Secondary Osteoporosis in Men and Women: Clinical Challenge of an Unresolved Issue

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ABSTRACT. ***Objective.*** To evaluate the clinical and etiological factors of osteoporosis. We also tested the FRAX algorithm to compare the assessment of fracture risk in patients with primary or secondary osteoporosis.

Methods. A prospective study carried out in a large sample of 123 men and 246 women. All subjects had a biochemical, densitometric, and radiological examination of thoracic and lumbar spine.

Results. The prevalence of primary (men 52.9% vs women 50%; p = nonsignificant) and secondary (men 21.1% vs women 17.5%; p = nonsignificant) osteoporosis did not differ between the sexes. In contrast, the prevalence of primary osteoporosis was significantly higher than secondary causes ($p < 0.0001$) in both men and women. While women came to our attention for prevention of osteoporosis, men sought help because of clinical symptoms or disease-related complications, such as fractures. As evaluated by the FRAX tool, patients with osteopenia do not need treatment, in agreement with Italian guidelines. The estimated risk of major osteoporotic and hip fractures was significantly higher in women with secondary osteoporosis compared to men and also compared to women with primary osteoporosis.

Conclusion. The prevalence of secondary osteoporosis in men is similar to that in women and it is less frequent than commonly reported. In patients with secondary osteoporosis, FRAX calculation may provide an estimate of a particularly high fracture risk in patients whose bone fragility is usually attributed to another disease. (J Rheumatol First Release June 1 2011; doi:10.3899/jrheum.110030)

Key Indexing Terms:
ALGORITHM BONE MINERAL DENSITY FRACTURE GENDER OSTEOPOROSIS

The prevalence of secondary osteoporosis in both men and women is widely debated[1,2,3]. In different studies, secondary causes are estimated to be present in > 50% of premenopausal and perimenopausal women. In postmenopausal women, additional processes commonly contribute to low bone mass[4,5,6]. Among men, secondary osteoporosis is diagnosed in about two-thirds of patients with the disease[7,8]. Multiple risk factors as well as several well defined clinical disorders may lead to a reduction of bone mass. In clinical practice, it is important to identify these secondary causes of bone loss, since the majority of these conditions are reversible with appropriate intervention. However, the broad differential diagnosis and the costs resulting from extensive clinical evaluation limit widespread performance of thorough investigations[9]. As a consequence, the numerous guidelines differ with respect to the diagnostic protocol, so that different populations are studied with different approaches. Moreover, in almost all retrospective studies, the prevalence of secondary osteoporosis is found in populations coming from different centers; this reflects inherent bias, since the comparison among series is carried out in patients studied not only by means of different diagnostic examinations, but also in different time periods. Another crucial point that can bias the results is the criteria used to define which patients undergo additional evaluation. Indeed, in different series, patients were selected on the basis of low bone mineral density (BMD) or the presence of vertebral fractures. This means that a significant portion of patients with a secondary cause of bone loss would be missed if they did not have reduced BMD or a vertebral fracture. The uncertainty of appropriate "routine tests" increases markedly when evaluating men with osteoporosis because, in different series, the prevalence of secondary osteoporosis in men has been estimated to be as high as 64%[10,11,12]. Therefore, a more thorough examination seems to be mandatory when a man with reduced bone mass and/or fragility fractures seeks medical attention[10].

Our prospective study was designed to evaluate the preva-

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lence of primary and secondary osteoporosis in a large sample of men and women consecutively admitted to our Center for Osteoporosis and Metabolic Bone Disease from March 2007 to February 2009. All the subjects underwent the same biochemical, densitometric, and radiological examinations. Information about the main reason for referral as well as the specialty of the physician prescribing the visit was also collected. Finally, the FRAX tool was used in order to compare the estimated 10-year fracture risk probability between men and women. The calculation was applied in all postmenopausal women aged 40–90 years and men aged more than 50 years without densitometric osteoporosis and/or spinal or femoral fractures, according to current guidelines on FRAX use[13,14]. We also chose to test the algorithm in subjects with osteoporosis to evaluate whether a sex difference in fracture risk exists among patients with either primary or secondary osteoporosis.

MATERIALS AND METHODS

Between March 2007 and February 2009, all men coming to our center were recruited. Each man was matched with 2 consecutive women patients of the same age, also coming to our center. After providing informed consent, each subject underwent an initial comprehensive health survey and a physical examination; biochemical, densitometric, and radiological evaluation was also performed. Basic laboratory tests included automated complete blood cell count, serum calcium, phosphate, total alkaline phosphatase, creatinine, serum electrophoresis, erythrocyte sedimentation rate, and 24-h urinary calcium and creatinine excretion. In order to exclude secondary causes of osteoporosis, the following serum assays were also performed: serum protein electrophoresis and immunofixation, 25-hydroxyvitamin D (25OHD), parathyroid hormone (PTH), total testosterone, thyroid stimulating hormone (TSH), ferritin, and antitissue transglutaminase antibodies. Free cortisol and Bence-Jones proteinuria were also measured on the 24-h urine collection. All but the 25OHD and PTH measurements were done by standardized laboratory procedures. Serum 25OHD concentrations were determined by RIA (Diasorin Inc., Stillwater, MN, USA); the intraassay and interassay coefficients of variation (CV) were 8.1% and 10.2%, respectively. Serum PTH levels were assessed using an IRMA (N-tact PTHSP, Diasorin); the intraassay and interassay CV were 3 and 5.5%[15]. An in-depth evaluation was successively performed in all patients presenting with abnormal test at baseline, in order to define the specific disorder.

BMD of the lumbar spine (L1–L4) in anteroposterior projection and/or of the femoral and total neck was measured in each patient (Hologic QDR 4500; Hologic, Waltham, MA, USA), using the manufacturer's database of men and women for spine and the National Health and Nutrition Examination Survey database for hip.

Standardized lateral radiographs of the thoracic and lumbar spine, centered at T8 and L3, respectively, were made at a film-focus distance of 105 cm. Vertebral deformity was defined according to the semiquantitative method of Genant[16].

Definition of disorders. Drug-induced bone loss was defined on the basis of a history of chronic treatment (at least 6 months) with medication influencing bone metabolism. The majority of patients considered in this category were taking glucocorticoids, aromatase inhibitors, and excessive doses of levothyroxine for thyroid replacement therapy, inducing TSH levels ≤ 0.1 μU/ml. Among other prescribed drugs known to affect bone metabolism, we more commonly found gonadotrophin-releasing hormone (GnRH) agonists, anticonvulsants, and antiretroviral drugs. Diagnosis of subclinical hypercortisolism was made after an abnormal 1-mg overnight dexamethasone suppression test, in those patients whose 24-h urinary free cortisol was higher than normal at baseline and without the classic signs or symptoms of the Cushing syndrome. Primary hyperparathyroidism was diagnosed on the basis of hypercalcemia together with elevated PTH levels. Diagnosis of hypogonadism in men was conservatively established on the basis of both clinical features and total testosterone serum levels below 300 ng/ml in men aged 25–60 years, and below 200 ng/ml in those aged over 60 years[17]. Secondary amenorrhea in young women was defined on the absence of menses for > 6 months. In hypogonadal patients of both sexes, subsequent measurements were also made of serum prolactin, luteinizing hormone, and follicle-stimulating hormone, together with the GnRH stimulation test, if indicated. The diagnosis of thyrotoxicosis was established on the presence of an abnormally elevated total serum thyroxine and a suppressed serum TSH (≤ 0.1 μU/ml). Hypercalciuria was defined on the basis of a urinary calcium excretion > 4 mg/kg/day; however, no additional evaluation was performed to distinguish between renal and idiopathic hypercalciuria. Finally, the diagnosis of gastrointestinal and hematological diseases, rheumatoid arthritis, and metabolic bone disease (such as osteogenesis imperfecta, osteomalacia, or Paget's disease of bone) was made on the basis of typical signs and symptoms.

FRAX calculation. In order to compare the 10-year risk of hip fracture and any major osteoporotic fracture between men and women, the FRAX tool was applied, using the World Health Organization Website (www.shef.ac.uk/FRAX/); the calculation tool for Italy was selected. The latest version of FRAX was used (accessed April 2009), since absolute femoral neck BMD (in g/cm^2) is entered rather than the T score; in this way, the calculation was independent of sex. The information about femoral neck BMD was available for all but 5 subjects. The US National Osteoporosis Foundation (NOF) guidelines were then considered, which recommend drug treatment if the FRAX 10-year probability exceeds 20% for 4 major osteoporotic fractures (hip, wrist, humerus, and clinical spine) or 3% for hip fracture[14].

Statistical analysis. Descriptive statistics were used to calculate frequencies and percentage of identified diseases. Continuous data are given as mean ± 1 SD. Comparisons between men and women were performed by t-test in the case of continuous variables and by chi-squared test for categorical variables. A p value < 0.05 was considered to be significant. The statistical analysis was performed using Sigma Stat version 3.5.

RESULTS

One hundred forty-three men and 286 age-matched women were initially recruited. During followup, 20 men and 40 women declined to participate in the study and were excluded. The characteristics of patients who declined were similar to those who entered the study; in particular, no difference was found in respect to mean age and comorbidities. Therefore, the final sample was composed from 123 men and 246 women, 30 of whom were premenopausal and 216 postmenopausal; the age range of the whole sample was 25–88 years.

Table 1 shows demographics and anthropometric measure-

Table 1. Demographic and anthropometric characteristics of patients who completed the study. Values are mean ± SD unless otherwise indicated.

Characteristics	Men, n = 123	Women, n = 246	p
Age, yrs	62.2 ± 13.0	62.3 ± 13.0	NS
Median age, yrs	65.2	65.8	
Age range, yrs	25–88	25–87	
Weight, kg	72.4 ± 11.0	63.4 ± 12.0	< 0.001
Height, m	1.7 ± 7.0	1.6 ± 6.3	< 0.001
Body mass index, kg/m^2	24.9 ± 3.3	25 ± 4.7	NS

NS: not significant.

ments of patients who completed the study. As expected, although mean height and weight were significantly higher in men compared to women, body mass index (BMI) did not differ between the 2 groups.

Regarding the reasons for referral, we observed that the majority of patients were self-referred (women 65% vs men 61%; p = nonsignificant). The remaining subjects were referred mainly by their primary care physician (women 10.2% vs men 13.9%; p = nonsignificant); a small percentage of patients were sent by other specialists in the field of mineral metabolism such as endocrinologists, orthopedists, rheumatologists, gynecologists, and so on. In general, no difference was found between men and women as far as the referring doctor.

Figure 1 reports the main reason for the first visit of patients, grouped by sex. Interestingly, compared to men, a significantly higher percentage of women came to our attention with the aim of preventing osteoporosis by undergoing BMD testing (men 22.8% vs women 58.1%; $p < 0.0001$). Men largely made the visit for more specific diseases or clinical symptoms such as arthralgia ($p < 0.01$), back pain ($p < 0.001$), kidney stones ($p < 0.05$), and/or disease-related complications such as fractures ($p < 0.0001$; in this case all fractures were reported, independent of the cause or trauma).

In Table 2, only osteoporotic fragility fractures are reported. As shown, the frequency of fractures was significantly higher in men compared to women, considering both total fractures (men 69.1% vs women 54.1%; $p < 0.01$) and vertebral fractures (clinical and morphometric; men 43.1% vs women 31.3%; $p < 0.03$). The percentage of clinical vertebral fractures did not differ between men (9.8%) and women (8.1%), while that of morphometric vertebral fractures was significantly higher in men (33.3%) compared to women (23.2%; $p < 0.05$). Moreover, among patients with clinical fractures, only about 18% of men and 47% of women were self-referred. No significant differences were found between the sexes when nonvertebral fractures and vertebral/nonvertebral fractures were collectively taken into account.

Figure 2 shows the frequency of primary and secondary osteoporosis for both sexes as well as the prevalence of subjects considered as nonosteoporotic. Diagnosis of osteoporosis was based on BMD T score values < –2.5 SD at lumbar spine and/or femoral neck, and/or the presence of fragility fractures. The prevalence of both primary (men 52.9% vs women 50%; p = nonsignificant) and secondary (men 21.1% vs women 17.5%; p = nonsignificant) osteoporosis did not differ between the sexes. By contrast, the prevalence of primary

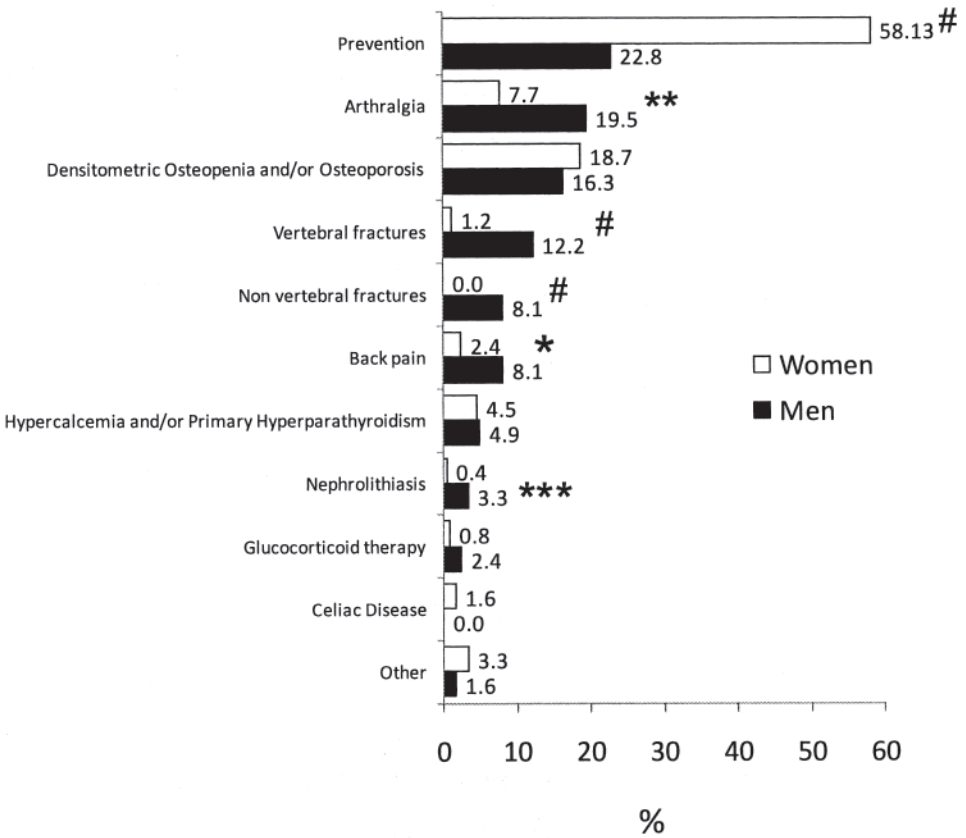

Figure 1. The main reason for the patient's first visit. Bars represent percentage of patients, by sex. Chi-squared tests showed significant differences between men and women for prevention, vertebral and nonvertebral fractures ($^{\#}p < 0.0001$ for all), back pain ($^{*}p < 0.001$), arthralgia ($^{**}p < 0.01$), and nephrolithiasis ($^{***}p < 0.05$).

Table 2. The prevalence (%) of fragility fractures in men and women.

Site of Fracture	Men, n = 123	Women, n = 246	p
Vertebral	43.09	31.3	< 0.03
Clinical, no.	12	20	NS
Morphometric, no.	41	57	< 0.05
Nonvertebral	8.13	8.13	NS
No.	10	20	
Both vertebral and nonvertebral	17.89	14.63	NS
No.	22	36	
All	69.11	54.07	< 0.001
No.	85	133	

NS: not significant.

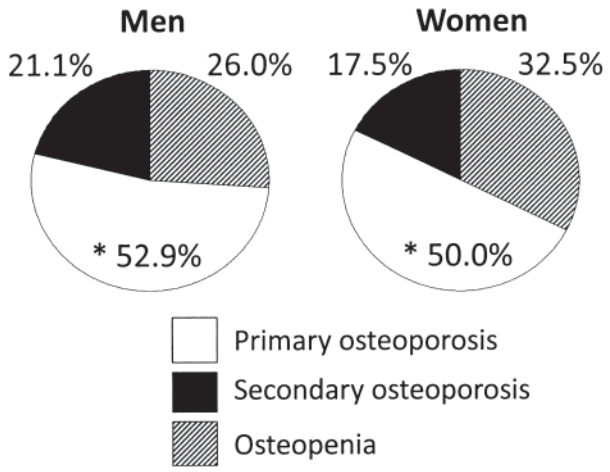

Figure 2. Frequency of primary and secondary osteoporosis, for both sexes; prevalence did not differ between sexes. In contrast, the prevalence of primary osteoporosis was significantly higher than for secondary causes (*p < 0.0001), in both men and women. The prevalence of osteopenia is also shown; percentages did not differ significantly between men and women.

osteoporosis was significantly higher than secondary causes ($p < 0.0001$), in both men and women. Figure 2 also shows the percentage of men and women patients with osteopenia, i.e., with BMD T score values > –2.5 SD and without fragility fractures. The percentages did not differ between men (26.0%) and women (32.5%). Among subjects with osteopenia, 8.7% of women and 12.5% of men had ≥ 1 strong risk factor, or disease, or metabolic condition causing bone loss, with primary hyperparathyroidism the most frequent diagnosis (data not shown).

Table 3 illustrates the frequency of secondary osteoporosis. The patients have been classified according to the most likely diseases or strong risk factors causing or contributing to low bone mass. For example, an intake of 3 or more units of alcohol daily was considered a significant risk factor. Drug-induced osteoporosis and gastrointestinal diseases were the most common causes of secondary osteoporosis both in men (28.6% and 10.7%, respectively) and in women (32.6% and

Table 3. The prevalence of secondary osteoporosis. Patients have been classified according to the most likely diseases or strong risk factors causing or contributing to low bone mass. Values are number (%).

Disorder	Men, n = 28	Women, n = 43	p
Drug-induced osteoporosis	28.5 (8)	32.5 (14)	NS
Primary hypoparathyroidism	7.1 (2)	34.8 (15)	< 0.01
Gastrointestinal diseases	10.7 (3)	16.2 (7)	NS
Hypercalciuria	14.2 (4)	0	< 0.01
Hypogonadism/amenorrhea	14.2 (4)	2.3 (1)	NS
Subclinical hypercortisolism	7.1 (2)	0	NS
Hyperthyroidism	0	6.9 (3)	NS
Rheumatoid arthritis and other autoimmune diseases	7.1 (2)	0	NS
Hematological disease	3.5 (1)	4.6 (2)	NS
Osteomalacia	0	2.3 (1)	NS
Alcohol consumption 3 or more units daily	7.1 (2)	0	NS

NS: not significant.

16.3%), without difference between sexes. Hypercalciuria was more prevalent in men than in women ($p < 0.01$; none of the subjects were taking furosemide or hydrochlorothiazide). As expected, the percentage of women with primary hyperparathyroidism was significantly higher than that of men ($p < 0.01$). Concerning the other causes, we found that rheumatoid arthritis, subclinical hypercortisolism, hypogonadism, and abnormal intake of alcohol were more prevalent in men compared to women, even if the respective percentages did not differ significantly between the sexes. Among women with secondary osteoporosis, only 6 were premenopausal (2 women had celiac sprue, 1 had amenorrhea due to prolactinoma, and 3 had drug-induced osteoporosis). The remaining premenopausal subjects were osteopenic.

Table 4 reports sex differences in FRAX calculation for

Table 4. The 10-year risk (%) for major osteoporotic and hip fractures according to FRAX calculation, in men and women. Postmenopausal women aged 40-90 years and men aged > 50 years have been considered. The algorithm was applied in subjects with primary and secondary osteoporosis, and in the osteopenic group.

Condition	n	Major Osteoporotic Fracture, %	Hip Fracture, %
Primary osteoporosis			
Men	57	11.9 ± 6.9	4.9 ± 6.0
Women	116	12.7 ± 7.0	4.4 ± 6.0
p		NS	NS
Secondary osteoporosis			
Men	26	14.4 ± 11.9	7.1 ± 10.1
Women	36	20.3 ± 13.6*	9.1 ± 12.4**
p		0.01	NS
Osteopenia			
Men	19	4.8 ± 4.0	1.4 ± 2.7
Women	61	6.9 ± 3.6	1.8 ± 2.8
p		< 0.001	NS

* $p < 0.001$ and ** $p < 0.04$ vs women with primary osteoporosis.

postmenopausal women aged 40–90 years and men aged > 50 years. The algorithm was applied in subjects with primary and secondary osteoporosis, and in the osteopenic population. As shown, the 10-year probability for major osteoporotic fractures was significantly lower in men compared to women in patients with secondary osteoporosis (men 14.4% ± 11.9% vs women 20.3% ± 13.6%; $p < 0.01$) and in patients with osteopenia (men 4.8% ± 4% vs women 6.9% ± 3.6%; $p < 0.001$). It is noteworthy that the 10-year risk for major fractures was > 20% only in women with secondary osteoporosis. The 10-year risk for hip fracture was > 3% in all groups except patients with osteopenia; no sex differences were found for probability of hip fracture. The comparison of risk factors included in the FRAX tool demonstrated a sex difference for only some of them. Indeed, femoral neck BMD was significantly lower in women compared to men, both in patients with primary osteoporosis ($p < 0.01$) and in those with osteopenia ($p < 0.001$). But femoral BMD did not differ between men and women with secondary osteoporosis. Alcohol intake was significantly higher in men with primary osteoporosis ($p < 0.0001$) and osteopenia ($p < 0.01$) as compared to women. Current smoking in women with primary osteoporosis (18.9%) was significantly more prevalent than in men of the same group (4.8%; $p < 0.05$). Finally, the prevalence of a previous fragility fracture was significantly higher in men with secondary osteoporosis (100%) than in women (77.7%; $p < 0.05$). No differences were found between the sexes for BMI, parental history of hip fracture, or use of glucocorticoids (Table 5).

DISCUSSION

In our prospective study we analyzed the clinical and etiological factors of osteoporosis in a large sample of men and women attending a center for metabolic bone diseases during a 2-year period. A major strength of our study is that patients of both sexes were investigated at the same time and with the same diagnostic protocol.

The majority of patients, independent of sex, were self-referred. This finding demonstrated that, in the population we studied, the knowledge and perception of osteoporosis and metabolic bone diseases was higher in this group than was commonly reported in other community-dwelling populations. On the other hand, results concerning physicians' prescription patterns confirmed previous observations on clinical practices about osteoporosis[18]. Indeed, we observed that relatively few patients were sent by their physicians. General practitioners, however, had the highest disease awareness. Considering that our sample was mainly composed of middle-aged patients, this finding confirmed the large gap between osteoporosis guideline recommendations and current practice[19]. This was not unexpected because a number of barriers to the application of osteoporosis guidelines have been identified, such as uncertainty about the indications and interpretation of BMD testing, confusion about available osteoporosis medications, and the perceived cost of investigations and treatment[20]. Besides this, limited time and comorbidities requiring multiple therapies in elderly patients seem, particularly among family physicians, to further complicate preventive care for osteoporosis.

A second interesting finding concerns the main reason for the first visit, which was different between sexes. Whereas women came to our attention for prevention of osteoporosis (i.e., to measure BMD), men came to the bone disease center because of clinical symptoms (arthralgia, back pain) or possibly disease-related complications such as fractures, but they were not usually aware of the usefulness of dual-energy x-ray absorptiometry (DEXA) evaluation. This finding is in line with the results reported in Table 2, showing that the percentage of men with fragility fractures (both total and vertebral fractures) was significantly higher compared to women. Thus,

Table 5. Comparison between men and women of risk factors considered in the FRAX tool. Patients are grouped according to diagnosis of primary and secondary osteoporosis, and osteopenia.

Condition	Age, yrs	BMI, kg/m^2	Femoral neck BMD g/cm^2	Alcohol, > 3 Units Daily, %	Smoking, %	Family History of Hip Fracture, %	Previous Fractures, %	Glucocorticoid Use, %
Primary osteoporosis								
Men	69.0 ± 8.9	24.9 ± 3.0	0.692 ± 0.134	12.28	4.8	21.0	92.9	0
Women	66.3 ± 9.8	25.1 ± 4.5	0.626 ± 0.102	0.86	18.9	17.2	83.6	0
p	NS	NS	< 0.003	< 0.0001	< 0.05	NS	NS	NS
Secondary osteoporosis								
Men	68.4 ± 7.6	24.6 ± 3.5	0.647 ± 0.114	7.1	20	20	100	30
Women	66.6 ± 12.2	23.9 ± 3.7	0.605 ± 0.113	0	16.6	22.2	77.7	16.6
p	NS	NS	NS	NS	NS	NS	< 0.05	NS
Osteopenia								
Men	63.5 ± 8.1	25.9 ± 3.9	0.811 ± 0.092	10.5	10.5	15.7	0	0
Women	63.9 ± 10.8	27.3 ± 4.9	0.731 ± 0.085	0	13.1	14.7	0	0
p	NS	NS	< 0.001	< 0.01	NS	NS	NS	NS

BMI: body mass index; BMD: bone mineral density; NS: not significant.

although low-trauma and high-trauma fractures in men are more frequent than in women, men are referred for the diagnosis and treatment of osteoporosis only when its consequences are apparent[21]. Figure 1 shows that a low percentage of men (16.3%) and women (18.7%) had undergone BMD testing before referral. This result is in line with several studies showing the suboptimal use of DEXA[22]. In many countries, physicians remain unaware of the prevalence and complications of osteoporosis, particularly in men, so that most men at risk were not screened by BMD testing as recommended in the majority of guidelines[23,24]. For example, in a longitudinal study carried out among older Americans in 1999-2005, only about 30% of women and 4% of men at least 65 years old had a central DEXA study[22]. Suboptimal use of DEXA can be associated with factors related to patients, healthcare providers, and legislation that regulates the reimbursement for DEXA. This finding is crucial, because many studies have shown that access to DEXA, as well as patient understanding of DEXA results, significantly improve the prescription and persistence of osteoporosis therapies, and therefore have the potential to reduce the burden of disease[25,26,27]. The lower use of DEXA testing among men means that men are also significantly less likely to be treated, as compared to women. In one study assessing fracture risk through clinical factors, only 3% of white men at high risk for hip fracture were receiving osteoporosis therapies[24]. Considering the high prevalence of osteoporosis in men and the high rate of morbidity and mortality after fractures, there is a strong need to increase awareness of the disease among physicians.

An important endpoint of our study was to assess the frequency of primary and secondary osteoporosis in both sexes. Surprisingly, as shown in Figure 2, no difference was found between men and women for the prevalence of both primary and secondary forms of the disease. In men and women, the prevalence of the secondary form was significantly lower than that for primary osteoporosis. Moreover, the percentage of secondary osteoporosis we found in men was lower (21.1%) than that reported in most studies, whereas in women, it was close to the percentage reported in the literature (17.5%). Our results are in line with those published by Peris, *et al*, which also showed that the percentage of primary osteoporosis in men was higher than the secondary form of the disease[28]. Several factors could account for the discordant results reported in studies investigating the frequency of secondary osteoporosis, such as diversities in the definition of causal factors. This is one reason why, for example, our study differs from that of Ryan, *et al*[8], in which chronic obstructive pulmonary disease (COPD) was considered a common secondary cause of osteoporosis. We included patients with COPD into the category of drug-induced osteoporosis because they were taking corticosteroids, and we were not able to collect information about smoking history. In addition, the mean age of our patients was considerably lower than that reported by Ryan, *et al* and also by Trimpou and coworkers, who identified smoking as an important risk factor for hip fracture in a large sample of elderly men[29]. As in any study of this kind, the conclusions depend on the definition of secondary osteoporosis and the population studied. Among other factors, the diagnostic protocols and the cutoff values for laboratory tests could account for the discordant results. Indeed, limited diagnostic evaluation results in low reported prevalence rates, while the contrary result occurs when exhaustive diagnostic protocols are used. As well, the clinical context in which the investigation is developed should be considered, because prevalence rates are higher in tertiary referral and specialty metabolic bone centers. Also crucial are the criteria used to select patients because the characteristics of the populations examined often differ among studies, and usually each single study investigated only men or women. A major strength of our study is that subjects of both sexes were studied at the same time and with the same diagnostic protocol. In one of the few similar studies on the prevalence of secondary osteoporosis, despite the extensive diagnostic procedures applied, no risk factors or subclinical disease were detected in 37% of women and 33% of men[7]. Another recent report, which evaluated the sensitivity and diagnostic usefulness of BMD Z-scores (the number of SD below an average person of the same age) to detect secondary osteoporosis, found it in only 31% of men and 16% of women[30].

Regarding the different causes of secondary osteoporosis, drug-induced osteoporosis accounts for a great percentage, both in men (28.6%) and in women (32.6%), with no difference between the sexes. This result is in line with the majority of epidemiological evidence showing that several drugs can induce significant bone loss through different mechanisms[31,32]. Also, gastrointestinal diseases are an important cause of secondary osteoporosis in our sample, independently of sex. The greater prevalence we found compared to other reported series could be partly due to the wide age range of our sample, which included a relatively high number of young patients. Therefore, a great number of subjects with inflammatory bowel disease and celiac sprue were studied. On the other hand, a 17-fold higher prevalence of celiac disease among patients with osteoporosis compared with nonosteoporotic subjects has recently been reported[33]. All these findings seem to support the usefulness of serologic screening for celiac disease in all patients with osteoporosis[33]. Primary hyperparathyroidism was the most important cause of secondary osteoporosis in women, whose frequency was significantly higher than that found in men (34.9% vs 7.14%; $p < 0.01$). Also in osteopenic women, primary hyperparathyroidism was the most commonly diagnosed disease. Our observations are in line with the epidemiological evidence showing that women are about 3 times more often affected by primary hyperparathyroidism than men[34,35,36]. Therefore, our results emphasize the importance of serum calcium screening in all subjects with osteoporosis or reduced bone mass. Hypercalciuria was among the more frequent causes of secondary

osteoporosis in men (14.1%), significantly higher compared to women. This metabolic disorder has been associated with low BMD and increased bone turnover[37]. The presence of kidney stones was one of the main reasons for which men made an appointment. In our sample, the percentage of men with hypogonadism and alcoholism was higher compared to women, although this difference did not attain statistical significance. Hypogonadism is a well known cause of secondary osteoporosis in men; however, the different and wide prevalence rates observed in published studies could be influenced by the controversial definition of hypogonadism, because longitudinal studies show an age-related decline in androgen levels in normal men. Subclinical hypercortisolism and rheumatoid arthritis also were more prevalent in men. Subclinical hypercortisolism has recently been reported to be more common in patients with osteoporosis than is generally appreciated, particularly in men[38]. However, because most studies do not screen for this condition, its real prevalence could be underreported. This finding underlines the need to perform evaluation for subclinical hypercortisolism in patients with osteoporosis, at least in men.

The application of the FRAX algorithm in our population was another endpoint of the study. FRAX is a computer-based tool that provides models for assessment of fracture probability. We applied FRAX calculation (1) to assess the 10-year fracture risk in subjects with osteopenia and without spine or hip fractures and to compare the intervention thresholds suggested in NOF guidelines with our clinical decisions about treatment, strongly influenced by the Italian guidelines available at the time of the study[39]; and (2) to evaluate whether fracture risk for both major osteoporotic and hip fractures differed between men and women with primary and secondary osteoporosis. The information about femoral neck BMD was available for all but 5 subjects. This was important, because it has been demonstrated that FRAX calculation with or without BMD could lead to discrepancies in fracture probability that result in different treatment recommendations[40].

Table 4 shows that, in the osteopenic population, fracture risk was lower than that currently considered by NOF guidelines as intervention thresholds, i.e., 3% for hip fracture and 20% for major osteoporotic fractures. This finding confirms that this population at very low risk of fractures does not need treatment for bone fragility; in this respect, fracture risk assessment provided by FRAX agrees with the Italian guidelines concerning treatment decisions. However, in women with osteopenia, the 10-year risk of major osteoporotic fractures was significantly higher compared to that of men in the same category (6.9% vs 4.8%; $p < 0.001$). Such a difference was probably due to the greater contribution of BMD compared to other risk factors in FRAX calculation, femoral neck BMD in osteopenic men being significantly higher than in women. Since smoking and alcohol intake are usually considered weaker risk factors, the higher alcohol consumption observed in osteopenic men probably did not influence the results of FRAX calculation (Table 5). The minimal validation of FRAX in men should be taken into account, so that our results in men could be influenced by this still unresolved limitation of the algorithm[41].

The application of the FRAX tool in patients with primary and secondary osteoporosis also raises interest. Our results showed that in patients with primary osteoporosis, clinical risk factors such as a prior fragility fracture and a parental history of hip fracture were strongly represented (Table 5). Interestingly, in our series alcohol consumption was higher in men while current tobacco smoking was more prevalent in women. Even if femoral neck BMD were significantly lower in women compared to men, no sex differences were found for probability of fracture estimated by FRAX, probably because the high prevalence of strong risk factors both in men and women outweighed that of BMD.

When applying FRAX calculation to patients with secondary osteoporosis, we found that the estimated risk for hip fracture was high in both sexes, but in women with secondary causes it was particularly higher than in those with primary osteoporosis (9.1% vs 4.4%; $p < 0.04$). Moreover, the risk for major osteoporotic fractures in women with secondary osteoporosis was significantly higher than that in men (20.3% vs 14.4%; $p < 0.01$) and in women with primary osteoporosis (20.3% vs 12.7%; $p < 0.001$; Table 4). The poor definition of secondary osteoporosis has been criticized as a limitation of FRAX. Indeed, this risk factor is automatically excluded by FRAX if BMD input is used because the World Health Organization, which developed FRAX, was unable to assess evidence for the effects of secondary osteoporosis on fractures independent of BMD[42]. The algorithm does not take account of multiple causes of secondary osteoporosis, and therefore it may underestimate fracture risk in patients with multiple comorbidities. The effect of BMD on fracture risk outweighs that of secondary osteoporosis in the FRAX model. However, when considering all risk factors computed by FRAX, we observed that these variables were strongly represented in patients with secondary osteoporosis, independently of sex. Indeed, a previous fracture, a family history of hip fracture, use of glucocorticoids, current smoking, and high alcohol consumption were all reported in a large percentage of patients (Table 5). Thus, FRAX calculation could be useful, because it may provide an estimate of a particularly high fracture risk in patients whose bone fragility is usually attributed to another disease. In other words, at least in our patients with secondary osteoporosis, other clinical risk factors could contribute to the highest fracture risk, as indicated by FRAX calculation.

The main limitation of our study is that it only reports the experience of a reference center for osteoporosis and metabolic bone diseases. Therefore, an inherent bias could have been present in the recruitment of patients, and consequently, the results may not be generalized. Another limitation is that we have arbitrarily classified patients with multiple risk fac-

tors and/or comorbidities in one category or another exclusively on the basis of our clinical judgment.

The prevalence of secondary osteoporosis in men is similar to that of women and, above all, it is significantly lower than commonly reported. While women sought medical attention for the prevention of bone loss, men were referred because of the presence of signs and symptoms indicating a more severe disease. In our population, the low prevalence of secondary osteoporosis in both sexes demonstrated that not only in women but also in men, an extensive, and therefore expensive, evaluation is not necessary, unless there are clues to underlying conditions. According to the FRAX calculation, patients with osteopenia and without fractures should not be treated for the disease, as they are at very low risk for future fractures. By contrast, patients with primary and secondary osteoporosis are at high risk for all fragility fractures, particularly postmenopausal women with secondary osteoporosis. This implies that a careful medical examination should be always carried out in each patient to exclude potentially reversible causes of bone loss.

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