OSTEOPOROSIS IN THE AGING MALE

[1]FLORINA LIGIA POPA, [2]MARIA ROTARU, [3]COSMINA DIACONU, [4]ADELINA BANCIU, [5]I. GH. TOTOIANU

[1,2,3,5]„Lucian Blaga" University of Sibiu, [4]"Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca

Abstract: *Osteoporosis has long been considered a disease of women. As awareness of the pervasiveness of this disorder increases, it is clear that men are also at risk regarding this disorder. Recent epidemiological studies have confirmed that osteoporosis in men is an increasing health problem. This development not only has its roots in increased longevity but also in increased awareness of this problem in men. The purpose of this article is to review what is known about the factors in men that lead to the acquisition, maintenance, and loss of bone, as well as new insights about the causes, pathogenesis, and treatment of osteoporosis in men.*

Keywords: *osteoporosis in men, etiology, physiopathology, treatment*

Rezumat: *Osteoporoza a fost mult timp considerată ca o boală ce afectează doar femeile. Prin creşterea conştientizării omniprezenţei acestei afecţiuni, rezultă că şi bărbaţii sunt la risc pentru această boală. Studii epidemiologice recente au confirmat faptul că osteoporoza la bărbaţi este o problemă de sănătate în creştere. Această dezvoltare îşi are rădăcinile atât în creşterea longevităţii cât şi în creşterea conştientizării acestei probleme la bărbaţi. Scopul acestui articol este de a trece în revistă ceea ce se cunoaşte despre factorii ce determină la bărbaţi formarea, menţinerea şi pierderea osoasă, precum şi despre noile intuiţii legate de cauzele, patogenia şi tratamentul osteoporozei la bărbaţi.*

Cuvinte cheie: *osteoporoza la bărbaţi, etiologie, patogenie, tratament*

INTRODUCTION

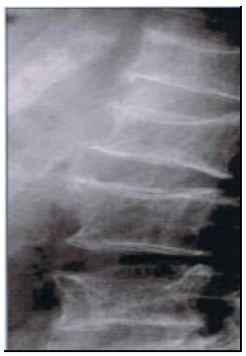
Osteoporosis has long been considered a disease of women. Male osteoporosis represents an important, although long underestimated, public health problem. Both in men and in women, aging is accompanied by continuous bone loss and by an exponential increase in the incidence of osteoporotic fracture. Morbidity after osteoporotic fractures appears to be more serious and mortality more common in men than in women. However, the mortality attributed to hip fractures is twice as high in men as in women. Unlike hip fractures, vertebral fractures occur more in middle-aged men than in very old men.

I. Symptoms

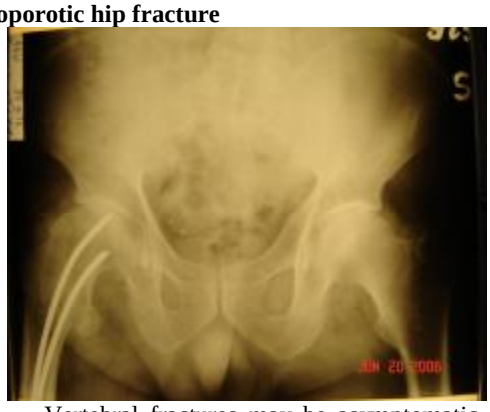
In absence of fractures, osteoporosis is asymptomatic. Gentle thoracho-lumbar pains can appear which increase in prolonged orthostatism or physical effort and attenuate in clinostatism and rest.

Osteoporosis becomes manifest in the presence of fractures or their consequences. In this case the pain is acute, severe and accompanied by important functional impotence. The fractures can appear spontaneous or after minor trauma. (Pictures 1, 2)

Picture no. 1. Radiographic aspect of osteoporotic vertebral fractures



Picture no. 2 Radiographic aspect of operated osteoporotic hip fracture



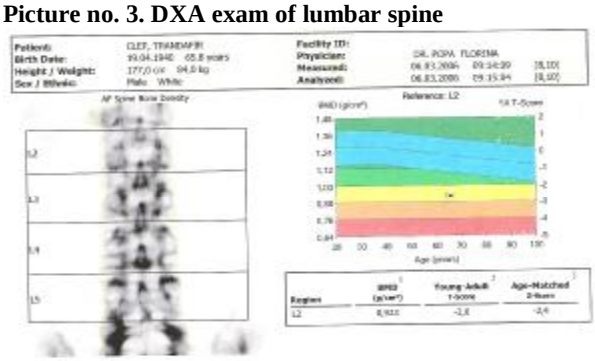
Vertebral fractures may be asymptomatic, only one of three being clinically manifested. However, all vertebral fractures influence the quality of life, either they are symptomatic or not.

II. Diagnosis

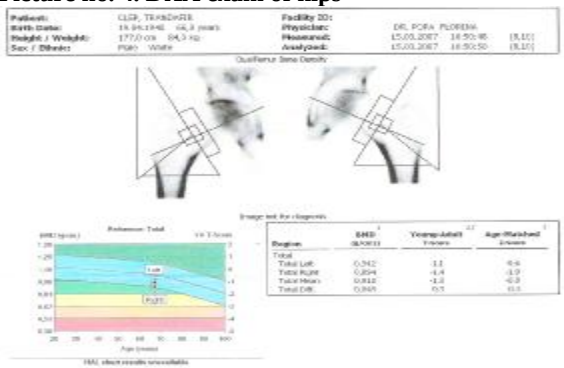
The diagnosis of osteoporosis is suggested by **anamnesis**, including the analysis of factors risk, and by **clinical examination**. The paraclinical investigations confirm the diagnosis of osteoporosis.

A **dual energy x-ray absorptiometry** (DXA) scan is the gold standard for diagnosing osteoporosis. This scan compares the patient's bone mineral density (BMD) with that of a young adult who has achieved peak bone mass. Results are expressed as the number of standard deviations (SDs) of BMD below young adult mean (T score). (Figure 3, 4)

Picture no. 3. DXA exam of lumbar spine



Picture no. 4. DXA exam of hips



The International Society of Clinical Densitometry recommends that osteoporosis in men be defined as a T score of -2.5 or below the young normal mean for men. It is further recommend that a male normative database be utilized to derive T scores for men. Since hip fracture is a severe complication of osteoporosis that predicts risk of all fractures, the hip is the gold-standard site for osteoporosis diagnosis.

The **laboratory tests** that may be helpful in the evaluation of men with osteoporosis are:

- Calcium and phosphorous (serum and urine)
- Total and bone-specific phosphatase
- 25-hydroxyvitamin D
- Parathyroid hormone
- Thyroid-stimulating hormone
- Serum protein electrophoresis
- Bioavailable or free testosterone
- Urinary deoxypyridinoline
- N-telopeptides, C-telpeptide, and other markers of bone resorption.

DXA screening should be considered for every man 65 years of age or older, and for younger men with low-trauma fractures, radiographic evidence of osteopenia, and other risk factors.

III. Etiology, risk factors and physiopathology

Several **risk factors** have been linked to osteoporosis in men:

- Chronic diseases that affect the kidneys, lungs, stomach, and intestines or alter hormone levels;
- Unhealthy lifestyle habits (smoking, excessive alcohol use, low calcium intake, inadequate physical exercise, reduced sunlight exposure);
- Advanced age;
- Heredity;
- Low weight and height;
- Race: Caucasian men appear to be at particularly high risk.

The most frequent **causes** of osteoporosis in men are:

- Excessive alcohol use;
- Glucocorticoid excess (exogenous or endogenous);
- Hypogonadism (primary or secondary);
- Primary hyperparathyroidism;
- Hyperthyroidism or;
- Multiple myeloma;
- Anticonvulsants;
- Androgen depletion therapy in men with prostate cancer;
- Gastrointestinal malabsorption;
- Immobilization;
- Inflammatory bowel disease;
- Chronic obstructive pulmonary disease.

Osteoporosis results when there is decreased bone formation, increased bone resorption, or a combination of these 2 conditions. There are 2 types of osteoporosis, based on etiology. When routine workup reveals no explanation for the osteoporosis, it is considered primary or idiopathic. Since age itself is a risk factor for osteoporosis, the term idiopathic is limited to this condition when it affects people younger than age 70.

1. Secondary osteoporosis

About half of the cases osteoporosis can be attributed to one of three major causes: excessive alcohol consumption, glucocorticoid excess, and hypogonadism.

Excessive alcohol consumption is responsible for 15-20% of cases of osteoporosis among men. In addition, excessive alcohol use has been linked to increased hip fracture risk.

Glucocorticoid excess is responsible for another 20% of cases. Recent studies indicate that fracture risk is increased even at low doses of glucocorticoids and that this increased risk is seen soon after the commencement of glucocorticoid therapy. Pathogenesis of this syndrome is multifactorial, and involves decreased calcium absorption from the intestinal mucosa, decreased renal reabsorption of calcium, and inhibition of the function of

osteoblasts.

Hypogonadism has been reported in 15-20% of men with spinal osteoporosis. In addition, the prevalence of hypogonadism was reported to be increased fivefold among older men with hip fractures.

2. Age-Associated Bone Loss and Primary Osteoporosis

Longitudinal studies suggest that the average annual rate of bone loss is 0.4% in men and 0.6% in women. Between 70 to 75 years, bone loss in men was found to be greater than in women of the same ages. **In the life time men lose 10% at cortical bone and 30% at trabecular bone.** Whereas genetic factors influence peak bone mass, their role in age-associated bone loss has not been established. Several studies have identified low vitamin D levels, low calcium intake and absorption, and slow decline in testosterone levels as important factors for age-associated bone loss.

With aging, in men there is a slow decline in gonadal function that is associated with decreased muscle mass, increased body fat, decreased sexual function, and osteopenia. However, unlike the abrupt menopausal decline of estrogen in women, elderly men have a gradual decline of testosterone levels with aging. Because serum sex hormone binding globulin (SHBG) levels increase with age, total testosterone levels remain relatively unchanged. Alternatively, bioavailable testosterone may be a better measure of gonadal status.

In about 40-50% of cases of male osteoporosis, no cause could be identified. **Idiopathic osteoporosis in men** has been linked to changes in sex steroid secretion, in growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis, and in vitamin D-parathyroid hormone 25(OH)D-PTH system.

Several reports have demonstrated age-related reduction in IGF-1 levels and have correlated these reductions with reduced BMD of the spine and forearm in osteoporotic men. Growth hormone deficiency does not fully explain why men with osteoporosis have low IGF-1 levels because these men respond normally to a GH stimulation test. However, it is likely that subtle abnormalities in GH dynamics that involve either pulsatility or circadian rhythm exist. More recently genetic studies indicate a possible genetic association for this observation.

Many reports support that bone loss in men may be related to declining levels of estradiol rather than testosterone. Some published reports linked a mutation in the estrogen receptor or the aromatase enzyme (aromatase enzyme activity is required for the conversion of androgens to estrogens) to the development of osteoporosis. Administration of conjugated estrogen resulted in increased bone mass in individuals with aromatase deficiency but not in those with mutation of the estrogen receptor. Such cases suggest that a major part of androgen action on the male skeleton is probably mediated by estrogen.

IV. Prevention

Although aging is a risk factor for bone loss, several measures can delay or prevent it. The first step is to increase awareness among clinicians and patients about the susceptibility of men to osteoporosis and fracture. The prevention of osteoporosis consists of controlling the risk factors. Alendronate, 5 mg/d or 35 mg/wk, is used to prevent postmenopausal osteoporosis and may also be beneficial in men.

V. Treatment

A comprehensive approach to the treatment of osteoporosis is essential to maximize bone density and minimize fracture risk.

1. Non-pharmacological therapies complement the pharmacologic treatment of osteoporosis and can have a significant role in minimizing fracture risk.

Orthoses, such as thoracolumbar braces and hip protectors, can help in the prevention and treatment of fractures. (Picture no. 5)

Picture no. 5. Thoracolumbar orthoses

Exercise programmes have a key role in the management of the osteoporotic patient. Exercise, such as tai chi and physical therapy programs, can provide overall increases in strength, flexibility, and balance, with diminished risk of falling. Exercise has also been shown to increase BMD.

Calcium and vitamin D are essential in the treatment of osteoporosis.

Fall prevention involves environmental modifications, minimization of potentially hazardous medications, exercise interventions and assistive devices should be used to facilitate a more steady gait.

Kyphoplasty is a minimally invasive spine procedure that involves the infiltration of bone cement into a fractured vertebral body after fracture reduction using a balloon tamp. Indications for this procedure include relatively acute, painful compression fractures refractory to coservative treatment. Kyphoplasty can decrease pain and reduce kyphosis. (Picture 6)

Picture no. 6. **Kyphoplasty**

2. Drug therapy

Testosterone replacement is the first choice for older hypogonadal men, although the efficacy of preventing fracture and the potential long-term side effects have not been tested in large clinical trials. Serum prostate specific antigen levels should be obtained, and rectal examination of the prostate should be performed prior to the initiation of therapy. Contraindications to testosterone therapy include known prostate cancer and male breast cancer. Testosterone can be replaced parenterally by intramuscular injection or a transdermal patch or, most recently, in a gel form.

Bisphosphonates are inhibitors of bone resorption and may be of benefit in preventing fracture in elderly men. Alendronate received FDA approval for the treatment of osteoporosis in men and it is available in a 70-mg/wk formulation. Risedronate, another bisphosphonate, is used in the treatment of glucocorticoid-induced bone loss at a dosage of 5 mg/d or 35 mg/wk and is probably beneficial in the treatment of idiopathic osteoporosis.

Selective androgen receptor modulators (SARMs) are another approach to male osteoporosis. These agents, analogous to selective estrogen receptor modulators in women, have selective testosterone agonist and antagonist effects in specific tissues. A SARM that has an agonist effect in bone, but an antagonist effect in male reproductive tissue would be ideal. These agents are in development.

Teriparatide is a recombinant segment of human parathyroid hormone and can be used for the treatment of idiopathic and hypogonadal osteoporosis in men. It is recommended at a daily dosage of 20 µg via sc injection for up to 24 months. Disadvantages include the need for sc injections and lack of long-term safety data.

Thiazide diuretics can correct glucocorticoid-induced hypercalciuria and are recommended if 24-hour urine calcium is $\geq$ 300 mg/day. Studies have shown that low-dose hydrochlorothiazide (12.5 and 25 mg/day) preserved BMD at the hip and spine in healthy older women and men and was protective against fracture. The beneficial effects of thiazides are related to their ability to reduce calcium excretion in the urine.

Selective estrogen-receptor modulators (SERMs)

Although estrogen therapy in men may not be appropriate, SERMs may be beneficial. Raloxifene has an estrogen-like effect on the bone without any feminizing side effects. A recent study showed that raloxifene had no effect on bone-turnover markers in elderly men but that it may decrease bone resorption in men with low estradiol levels.

Theoretically, **calcitonin** should be as effective in treating osteoporosis in men as in women. As of now, however, there is no evidence in men to support its use.

CONCLUSIONS

As longevity improves, osteoporosis has been recognized as an important geriatric problem in men because this disorder has the potential to significantly influence mortality and the quality of life. A thorough medical history and a physical examination, accompanied by appropriate laboratory evaluation to seek out secondary causes, are essential to the diagnosis of osteoporosis in men.

A comprehensive approach to the treatment of male osteoporosis, using non-pharmacologic and pharmacologic therapy, is essential to maximize bone density, minimize fracture risk and improve quality of life.

BIBLIOGRAPHY

1. Julie TL, Joseph ML. Non-pharmacologic management of osteoporosis to minimize fracture risk Nat Clin Pract Rheumatol 2008;4(1):20-25.
2. Yang S, Taxel P. Osteoporosis in older men: an emerging clinical problem Clinical Geriatrics 2002;10(8):1370-1389.
3. Janet MC, Michael JM. Osteoporosis in men American Family Physician 2003;67:1521-1526.
4. Ringer JD, Faber H, Farahmand P, Dorst A. Efficacy of risendronat in men with primary and secondary osteoporosis: results of an one year study Rheumatol Int 2006;26(5):427-431.
5. Gayathri B. Men's Health: The challenge of osteoporosis in elderly men Patient Care 2003;37:60-70.
6. Hosam K. Osteoporosis in the aging male Annals of Long-Term Care: Clinical Care and Aging 2004;12(6):40-45.
7. Gennari L, Bilezikian JB. Osteoporosis in men Endocrinol Metab Clin North Am Jun 2007;36(2):399-419.