Aetiology and clinical characteristics of male osteoporosis. Have they changed in the last few years?

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Abstract

Objective

The aim of this study was to analyse the clinical characteristics and etiological factors related to male osteoporosis in patients attending an out-patient rheumatology department during an 11-year period (1995-2006), as well as to compare them with the observed characteristics in a previous study performed 12 years ago.

Methods

232 males aged 21-88 (mean 56.1±14) with osteoporosis were included in the study. Previous skeletal fractures and family history of osteoporosis were recorded. Bone mass assessment, automated biochemical profile and hormonal measurements (including PTH, 25-OH vitamin D, cortisol, thyroid and sexual hormones) were performed on most patients as well as 24 h urinary calcium, and bone markers. In patients with idiopathic osteoporosis 1-25-OH_2 vitamin D was also determined. In addition, x-rays of the spine were obtained for all patients.

Results

67% of the patients had previous skeletal fractures and 51% had vertebral fractures. 57% of the patients had idiopathic and 43% had secondary osteoporosis whereas in the previous series only 22% of the patients had idiopathic disease. The most frequent causes of secondary osteoporosis were corticosteroid therapy, hypogonodism and alcoholism. 38% of the patients with idiopathic osteoporosis had associated hypercalciuria. Patients with secondary osteoporosis were older, shorter, had lower femoral neck T-score and lower serum values of 25-OH vitamin D and testosterone, as well as higher gonadotrophin and PTH values than the patients with idiopathic osteoporosis, whereas patients with idiopathic osteoporosis had higher urinary calcium and more frequent family history of osteoporosis. Hypercalciuric patients were younger, had lower lumbar BMD, higher urinary calcium and greater incidence of lithiasis than normocalciuric patients with idiopathic osteoporosis. Back pain, frequently associated with vertebral fractures, was the most common cause of referral in all groups of patients.

Conclusion

Idiopathic osteoporosis is the most frequent cause of male osteoporosis in this study. In these patients, family history of osteoporosis and associated hypercalciuria are frequent. The most frequent causes of secondary osteoporosis in males include corticosteroid therapy, hypogonadism and alcoholism. Although clinical characteristics of male osteoporosis are similar to that previously reported, in this study the percentage of patients with idiopathic osteoporosis was higher than previously observed.

Key words

Male osteoporosis, primary osteoporosis, idiopathic osteoporosis.

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Introduction

Male osteoporosis is increasingly recognised as a problem in clinical medicine, but contrary to what happens in women, men frequently have an underlying secondary cause for bone loss (1-7). Indeed, we have previously observed the presence of secondary causes for osteoporosis in 78% of these patients, glucocorticoisteroid therapy, hypogonadism and alcoholism being the most frequently associated disorders (8). On the other hand, idiopathic osteoporosis has also been considered a frequent cause of osteoporosis in males (4, 6). Although few studies have focused on idiopathic osteoporosis in males, it is likely that the pathogenesis of this disorder is heterogeneous. Indeed, in these patients several associated conditions, such as genetic factors, hypercalciuria, or osteoblast dysfunction, among others, have been reported (9, 12). However, due to the increasing knowledge of osteoporosis in males, its diagnosis has been developed in the past few years, thus the clinical characteristics and the etiological factors related to male osteoporosis could have changed.

Therefore, the aim of this study was to analyse the clinical characteristics and etiological factors related to male osteoporosis in patients attending an out-patient Rheumatology department during an 11-year period and to compare them with those observed in a previous study performed 12 years ago in a group of 81 males with osteoporosis (8).

Patients and methods

The study was carried out on 232 osteoporotic males aged 21-88 years (mean 56.1±14), who were referred to the Rheumatology department for osteoporosis study during an 11-year period (1995-2006). Only patients diagnosed with osteoporosis as the main reason for clinical evaluation were included in the study. Patients who were previously included in study protocols or those with inflammatory joint diseases were not included in the study, and none of the 81 patients from the previous study was included in the present study. Patients were consecutively included. Indeed, all males with osteoporosis attended to in our Service are evaluated according to a standard protocol.

Osteoporosis was defined by the presence of one or more atraumautic skeletal fractures associated with low bone mass (bone mineral density [BMD] below -1 T-score) and/or by densitometric criteria, *i.e.,* BMD in the lumbar spine or femur below -2.5 T-score. The clinical data were obtained from a detailed review of medical records, after a standardized evaluation, which included a careful history and physical examination. Previous skeletal fractures, the use of glucocorticoids and anticonvulsant drugs, weight, height, body mass index (BMI), dietary calcium intake, renal lithiasis, as well as a family history of osteoporosis were recorded in all patients. The patients considered as having alcohol-related osteoporosis consumed >100g ethanol/day. The presence of atraumatic fractures, and/or densitometric osteoporosis (confirmed by a physician) in a first-degree relative was considered a positive family history of osteoporosis. The BMI was expressed as weight/height (kg/m^2). Automated biochemical profile, complete blood count, protein electrophoresis and 24-h urinary calcium excretion were obtained in all patients. Hormonal measurements, including testosterone, gonadotrophins, parathyroid hormone (PTH), cortisol, vitamin D metabolites and thyroid hormones, were performed on patients in whom a specific aetiology was not readily apparent. In addition, biochemical parameters of bone turnover were measured in most patients.

Biochemical and hormonal determinations

Automated biochemical profile, complete blood cell count, protein electrophoresis and 24-h urine calcium were measured by standard procedures; total alkaline phosphatase (Total AP) was determined by spectrophotometric kinetic assay, according to the recommendations of the Scandinavian Committee for Clinical Chemistry and Clinical Physiology, using DEA buffer in a DAX 72 analyser (Bayer Diagnostics Technicon, Tarrytown, NY, USA); Serum 25-hydroxyvitamin D (25OHD) was determined by radioimmunoassay

(Diasorin. Stillwater, MN, USA); 1.25 dihydroxyvitamin D (1-25OH_2D) was measured with a radioreceptor assay (Diasorin. Stillwater, MN, USA); Serum PTH was determined by an immunoradiometric assay (Allegro Intact PTH Nichols Institute Diagnostics). Serum testosterone (T), luteinizing hormone (LH), follicle-stimulating hormones (FSH), prolactine, TSH, FT_4 and cortisol were measured by immunoenzymatic methods in automated system (immuno 1, Bayer, Tarrytown, USA) Urinary free cortisol was measured after extraction with diclorometane. The markers of bone turnover measured were: urinary hydroxyproline (HYP) (measured by high-performance liquid chromatography on 121 patients), and urinary N-terminal cross-linked telopeptide of type I collagen (NTX), which was measured in 108 patients (Osteomark; Ostex Internationl, Seattle, WA, USA). Results of NTX and HYP determinations were expressed as a ratio to urinary creatinine and were obtained from second morning urine samples between 8:00 and 10:00 a.m. after an overnight fast.

Hypercalciuria was defined as an average excretion rate of calcium >4mg/kg body weigth/24-h urine. Values of serum testosterone lower that 275 ng/dl in at least two measurements were considered indicative of hypogonadism.

Normal ranges of biochemical tests were provided by our reference laboratory from a significant sample of healthy men adjusted by age, except for sexual hormones which were obtained from healthy men up to 50 yeas old.

Bone mineral density and x-ray measurements

Bone mineral density of the lumbar spine (L2-L4) and femur was measured by dual x-ray absorptiometry (Lunar DPX-L, Lunar Radiation Corporation, Madison, WI, USA). Standard x-rays of the spine in lateral projection were obtained for all patients. Vertebral fracture was defined as a reduction of ≥20% in the anterior, middle or posterior height of the vertebral body. Osteoporosis was considered to be present when lumbar and/or femoral BMD was below -2.5 T-score, or when at least one atraumatic skeletal fracture associated with low BMD (lumbar and/or femoral BMD below -1 T-score) was present.

Table I. Characteristics of the patients (mean ± SD).

	Idiopathic osteoporosis (n=130)	Secondary osteoporosis (n=102)
Age (years)	54 ± 13	58.6 ± 15*
Calcium intake (mg/day)	532.6 ± 342	477 ± 293
Weight (kg)	72.7 ± 10	70.6 ± 11
Height (cm)	169.4 ± 7	165.7 ± 8*
BMI (kg/m^2)	25.4 ± 2.6	25.8 ± 3.6
Family history of osteoporosis	26%	11 %*
Lumbar BMD (g/cm^2)	0.912 ± 0.1	0.915 ± 0.1
Lumbar T-score	-2.68 ± 1.1	-2.68 ± 1.2
Lumbar Z-score	-2.35 ± 1.1	-2.2 ± 1.2
Femoral neck BMD (g/cm^2)	0.807 ± 0.1	0.734 ± 0.1*
Femoral neck T-score	-2.05 ± 1.1	-2.63 ± 0.8*
Femoral neck Z-score	-1.25 ± 1	-1.45 ± 0.7
Peripheral fractures	20%	26%
Vertebral fractures	48%	54%

BMI: body mass index; BMD: bone mineral density.
*p<0.05

Statistical analysis

Data are expressed as mean ± SD. The student's *t*-test was used to compare differences for continuous variables and the chi-square test was used for proportions. A *p*-value of <0.05 was considered statistically significant.

Results

Most of the patients (67%) had previous skeletal fractures and 51% had vertebral fractures. When evaluating the causes of osteoporosis, 130 (57%) patients had idiopathic osteoporosis and 102 (43%) patients had secondary osteoporosis. Patients with secondary osteoporosis were older (58.6±15 *vs*. 54±13 years, p=0.023) and had lower stature (166±8 *vs*. 169±7 cm, p=0.006) than patients with idiopathic disease. Indeed, when analysing the causes of osteoporosis as a function of age, among patients under 60 years idiopathic osteoporosis was the most frequent cause (63% *vs*. 37%) whereas among patients over 60 secondary osteoporosis was slightly more frequent (53% *vs*. 47%).

Patients with secondary osteoporosis had lower femoral neck BMD (0.734±0.1 *vs*. 0.807±0.1, p=0.002) and T-score (-2.63±0.8 *vs*. -2.05±1.1, p<0.001) than the patients with idiopathic disease (Table I); in addition, secondary osteoporotic patients showed lower serum values of 25-OHD and testosterone, and higher total AP, gonadotrophin and PTH serum values (Table II), whereas patients with idiopathic disease showed higher urinary calcium excretion and more frequent family history of osteo-porosis (11% *vs*. 26%, p=0.04) than patients with secondary disease. The clinical and biochemical characteristics of patients with idiopathic and secondary osteoporosis are shown in Tables I and II.

The most frequent causes of secondary osteoporosis were: hypogonadism (27 patients [in 3 of them it was secondary to androgen deprivation for prostate cancer treatment]), corticosteroid therapy (21 patients), and alcoholism (19 patients). The remaining patients with secondary osteoporosis were found to have different causes; intestinal malabsorption (7 patients) due to gastrectomy or intestinal resection, haematological disorders (4 patients), and HIV infection, haemochromatosis and mastocytosis (3 patients in each), were the most frequent diagnoses among these patients. Multiple causes were observed in 9 patients, with alcohol consumption associated to hypogonadism being the most frequent association. Table III shows the aetiological causes of osteoporosis in all patients.

Table II. Biochemical characteristics of the patients (mean ± SD).

	Normal values	Idiopathic osteoporosis (n=130)	Secondary osteoporosis (n=102)
Calcium (mg/dl)	8.5-10.5	9.6 ± 0.4	9.6 ± 0.5
Phosphate (mg/dl)	2.3-4.3	3.3 ± 0.5	3.4 ± 0.5
Total AP (U/l)	90-235	176.4 ± 52	193.8 ± 75*
PTH (pg/ml)	10-65	40 ± 18	47.3 ± 26*
25-OHD (ng/ml)	10-42	23.5 ± 10	19.8 ± 12*
Testosterone (ng/dl)	275-850	534.5 ± 208	413.3 ± 220*
LH (U/l)	1.5-7.7	5.1 ± 2.7	8.7 ± 8*
FSH (U/l)	1.7-8	6.3 ± 3	11.6 ± 10*
NTX (nM/mM)	16-65	41.6 ± 19	42.2 ± 28
HYP (mg/mg creat)	40-154	90.5 ± 50	96.6 ± 48
Calciuria (mg/24h)	< 4mg/kg	266.7 ± 131	192.9 ± 132*

Total AP: total alkaline phosphatase; 25-OHD: 25 hydroxyvitamin D; 1-25OH_2D: 1-25 dihydroxyvitamin D; PTH: parathyroid hormone. HYP: hydroxiproline; NTX: N-terminal cross-linked telopeptide of type I collagen.
*p<0.05

Among the 130 patients with idiopathic osteoporosis, 49 patients (38%) had associated hypercalciuria, and 40% of them had renal lithiasis. Hypercalciuric patients were younger (50.4±12 *vs*. 56.4±13, p=0.014), had lower lumbar BMD, higher urinary calcium and greater incidence of lithiasis than normocalciuric patients (Table IV). Interestingly, 5 patients with idiopathic osteoporosis aged 30-75 years (mean 59 yrs) presented a monoconal gammopathy of undetermined significance (MGUS); in 2 cases it was observed at the diagnosis, and in the other 3 cases it was observed after 2, 3 and 4 years of follow-up, respectively. None of these patients has developed any other plasma-cell disorder after a mean of 39.2 months of follow-up (range 14-60 months), and all of these patients have also been followed-up by the Haematology Service of our Hospital. In patients with secondary osteoporosis MGUS was observed in 5 cases, 2 of them had osteoporosis associated with corticosteroid therapy, 1 haemochromatosis, 1 hypogonadism (secondary to androgen deprivation for prostate cancer) and the last had various causes (ethanol + hypogonadism).

Table III. Aetiology of male osteoporosis.

Aetiology	No. of patients (%)
Secondary osteoporosis	102 (43%)
Hypogonadism	27
Corticosteroid therapy	21
Ethanol	19
Multiple causes	
Ethanol + hypogonadism	3
Ethanol + gastric surgery	2
Corticosteroid + gastric surgery	2
Corticosteroid + hypogonadism	2
Other causes	
Malabsorption	7
Haematological disorders	4
Haemochromatosis	3
Mastocytosis	3
AIDS	3
Osteogenesis imperfecta	2
Anticonvulsants	1
Primary biliary cirrhosis	1
Cushing´s disease	1
Growth hormone deficiency	1
Idiopathic osteoporosis	130 (57%)

In 129 patients (56%), back pain was the main complaint and the principal cause for referring the patient to our unit; in 62% of these patients it was associated with vertebral fractures. The remaining 111 patients (48%) were evaluated because of different complaints: peripheral skeletal fractures (29% of the patients), regional rheumatic pain syndromes (11% of the patients), or because radiological evidence of osteopenia was found during a previous clinical evaluation (4% of the patients). No differences in the cause of referral were observed between both groups of patients. Thus, back pain was the main complaint in most patients (58%) with idiopathic osteoporosis (52% of these cases associated to vertebral fractures), and this symptom was also the principal cause of referral (in 53% of the patients) of secondary osteoporosis, 54% of them associated with vertebral fractures.

Discussion

In this study, idiopathic osteoporosis was the most frequent diagnosis of male osteoporosis, especially under 60 years of age. Thus, although clinical characteristics of these patients are similar to those previously reported, the most frequent aetiology has changed to the idiopathic form. In patients with idiopathic osteoporosis, family history of osteoporosis and associated hypercalciuria are frequent. Meanwhile, the most frequent causes of secondary osteoporosis are corticosteroid therapy, hypogonadism and alcoholism. In rheumatological clinical practice, back pain is the most common cause of referral in all patients, frequently associated with vertebral fractures.

Previous studies on osteoporosis in men have reported a frequent association with secondary causes, especially with corticosteroid therapy, hypogonadism and alcoholism (2, 4, 5, 7, 8, 13). In the present series these causes, again, are the most frequent. In addition, other known causes related to osteoporosis, such as HIV infection and mastocytosis, have been observed in the present series. Multiple causes of osteoporosis are not infrequent, in fact they are found in 9% of the patients with secondary osteoporosis, with hypogonadism associated with alcoholism or corticosteroid therapy being particularly frequent.

When comparing patients with idiopathic and secondary disease, patients with secondary osteoporosis have lower femoral neck BMD and T-scores than the patients with idiopathic disease. Similarly, Evans *et al*. (4) noted lower femoral neck BMD in male patients with secondary osteoporosis compared to those with idiopathic disease, and we have also observed this finding in young women with osteoporosis (14). These differences have

Table IV. Clinical characteristics of patients with idiopathic osteoporosis (mean ± SD).

	Hypercalciurics (n=49)	Normocalciurics (n=81)
Age (years)	50.4 ± 12	56.4 ± 13*
BMI (kg/m^2)	25.2 ± 2.6	25.4 ± 2.7
Lumbar BMD (g/cm^2)	0.885 ± 0.1	0.928 ± 0.1
Lumbar T-score	-2.90 ± 0.9	-2.56 ± 1.1
Lumbar Z-score	-2.70 ± 0.9	-2.14 ± 1.1*
Femoral neck BMD (g/cm^2)	0.808 ± 0.1	0.804 ± 0.1
Femoral neck T-score	-1.99 ± 0.1	-2.09 ± 0.1
Femoral neck Z-score	-1.36 ± 0.1	-1.19 ± 0.1
Calcium (mg/dl)	9.6 ± 0.4	9.6 ± 0.4
Phosphate (mg/dl)	3.3 ± 0.5	3.3 ± 0.5
Total AP (U/l)	164.9 ± 44	183 ± 55
PTH (pg/ml)	42.8 ± 17	38.3 ± 18
25-OHD (ng/ml)	25.6 ± 11	22.4 ± 9
1-25OH$_2$D (pg/ml)	36.4 ± 11	31.1 ± 12
NTX (nM/mM)	47.3 ± 19	39.5 ± 19
HYP (mg/mg creat)	79 ± 24	95.4 ± 58
Calciuria (mg/24h)	391.7 ±107	187 ± 66*
Renal lithiasis	40%	19%*

Total AP: total alkaline phosphatase; BMD: bone mineral density; 25-OHD: 25 hydroxyvitamin D; 1-25OH$_2$D: 1-25 dihydroxyvitamin D; PTH: parathyroid hormone. HYP: hydroxiproline. NTX: N-terminal cross-linked telopeptide of type I collagen.
*p<0.05

been related to the predominant effect of idiopathic disease on cancellous bone instead of on cortical bone (4). In addition, patients with secondary osteoporosis showed lower testosterone and higher gonadotrophin values than patients with idiopathic disease, as well as lower 25-OHD levels and higher PTH and total AP values. Such differences could be related, in part, to the aetiology of osteoporosis. Thus, in this study hypogonadism was the most frequent secondary cause, clearly influencing the values of sexual hormones, whereas patients with alcoholism and malabsorption contributed to the lower serum levels of 25-OHD and the secondary increased PTH values observed in this group of patients (15). Indeed, in the present series only three alcoholic patients showed normal 25-OHD levels, and nearly 70% of them had values below 15 ng/ml (data not shown). Again, the higher total AP values found in these patients are attributed to the associated diseases. Thus, patients with alcoholism, haemochromatosis and one patient with primary biliary cirrhosis (the latter with marked increased total AP levels) clearly influenced the serum total AP values.

Few studies have focused on idiopathic osteoporosis in men. In the present study, this was the most frequent cause of osteoporosis, likewise it has been reported by other authors (1, 5, 7), especially in young and middle aged patients (20). In our previous study, 22% of the patients presented idiopathic disease (8), and these patients were also younger than patients with secondary disease. Although the reasons for the apparent increase in the proportion of patients with idiopathic osteoporosis in this series is not completely known, it is probable that several factors may partly explain this finding, such as, the awareness of the disease, and the referral patterns. Indeed, in the present series in addition to the usual causes of referral (patients with fractures and those with low bone mass) the more complex cases (those without an specific clinical diagnosis after a basic clinical and biochemical study) were also referred to our unit for evaluation, diagnosis and treatment, most of them with idiopathic disease. Nevertheless, it should be pointed out that this apparent change in the proportion of patients with idiopathic disease, due to the limitations inherent in the design of this study, can only be applied to our series.

It seems likely that idiopathic osteoporosis has a heterogeneity in pathogenic mechanisms. In fact, in these patients several associated conditions have been reported, such as low insulin-like growth factor (21) or transforming growth factor-beta 1 serum levels (22), an increase in sex hormone-binding globulin (23), an osteoblastic dysfunction (12) and an increase in free oxygen radical levels, among others, the latter suggesting that oxidative stress may play a role in the pathogenesis of this disorder (24). Interestingly, and similar to our previous study, associated hypercalciuria was frequent in men with idiopathic disease since nearly 40% of them were hypercalciuric and most of them had previous renal lithiasis. Both factors, hypercalciuria and renal lithiasis, have been previously associated with bone loss and osteoporosis (9, 16-19), and their presence in men should alert us to this condition. Although hypercalciuria can be considered as a secondary cause of osteoporosis, the mechanisms of bone loss in this process are still unclear, this fact has probably influenced the inclusion of this disorder in the subgroup of idiopathic osteoporosis in various studies (5, 9, 20).

Another finding was the high frequency of family history of osteoporosis in patients with idiopathic disease. Genetic factors are important determinants of bone mass, and previous studies indicated that family history of low trauma fractures is an important risk factor for osteoporosis (25, 26), not only in women but also in men (27-29). In addition, previous reports showed low BMD in the relatives of men with idiopathic osteoporosis (11, 30). In agreement with this finding, we have previously observed an association between COL1A1 genotype and idiopathic osteoporosis in males (31), a collagen type I gene polymorphism that has been related with osteoporotic fractures in both sexes (32). Moreover, recent studies have also reported an association between LRP5 variants and idiopathic osteoporosis in males (33) and a maturational defect in bone acquisition genetically determined in these individuals (10). Overall, these

data reinforce the contribution of genetic factors to this disorder.

Interestingly, five patients with idiopathic osteoporosis presented an associated MGUS, most of them during follow-up, and none developed any associated plasma-cell disorders, such as multiple myeloma. The pathogenesis of MGUS remains poorly understood (24), but these patients have an increased risk of myeloma and also for bone loss and osteoporosis (35, 36). Indeed, these individuals present a 2.7-fold increase in the risk of axial fractures, and although the pathophysiologic mechanism related to bone loss in this process needs to be elucidated, it has been suggested that these patients be evaluated for excessive bone loss or elevated bone turnover because both are clearly associated with increased fracture risk (37). Therefore, it is important to be aware of this condition in males with osteoporosis.

Similar to our previous study and to other series (8, 4), back pain was the most common cause of referral, frequently associated with vertebral fractures, followed by peripheral fractures and regional rheumatic syndromes. In the present study no differences were observed between patients with secondary and idiopathic osteoporosis in relation to the referral cause. We would like to emphasize that these results do not imply that osteoporosis in men is symptomatic, rather they suggest that men with musculoskeletal symptoms are particularly referred to evaluation.

In conclusion, idiopathic osteoporosis was the most frequent cause of male osteoporosis in the last few years, especially in males under 60. In these patients, family history of osteoporosis and associated hypercalciuria are frequent. Some patients with idiopathic disease develop an associated MGUS. Hypercalciuric patients were younger and had lower lumbar BMD and greater incidence of lithiasis. The most frequent causes of secondary osteoporosis in males are, as in the previous series, corticosteroid therapy, hypogonadism and alcoholism. Back pain, frequently associated with vertebral fractures, is the most common cause of referral. Although clinical characteristics of male osteoporosis are similar to those previously reported, in this study the percentage of patients with idiopathic disease was higher than previously observed.

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