or hip fractures in older men is about one-third that of women, the mortality rate associated with hip fractures, as well as vertebral and other major fractures, is higher in men. Compared to women, men are about two times more likely to die in the hospital after a hip fracture [10].

1.2 Etiopathogenesis in Males

Decreased bone mass can occur because either peak bone mass is low, or bone resorption is excessive after peak bone mass is obtained, or bone formation during remodelling is decreased. All three processes are likely to contribute, in varying degrees, to osteoporosis in individual patients. As opposed to postmenopausal women, reduced bone formation is the predominant mechanism of age-related bone loss in men [11].

Age-related bone loss is a universal phenomenon affecting both men and women. Apart from bone mass, bone microarchitecture in males deteriorates with ageing due to increased cortical porosity, endocortical resorption and decreased trabecular thickness. These changes are linked to decreased testosterone levels and increased SHBG levels during ageing. Factors such as smoking, alcohol consumption, certain childhood diseases, and drugs such as glucocorticoids may adversely affect the peak bone mass in young males [12,13].

Age-related BMD loss is gender different, affecting lesser men than women. Men do not experience a significant decrease in sex hormone levels as seen during menopause. 25(OH)D is higher in men than in women of all ages. In addition, men have a shorter life expectancy, which contributes to less bone fragility in men compared to women [7].

Osteoporosis in men is a heterogeneous clinical entity. Osteoporosis in men can be classified as primary or secondary, with primary osteoporosis often divided into idiopathic and age-related based on the age of diagnosis. Major causes of osteoporosis in men described in the Table No.1. Primary osteoporosis comprises more than one third (30-35%) the cases in men and is a heterogeneous multi-factorial condition referring to the development of osteoporosis when no secondary cause is identified [14]. Male osteoporosis that results from specific clinical disorders or medical therapeutic treatment is classified as secondary osteoporosis, contributing to 65-70% cases. [15,16].

1.3 Diagnostic Evaluation

The diagnosis of osteoporosis is established in two ways: (i) by measurement of bone mineral density (BMD), and (ii) on the basis of a history or evidence of a fragility fracture. The bone densitometry definition of osteoporosis in men is not as well-standardized as it is in postmenopausal women [18]. However, as in women, bone mineral density measurements are useful for predicting osteoporotic fractures in men [19]. The reduction in Hip BMD is strongly associated with risk of nonvertebral, and especially hip fracture, in older men. These associations are at least as strong as in women or even greater than, the relative risk in women [20].

The World Health Organization (WHO) recommends using the similar cut-off value for

femoral neck BMD Table 2, can be used for the diagnosis of osteoporosis in men as in women [21].

The National Osteoporosis Foundation (NOF), International Society for Clinical Densitometry (ISCD), and the Endocrine Society recommend BMD testing for all men older than 70 years, and in men 50 to 70 years when risk factors are present.

The male osteoporosis risk estimation score (MORES, Table 3 is a clinically useful approach to identifying men 60 years and older who are at risk of osteoporosis [23].

In men who are candidates for BMD testing, guidelines suggest DXA measurements of the spine and hip. The initial history and physical examination will provide an explanation for low bone mass. The initial evaluation should also include routine biochemical tests for renal or hepatic disease, a complete blood count, serum testosterone, calcium, alkaline phosphatase, 25-hydroxyvitamin D and 24-hour urine calcium.

The goal of the evaluation of men with low bone mass (T-score below -2.0) or fragility fracture is to rule out secondary causes. More than 50% of the cases of osteoporosis in men are due to secondary osteoporosis. It is necessary to rule out these secondary causes, particularly alcoholism, malabsorption syndromes, immobilisation, rheumatic arthritis and drug induced such as anticonvulsant, glucocorticoid therapy. Men who have abnormalities on the initial laboratory testing, have suspicious findings on history and physical examination, or who have unexplained low bone mass after the initial evaluation may also require additional laboratory tests. It includes second tire investigations Table 4 for renal or liver disease, hyperparathyroidism, Cushing's syndrome, celiac disease and other forms of malabsorption, or idiopathic hypercalciuria etc. The Fig. 1 shows simplified diagnostic algorithm for diagnostic evaluation of osteoporosis in men.

2. MANAGEMENT

The treatment of osteoporosis in men includes lifestyle modification and drug or hormonal therapy. Potential causative agents (eg, glucocorticoids, alcohol, tobacco, etc) should be avoided.

Table 1. Major causes of osteoporosis in men [17]

Primary osteoporosis (30–35%)	
Idiopathic	
Age related	
Secondary osteoporosis (65–70%)	
Alcoholism	Anticonvulsant:
Glucocorticoid induced	Phenytoin,
Hypogonadism	Phenobarbital,
Hypothyroidism	Carbamazepine,
Hyperparathyroidism	Valproate
Malabsorption syndromes	Chemotherapeutic agent
Inflammatory bowel diseases	Other drugs:
Primary biliary cirrhosis	Thyroid replacement therapy
Post gastrectomy	Gonadotropin-Releasing Hormone Agonists
COPD	(GnRHs),
Hypercalciuria	Heparin,
Neuromuscular disorder	Proton Pump Inhibitors
Rheumatoid arthritis	Aromatase Inhibitors (Letrozole, Anastrozole)
Malignancy	Serotonin Selective Reuptake Inhibitors Or
Multiple myeloma	Lithium Salts
Other Hematopoietic disorders	
Beta Thalassemia Major	
Systemic Mastocytosis	
Monoclonal Gammopathy of Uncertain Significance (MGUS)	

Table 2. World health organization diagnostic categories of BMD [22]

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

BMD: bone mineral density.

Table 3. Male Osteoporosis risk estimation score [23]

Risk factors	Points
Age	
≤ 55 years	0
56 to 74 years	3
≥ 75 years	4
Presence of chronic obstructive pulmonary disease	3
Weight	
≤ 70 kg	6
70 to 80 kg	4
> 80	0

A total score of 6 points or greater is the screening threshold for dual-energy x-ray absorptiometry

Lifestyle modifications should be encouraged for all men with osteoporosis. Smoking and alcohol intake should be avoided. A weight-bearing exercise regimen may be beneficial in men. One should receive adequate dietary calcium (1000 mg/day in younger men, 1000 to 1200 mg daily in older men) and vitamin D (600 to 800 IU/day).

The guidelines (NOF and Endocrine Society guidelines) [25-26]. recommend treatment of men ≥50 years with a history of hip or vertebral fracture or with osteoporosis based upon BMD measurement (T-score ≤-2.5). Bisphosphonates should be used as first-line pharmacologic treatment for osteoporosis. Bisphosphonates (a weekly alendronate or risedronate (5 mg daily)) is the treatment of choice for most men with osteoporosis requiring pharmacologic therapy [26]. For men who cannot tolerate oral bisphosphonates, an intravenous (IV) bisphosphonate (Zoledronic acid) can be used. Denosumab is an alternative option for men who cannot tolerate oral or IV bisphosphonates [25].

Teriparatide (20 or 40 mcg/day) is used for men with severe osteoporosis, or men who have failed previous therapy [27]. Testosterone therapy has beneficial effects on bone mineral density (BMD) in case of hypogonadism. Table 5 depict the current evidence regarding pharmacological therapies for male osteoporosis.

Patients can be monitored with bone mineral density (BMD) measurements. For patients on treatment, a follow-up DXA of hip and spine after two years. If follow up BMD is stable, less frequent monitoring is required [26].

Table 4. Second tier investigations for osteoporosis [24]

Investigations	Secondary cause for osteoporosis	Consider in
Parathyroid hormone	Primary hyperparathyroidism	Men with hypercalcemia
Estradiol	Acquired hypogonadism	Men with clinical features of hypogonadism
Serum free testosterone	Hypogonadism	Men with clinical features of hypogonadism
Tissue transglutaminase antibodies	Celiac disease	Men with low 25-hydroxyvitamin D level and/or low urinary calciumMen with idiopathic osteoporosis
Serum and urine protein electrophoresis	Myeloproliferative disorder	Men with anemia and/or vertebral compression fractures.
24-hour urinary free cortisol	Cushing's syndrome	Men with clinical manifestations of Cushing's syndrome
Serum tryptase	Systemic mastocytosis	Men with fractures, unexplained osteoporosis, or bone pain
Anti-HIV antibodies	HIV disease	Men with fractures, wt. Loss, opportunistic infections, unexplained osteoporosis
Iliac crest biopsy	Systemic mastocytosis, myeloma, osteomalacia, leukemia/ lymphoma	Men with fractures, unexplained osteoporosis, or bone pain

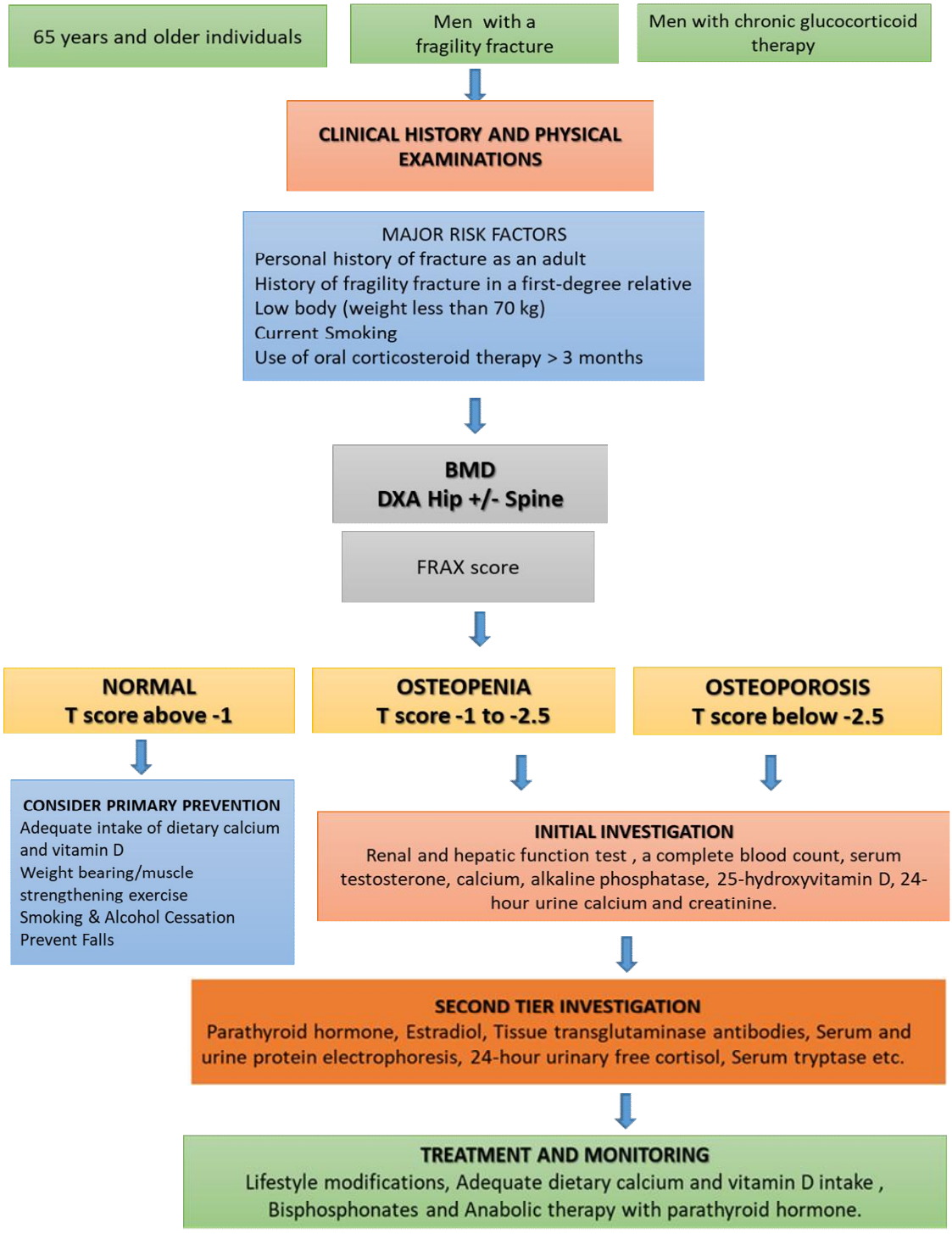

Fig. 1. Diagnostic algorithm for osteoporosis in men

Table 5. Evidenced regarding pharmacological therapies for male osteoporosis

Treatment	Trial	No. of patients (drug/placebo)	BMD improvement	Vertebral fracture reduction	Non-VF reduction	Guideline recommendations
Alendronate Oral, 10mg/d	(E. Orwoll et al. [28]	241 (146/95)	Yes	Yes	Not significant	First line AACE/ACE, ACR, NAMS, and the Endocrine Society
Risedronate Oral, 5 mg/d	(Ringe et al. [29]	134 (68/66)	Yes	Yes	Yes	
Zoledronic acid IV, 5mg/year	(Boonen et al. [30]	1199 (588/611)	Yes	Yes	Not significant	For men who cannot tolerate oral bisphosphonates
Denosumab SC, 60 mg/6 months	(E. Orwoll et al.)[30] (Smith et al.)[31]	242 (121/121) 1468 (467/445)	Yes	Yes	Not significant	AACE/ACE recommends denosumab as first-line therapy for patients who are unable to use oral therapy.
Teriparatide SC, 20 or 40 mcg/d for 18–24 months	(E. S. Orwoll et al.)[27] (Kaufman et al.)[32]	437 (139 +151/147) 437	Yes	Not significant	Not significant	AACE/ACE suggests the use of teriparatide for high fracture risk and for those who are unable to take oral therapy
Testosterone IM, Testosterone enanthate 200 mg every 2 week	(Amory et al.)[33] (Tracz et al.)[34]	71 365 (Eight RCTs)	Moderate increase at lumbar spine only	Not significant	Not significant	Endocrine Society recommends Testosterone monotherapy those in whom antiosteoporotic therapy is contraindicated and whose testosterone levels are less than 200 ng/dL

3. CONCLUSION

Osteoporosis is an important and often overlooked problem in men. The goal of the evaluation of men with osteoporosis or fragility fracture is to detect early and to rule out secondary causes. Many of them can be determined on history and physical examination. Based on the results of the history, physical examination, and basic laboratory testing, more extensive testing may be indicated.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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