Original Article
Health promotion, disease prevention, and lifestyle

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2021 Oct 39(4): 750-759
https://doi.org/10.5534/wjmh.200099

The World Journal of MEN's HEALTH

Gender Differences in Osteoporosis: A Single-Center Observational Study

Massimo De Martinis[1,2], Maria Maddalena Sirufo[1,2], Matteo Polsinelli[3], Giuseppe Placidi[3], Daniela Di Silvestre[1,2], Lia Ginaldi[1,2]

[1]Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, [2]Allergy and Clinical Immunology Unit, Center for the Diagnosis and Treatment of Osteoporosis, Teramo, [3]A2VI-Lab, Department of Life, Health and Environmental Sciences, L'Aquila, Italy

Purpose: Osteoporosis affects more than 200 million people worldwide: its prevalence increases with age and is actually growing due to the constant population aging. Women are at greater risk than men, but in recent years it has become increasingly evident that osteoporosis represents a significantly important problem also for men. However, osteoporosis in men is still poorly studied, underdiagnosed and inadequately treated.

Materials and Methods: We conducted an observational study to identify any gender disparities in osteoporosis screening. For this purpose we observed people consecutively admitted at our Outpatient Service for the Diagnosis of Osteoporosis during the last 3 years. Patients underwent clinical and laboratory assessment and bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry. Bone turnover serum markers have been evaluated and stratified according to gender.

Results: Out of 3,752 patients, 2,376 subjects who met the inclusion criteria were identified. As expected, the great majority (94.5%) of the screened subjects were women and only 5.4% were men. Women exhibited lower BMD compared to men (T-score values: -2.33±1.14 *vs*. -1.31±1.55; p<0.001), whereas the prevalence of fractures in osteoporotic men was significantly higher (50% *vs*. 31%; p<0.001). Women had lower vitamin D and higher bone remodeling markers compared to men. Secondary osteoporosis was more frequent in men (66.67%) than in women (20.83%) and the calculated risk for hip fractures was higher in osteoporotic men compared to women (11.47±10.62 *vs*. 6.87±7.73; p<0.001).

Conclusions: Here we highlighted that men are under-screened for osteoporosis and exhibit secondary osteoporosis more frequently than women.

Keywords: Aging; Bone; Bone density; Gender; Men; Osteoporosis

INTRODUCTION

Osteoporosis is defined as a systemic skeletal pathology characterized by loss of bone mass, decreased bone mineral density (BMD), loss of microarchitectural integrity and compromised bone strength, leading to increased bone fragility and consequent increased risk of fracture, mainly at the level of the spine and femur [1].

It affects more than 200 million people worldwide. It has been calculated that a vertebral or femoral fracture occurs every 200 seconds, with a mortality rate ranging from 15% to 25% [2].

Received: Jun 8, 2020 **Revised:** Sep 28, 2020 **Accepted:** Oct 28, 2020 **Published online** Nov 26, 2020
Correspondence to: Massimo De Martinis https://orcid.org/0000-0003-4253-1312
Department of Life, Health and Environmental Sciences, University of L'Aquila, Piazzale Salvatore Tommasi n. 1, 67100 L'Aquila, Italy.
Tel: +39-0861-429548, **Fax:** +39-0861-211395, **E-mail:** demartinis@cc.univaq.it

Globally in both men and women, osteoporosis and osteoporotic fractures are important public health concerns because of related morbidity and mortality, diminished health-related quality of life, and associated costs. In 2010, about 5.5 million men in Europe were suffering from osteoporosis, and nearly 1.2 million suffered a fragility fracture [3]. More than 168.000 hip fractures have affected men, accounting for 28% of the total number of hip fractures in both genders. The cost was almost 11.6 billion euros. Estimates indicate that the total number of fractures will increase by 34% by 2025, to nearly 1.6 million cases a year, with a cost of assistance of 15.5 billion euros. A study by Burge et al [4] calculates that in the United States the burden of total fractures were >2 million, costing nearly 17 billion dollars in 2005. Men account for almost 30% of total osteoporotic fractures and costs (5.1 billion dollars), showing that this disease is not restricted to women, thus suggesting that appropriate attention is warranted for men. By 2025, the burden in the United States is projected to grow by almost 50% to >3 million fractures and 25.3 billion dollars in costs.

Osteoporosis is one of the most common inflammatory bone loss condition [5,6] and is an age-related disorder: its prevalence increases with age and is actually growing due to the constant aging of the population [7-9]. Osteoporosis is also a predominantly female pathology: among diseases afflicting women more than men, osteoporosis is at the first place [10,11]. In addition to aging and menopausa, other conditions, such as underlying diseases and/or the use of drugs impacting the bone, can also cause "secondary" osteoporosis [12,13]. Five per cent of people aged 50 and 50% at age 85 have decreased BMD, whereas more than 75% of women over 60 are affected. There is therefore a significant gender difference in disease prevalence: 4 million females and 1 million males in Italy suffer from osteoporosis, and 1 in 2 women and 1 in 4 men aged more than 50 will have an osteoporosis-related fracture in their lifetime [2].

Women are therefore known to be at greater risk of developing osteoporosis than men. However, in recent years it has become increasingly evident that osteoporosis represents a significantly important problem also for men. Men are not well represented in osteoporosis trials, and clinical and laboratory findings of male osteoporosis, as well as differences in efficacy and side effects of anti-osteoporotic drug, are poorly known. As a consequence, men are poorly studied, underdiagnosed and inadequately treated, although osteoporotic fractures are generally accompanied by more serious complications and greater mortality in males compared to females [14-16].

The indications for osteoporosis screenings in men, the age and any categories at greatest risk in which to plan them, as well as the most appropriate diagnostic tools to be used from a gender perspective, still seem unclear. Based on few papers comparing osteoporosis in men and women, screenings for osteoporosis are recommended for all men aged 70 or older regardless of risk factors for osteoporosis [17]. However, in the clinical practice these reccomandations seems to be still disregarded. Despite the increased attention of research, the still low sensitivity of the population to this problem, in many situations limits the access of males to services for the diagnosis of osteoporosis with insufficient prevention of osteoporotic fractures in men.

The aim of our study was therefore to identify any gender disparities in osteoporosis screening in a routinely clinical setting. For this purpose, we assessed gender differences in BMD, bone remodeling serum markers and fractures in subjects observed in the last 3 years at the Outpatient Service for the Diagnosis of Osteoporosis at Teramo Hospital.

MATERIALS AND METHODS

To assess gender disparities in osteoporosis in the clinical practice, we observed people consecutively admitted at our Outpatient Service for the Diagnosis of Osteoporosis during the last 3 years. Patients referred to our medical center for known osteoporosis or osteopenia and already taking anti-osteoporotic therapies were excluded.

In each subject, BMD at the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500 W machine; Hologic Inc., Bedford, MA, USA). All DXA evaluations were performed by the same certified radiologist. BMD values obtained by DXA technique were expressed as T-score, *i.e.*, the difference (number of standard deviations) between the BMD value of the examined subject and the mean value in the healthy reference population, according to the current World Health Organization (WHO) diagnostic criteria for osteoporosis [18], for which osteoporosis corresponds to T-score values of -2.5

The World Journal of MEN's HEALTH

and lower, osteopenia ranges from -1.0 to -2.5, whereas T-score values of -1.0 and higher are considered normals.

A carefull anamnestic and clinical evaluation had been performed in each patient, to search for fractures, as well as underlying diseases and/or assumption of bone impacting drugs capable of causing "secondary" osteoporosis [19]. The fracture risk assessment (FRAX) score, supported by the WHO for estimating the 10-year probability of hip and other major osteoporotic fractures [20] was also determined for each subject, based on the clinical and anamnestic data obtained from patient records. Moreover, data obtained from laboratory exams carried out at the time of the visit, including and bone turnover serum markers, were considered. All clinical, laboratory and instrumental findings were collected in a Microsoft Excel spreadsheet for subsequent processing.

1. Ethics statement

The present study protocol was reviewed and approved by the Internal Review Board University of L' Aquila ex "Academic Ethics Committee" D.R. n. 206/2013 modified D.R. n. 46/2017 (Ginaldi 15/04/2014). Informed consent was submitted by all subjects when they were enrolled.

2. Statistical analysis

Data were expressed as percentages and means± standard deviations, as appropriate. Numerical analyses were performed with Matlab software (https://mathworks.com) and SPSS for Windows (ver. 17.0; SPSS Inc., Chicago, IL, USA). The comparison between two proportions and the Mann-Whitney test were used to analyze the differences between the two unpaired groups, and the level of statistical significance was set at $p<0.05$.

RESULTS

Out of a total of 3,752 patients admitted to the Outpatient Service for Osteoporosis over the last 3 years, 2,376 subjects (mean age 65.37±10.06 years) who met the inclusion criteria were identified. As expected, the great majority (94.5%) of the screened subjects were women (n=2,247) and only 5.4% were men (n=129) ($p<0.001$), with mean ages of 65.29±10.04 years and 66.62±10.99 years, respectively (Fig. 1).

Fig. 2 shows the T score mean values in men and women as well as in normal, osteopenic and osteoporotic subjects in both genders. Men exhibited higher BMD compared to women at the same age ($p<0.001$) (Fig. 2A). Stratifying subjects according to the T score ranges, no

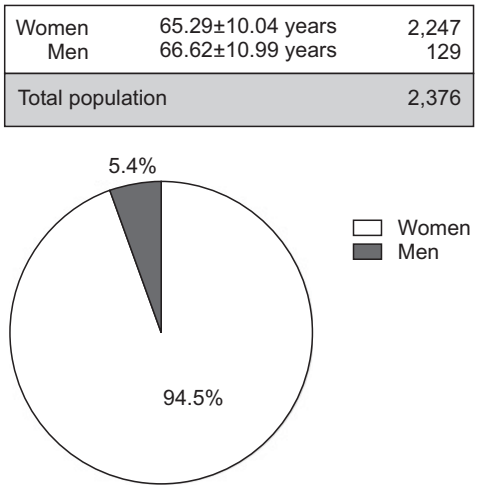


Fig. 1. Gender distribution of the population admitted for the first time to the outpatient service for the diagnosis and treatment of osteoporosis within 3 years.

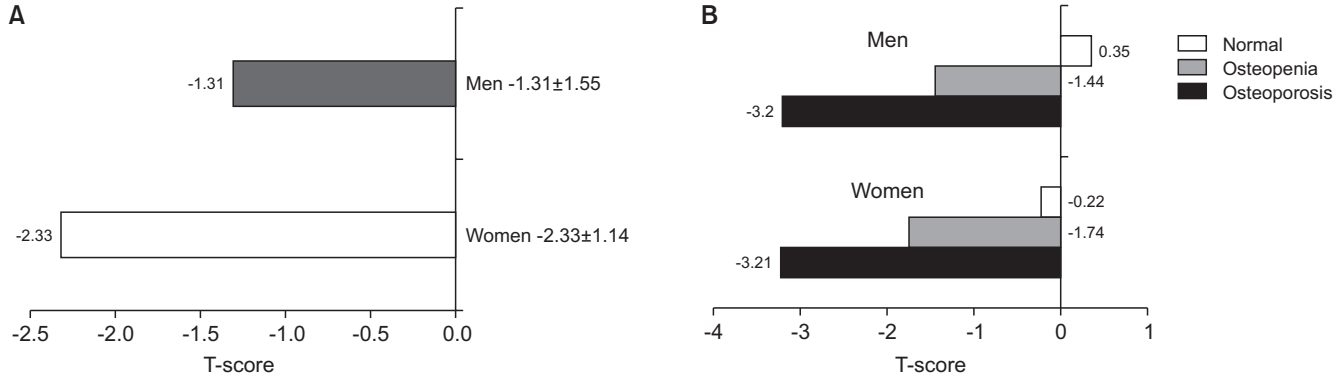


Fig. 2. T-score mean values in men and women (A) as well as in normal, osteopenic, and osteoporotic subjects in both genders (B).

statistically significant differences between the mean T score values of women and men with osteoporosis were observed, whereas osteopenic and normal men patients showed higher mean T score values than osteopenic and normal women patients, respectively (p<0.001) (Fig. 2B).

Eighty-nine percent of women had reduced BMD (osteopenia and osteoporosis) *vs.* 65% of men (p<0.001), and there is a higher prevalence of osteoporosis among women (51.27%) compared to men (27.91%) (p<0.05), although no gender differences were observed among osteopenic patients. Therefore, in people undergoing screening, women are more likely to experience reduced bone density (Fig. 3).

The proportions of fractured and unfractured men and women are compared in Fig. 4. A total of 28.74% of men and 27.91% of women have one or more fractures (vertebral, femoral, or both). Therefore, although the higher T score values in men, the proportions of fracture events were quite similar.

Fig. 5 illustrate the prevalence of fractures in osteoporotic (T-score<-2.5), osteopenic (T-score ranging from -1.0 to -2.5), and normal (T-score>-1.0) women and men. Stratifying patients according to BMD, 30.73% of women with osteoporosis presented with fractures, whereas up to 50% of osteoporotic men had one or more fractures. Thus, men affected by osteoporosis had a higher incidence of fractures compared to osteoporotic women (p<0.001).

Gender	Normal	Osteopenia	Osteoporosis	Total
Women	240 (10.68%)	855 (38.05%)	1,152 (51.27%)	2,247
Men	45 (34.88%)	48 (37.21%)	36 (27.91%)	129
Total	285	903	1,188	2,376
p-value	<0.001	ns	<0.05	

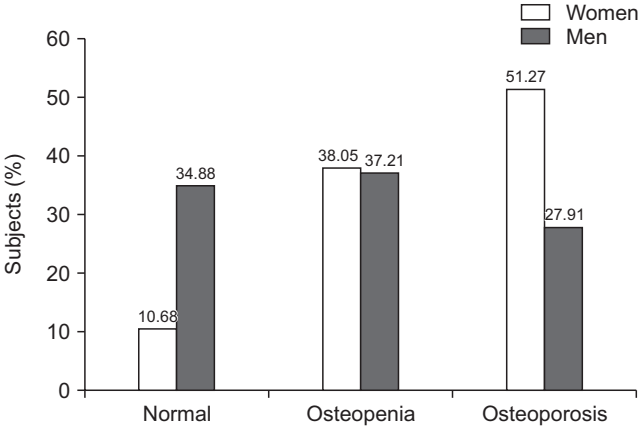


Fig. 3. Gender differences in the distribution of normal, osteopenic, and osteoporotic subjects in people undergoing screening. ns: not significant.

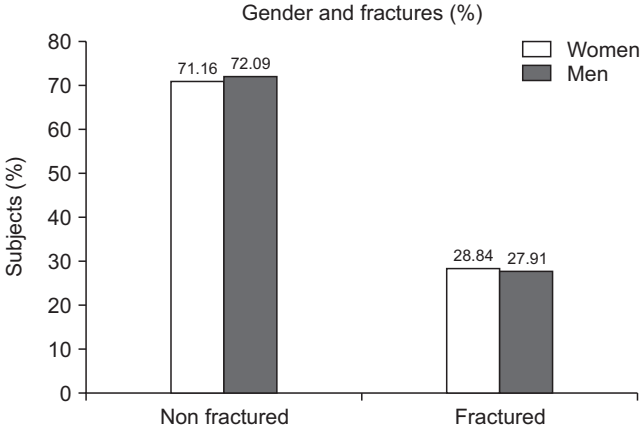
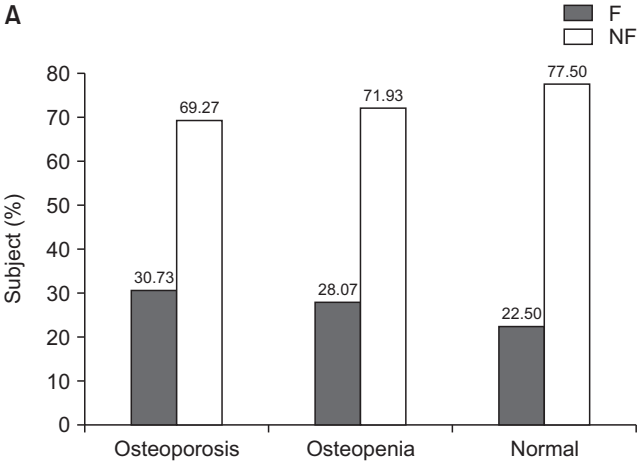


Fig. 4. Proportions of fractured and unfractured men and women.



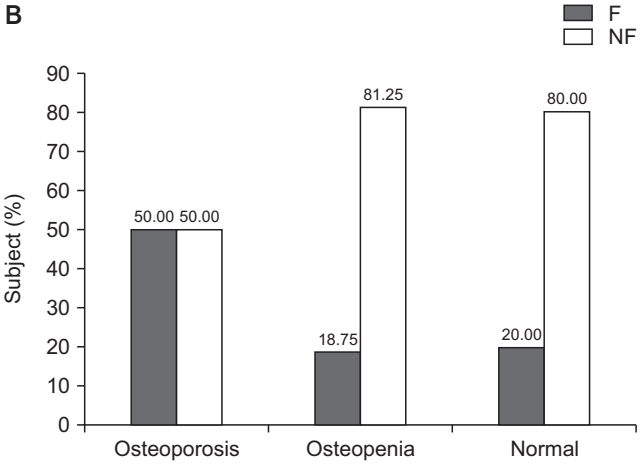


Fig. 5. Proportion (%) of fractured (F) and non fractured (NF) osteoporotic (T-score<-2.5), osteopenic (T-score ranging from -1.0 to -2.5), and normal (T-score > -1.0) women (A) and men (B).

Table 1. Serum markers of bone turnover in women and men

Variable	Total screened subject		Osteoporosis		Osteopenia		Normal	
	Women (n=749)	Men (n=43)	Women (n=384)	Men (n=12)	Women (n=285)	Men (n=16)	Women (n=80)	Men (n=15)
Ca (mg/dL)	9.29±0.85	9.33±1.13	9.36±0.59	8.95±2.05	9.21±1.07	9.44±0.40	9.22±1.00	9.53±0.47
P (mg/dL)	3.36±0.68	2.92±0.53	3.34±0.66	2.66±0.63	3.37±0.73	2.96±0.49	3.43±0.57	3.09±0.41
Vit D (ng/mL)	25.08±14.44	34.12±20.31	25.27±14.07	42.98±30.15	25.28±14.55	29.37±12.34	22.92±15.67	32.11±15.93
PTH (pg/mL)	58.58±42.46	50.93±26.99	60.75±34.88	63.56±37.86	60.06±42.53	42.37±21.76	55.05±26.84	49.96±16.94
CTX (pg/mL)	195.80±252.02	60.09±101.05	198.90±220.06	185.29±160.16	207.11±280.37	31.60±54.83	143.87±269.94	44.69±87.04
BAP (μg/L)	17.23±11.34	8.68±6.60	17.83±12.08	9.86±7.18	16.68±9.31	6.58±4.99	14.72±9.72	9.17±6.91
OC (ng/mL)	18.33±11.73	12.75±5.16	18.68±13.08	16.12±5.83	17.87±9.74	11.73±3.86	16.98±10.67	11.29±5.11

Values are presented as mean±standard deviation.
Ca: serum calcium, P: phosphorus, Vit D: 25(OH) vitamin D, PTH: parathyroid hormone, CTX: C-telopeptide cross-linked collagen type 1, BAP: bone alkaline phosphatase, OC: osteocalcin.

Mean values of FRAX score for major osteoporotic fractures were globally higher in women compared with men (12.23±9.25 *vs.* 8.21±8.33; p<0.001). Considering the FRAX score for hip fracture risk, mean values were significantly higher (p<0.01) in osteoporotic and osteopenic men compared to women (11.47±10.62 *vs.* 6.87±7.73 and 2.38±1.71 *vs.* 1.39±1.31, respectively), whereas women with BMD in the normal range exhibited higher values than men (1.54±1.63 *vs.* 0.5±0.47; p<0.01).

Bone turnover serum markers have been evaluated in both genders and data from total women and men screened populations, as well as normal osteopenic and osteoporotic subjects, stratified according to gender, are shown in Table 1. Both new bone formation markers, such as bone alkaline phosphatase and osteocalcin, and the bone resorption marker C-telopeptide cross-linked collagen type 1, were higher in women then in men (p<0.001). Higher levels of parathyroid hormone (PTH) were also observed in women compared to men (p<0.05), as well as in osteopenic women compared to osteopenic men, whereas in the stage of osteoporosis it resulted slightly higher in men, although without statistical significance. Conversely, women exhibited significantly lower 25(OH) vitamin D serum levels than men, both in normal and decreased BMD conditions (p<0.001). Higher serum levels of phosphorus were detected in women in all groups (p<0.001). Serum calcium was respectively higher in osteoporotic women (p<0.001) and lower in normal women (p<0.05) compared to men.

Out of 2,247 women and 129 men who underwent osteoporosis screening for the first time, 1,554 women (69.16%) and 78 men (60.47%) had pathologies (mainly autoimmune and neoplastic diseases, cardiovascular and renal dysfunctions, chronic obstructive pulmonary disease, diabetes mellitus and metabolic syndrome, neuro-psychiatric disorders, thyroiditis and other endocrinopathies) and/or were taking drugs potentially impacting the bone (corticosteroids and other immunosuppressant drugs, radio-chemotherapies, sexual hormone antagonists, anticoagulants, proton pump inhibitors and antidepressants), without a statistically significant difference. Frequencies of the various pathologies and drugs in men and women are shown in Table 2.

Table 2. Frequencies (%) of the main pathologies and drugs in men and women

	Women (%)	Men (%)
Diseases		
Cardiovascular and renal diseases	30.88	30.77
Autoimmune/rheumatic pathologies	11.58	15.38
Neoplastic diseases	22.20	23.08
Diabetes/metabolic syndrome	15.25	11.54
Thyroiditis and other endocrinopathies	17.95	7.70
Neuropsychiatric diseases	18.15	11.54
Chronic obstructive pulmonary disease	3.28	23.08
Drugs		
Corticosteroids	13.32	19.23
Radio-chemioterapies	4.44	3.84
Sexual hormone antagonists	16.80	15.38
Antidepressants and anticonvulsivants	45.36	19.23
Anticoagulants	29.92	23.08
Proton pump inhibitors	16.79	30.77

Finally, Fig. 6 shows the prevalence of secondary osteoporosis in men and women, as assessed by the presence of underlying conditions besides aging and menopause, such as diseases and/or therapies with bone impacting drugs: 24 out of 36 osteoporotic men (66.67%)

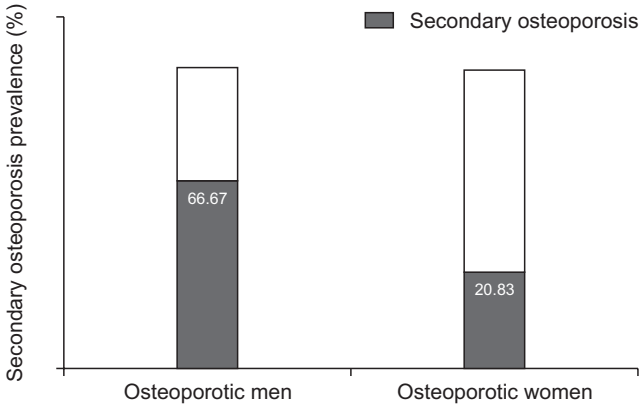


Fig. 6. Prevalence of secondary osteoporosis (osteoporosis caused or exacerbated by undelying diseases or medication exposures in men and women). Twenty four out of 36 osteoporotic men (66.67%) and 240 out of 1,152 osteoporotic women (20.83%) suffered from secondary osteoporosis.

and 240 out of 1,152 osteoporotic women (20.83%) have been shown to suffer from secondary osteoporosis. Osteoporosis secondary to diseases and drugs was therefore more common in men compared with women ($p<0.001$), in which primary osteoporosis was the most represented.

DISCUSSION

This study is not intended to be an epidemiological evaluation of the prevalence of osteoporosis in men and women in our region. Its purpose is rather to highlight a still marked gender bias in the clinical management of osteoporosis which penalizes men. Osteoporosis is one of the most emblematic gender pathologies, both as regards prevalence and for the various causes that underlie men and women osteoporosis. Prevalence rates of osteoporosis and osteopenia are higher in women than in men, and, in both genders, the rates of osteoporosis increases significantly with age. Concerning prevalence data obtained by population based epidemiologic studies, usually osteoporosis difference of gender is around 50% in men *vs.* 80% in women among over 65 years old people. As for the causes, postmenopausal osteoporosis is the most common form of osteoporosis in women, while secondary and senile forms prevail in men. The fact that osteoporosis is a much more common disease in women than men, has led researchers and clinicians to focus most studies and treatments on women osteoporosis. As a consequence, most of the diagnostic algorithms are designed for women osteoporosis. Furthermore, the women population, especially in the peri- and post-menopausal age, is more aware of the problem and therefore undergoes screenings and therapies. Unfortunately, both practitioners and patients are not sufficiently attentive to men osteoporosis. There are no specific indications for men osteoporosis screening programs. Men with osteoporosis are therefore underdiagnosed as they rarely undergo diagnostic tests for osteoporosis.

Our 3-year observational study highlights precisely this socio-sanitary gender bias that penalizes men in daily practice, especially as regards access to diagnostic tests for osteoporosis, such as bone densitometry. Despite numerous elderly men may therefore incur serious osteoporotic fractures, especially femoral fractures, men osteoporosis still remains largely undiagnosed and consequently not treated. To overcome this cultural gender bias it is necessary to sensitize the population and promote access to screenings also for men. We in fact highlighted how men are much less often screened for osteoporosis than women of the same age. In fact, in our clinical experience, DXA osteoporosis screening rates do not reach 6% in men, unlike more than 94% in women over 65 years of age. Moreover, we observed a higher prevalence of secondary osteoporosis in men (66.67%) than in women (20.83%) among the population that referred to our outpatient Service for Osteoporosis screening. Our experience therefore confirms that the prevalence of osteoporosis secondary to underlying pathologies and drugs is more common in men than in women, in whom postmenopausal and senile osteoporosis are mainly represented. Screenings for osteoporosis could therefore represent a useful tool for early diagnosis and treatment of underlying diseases as well [19-25]. Similar results were previously described in a retrospective study on a total of 961 DXA scan reports reviewed at the outpatient clinic of the George Washington University in the 2012 [26], where the authors observed that males were screened for osteoporosis by DXA less frequently compared to females, although they exhibited a comparable osteoporosis prevalence. They included in their study only subjects with previous routine health maintenance exam to assure that their primary care physician have had the opportunity to sensitize them on the most suitable age to undergo screening for osteoporosis by DXA, concluding that an adequate information could increase the percentage of males who undergo the DXA scan screening. Data

from our screened subjects also confirm that although older women tend to get sicker and take more therapies, secondary osteoporosis is much more frequent in men. Moreover, although our results indicate a greater risk for major osteoporotic fractures (distal radius, hip, or vertebral) in women, men suffering from osteoporosis and osteopenia appear to have a higher risk of hip fractures than women with comparable BMD values. These findings suggest a greater severity of osteoporosis in men, since femoral fractures are the most disabling and life threatening. Despite this, women tend to undergo check up and screening for the prevention of osteoporosis more often than men because they are more sensitive to this gender pathology, while men tend to perform densitometric exams only if fractures and/or pathologies are already present. DXA therefore continues to be underutilized as a screening tool in males, where the diagnosis of osteoporosis is often not made until a fracture occurs, most often in the femur. On the contrary, in women there is a greater chance that the diagnosis of osteoporosis will be made in an early stage by DXA scan before a fracture [27]. It has been observed that screening rates for osteoporosis in postmenopausal women vary widely, with an overall average rate of 56%. Additionally, it has been found that men are not only usually under-screened for osteoporosis, but are also often under-treated, even if they are users of long-term corticosteroids [28].

The United States Preventive Services Task Force recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older, as well as in postmenopausal women younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool, but concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men [29].

Current Endocrine Society clinical practice guidelines recommend DXA scan in men from 70 years of age [30], but males may also have to undergo DXA scanning before the age of 70, as there may be risk factors, such as hyperparathyroidism, chronic renal failure, hyperthyroidism, hypogonadism, *etc.* [31].

Although postmenopausal women have a higher risk of developing fractures, older men tend to have a worse prognosis after a fracture, particularly of the femur, and lower treatment rates. The drugs commonly used to treat osteoporosis, as well as most of the guidelines for screenings and FRAX methods, have been developed for women and therefore adapted to men [32]. Moreover, measurement of BMD by DEXA and expressed as a T score for osteoporosis diagnosis and fracture risk prediction, expecially in men, is still debated, since the use of female T-score references in men may not be entirely correct.

As expected, in our study we observed that BMD is higher in non-osteoporotic men than in women, but the average T score values are similar in osteoporotic patients. Thus, bone loss appears to be greater in men osteoporosis. Interestingly, despite a comparable BMD, the number of fractures was significantly greater in osteoporotic men than in women. The FRAX index of our patients, calculated by evaluating a number of clinical risk factors in addition to instrumental BMD data [20], also suggests a greater risk of hip fracture in men osteoporosis, confirming that, beyond the traditional T score, other gender specific instrumental and laboratory parameters for the prediction of the risk of fractures should probably be considered for their application also in routine screenings. This gender oriented approach to the diagnosis of osteoporosis and the risk of fracture could be especially useful in men.

Sex-specific differences may influence bone structure and biology, thus affecting both pathophysiology and clinical presentation of osteoporosis. There are differences in bone growth, size and catabolism between men and women. For example, in postmenopausal women the rate of bone turnover is higher than in men of the same age [15], as confirmed by our observation of higher levels of PTH and bone turnover markers in women, whereas the vitamin D levels are lower in women than in men. Estrogens play a central role in fracture healing and prevention, the aging bone in males exhibits more periosteal apposition and less endocortical resorption, and sex differences in the generation and activity of bone resorbing osteoclasts have been demonstrated [33]. Moreover, T score results do not exactly account for bone quality, especially in secondary osteoporosis that often affects men. The age at which the BMD peak is reached varies according to the sex and bone segment considered. Furthermore, depending on the reference standards adopted, the prevalence of osteoporosis can vary significantly.

In summary, we can confirm that women have lower bone density, higher bone remodeling markers, lower

vitamin D levels and higher prevalence of osteoporosis, but men osteoporosis is characterized by a greater number of complications and fractures. Moreover, secondary osteoporosis is more common in men, which usually have fractures at a higher bone density compared to women. It is significant that of those who fractured, men had higher T-scores, suggesting the opportunity of gender specific cut-off values and/or additional parameters to evaluate the risk of fractures in men and the need of any therapeutic interventions.

This study has some limitations. First, the observations were made by retrospectively reviewing records at a single osteoporosis clinic. Furthermore, the data were obtained from an unselected population. Such characteristics, in addition to the numerical discrepancy between men and women, limit the applicability of the findings, in particular those concerning the main biological and instrumental parameters investigated, to the population at large. Finally, another limitation of the study is the lack of data on patient follow-up and/or response to anti-osteoporotic therapies. Therefore, this observational study mainly provides evidence of a gender bias in the approach to osteoporosis screening in a routinely clinical setting.

These observations are particularly relevant when we consider that gender-oriented recommendations for osteoporosis screening and prevention could significantly influence appropriate diagnosis and management of osteoporosis. Primary, secondary and tertiary prevention measures in men are still delayed due to the lack of consensus regarding the guidelines for the screening of osteoporosis in men but above all for the lack of awareness, not only of patients but also of doctors, on osteoporosis and its potentially debilitating consequences especially in men [34,35]. Considering that osteoporosis in men is responsible for significant morbidity and mortality and that low BMD is a good predictor of future fractures [33], awareness of the benefits of adequate screening for osteoporosis in both men and women is an important goal to achieve.

CONCLUSIONS

There is a scientific and cultural gender bias in clinical practice: men are usually under-screened for osteoporosis and as a consequence undertreated, and they are still disadvantaged by the lack of a proper gender culture. The main clinical challenges are therefore to make both men and women aware of prevention and screening programs and promote a personalized gender-oriented approach [36].

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: MDM, MMS, MP, GP, LG. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Methodology: all authors. Project administration: MDM, MMS, LG. Resources: MDM, MMS, LG. Software: all authors. Supervision: MDM, MMS, MP, GP, LG. Validation: MDM, MMS, MP, GP, LG. Visualization: all authors. Writing – original draft: all authors. Writing – review & editing: MDM, MMS, MP, GP, LG.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

REFERENCES

1. Akkawi I, Zmerly H. Osteoporosis: current concepts. Joints 2018;6:122-7.
2. Maggi S, Noale M, Giannini S, Adami S, Defeo D, Isaia G, et al.; ESOPO Study Group. Quantitative heel ultrasound in a population-based study in Italy and its relationship with fracture history: the ESOPO study. Osteoporos Int 2006;17:237-44.
3. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007;22:465-75.
5. De Martinis M, Sirufo MM, Suppa M, Ginaldi L. IL-33/IL-31 axis in osteoporosis. Int J Mol Sci 2020;21:1239.
6. De Martinis M, Ginaldi L, Sirufo MM, Pioggia G, Calapai

G, Gangemi S, et al. Alarmins in osteoporosis, RAGE, IL-1, and IL-33 pathways: a literature review. Medicina (Kaunas) 2020;56:138.
7. Qadir A, Liang S, Wu Z, Chen Z, Hu L, Qian A. Senile osteoporosis: the involvement of differentiation and senescence of bone marrow stromal cells. Int J Mol Sci 2020;21:349.
8. De Martinis M, Di Benedetto MC, Mengoli LP, Ginaldi L. Senile osteoporosis: Is it an immune-mediated disease? Inflamm Res 2006;55:399-404.
9. Ginaldi L, Di Benedetto MC, De Martinis M. Osteoporosis, inflammation and ageing. Immun Ageing 2005;2:14.
10. Shetty S, John B, Mohan S, Paul TV. Vertebral fracture assessment by dual-energy X-ray absorptiometry along with bone mineral density in the evaluation of postmenopausal osteoporosis. Arch Osteoporos 2020;15:25.
11. Ginaldi L, De Martinis M, Saitta S, Sirufo MM, Mannucci C, Casciaro M, et al. Interleukin-33 serum levels in postmenopausal women with osteoporosis. Sci Rep 2019;9:3786.
12. Stein E, Shane E. Secondary osteoporosis. Endocrinol Metab Clin North Am 2003;32:115-34, vii.
13. De Martinis M, Sirufo MM, Nocelli C, Fontanella L, Ginaldi L. Hyperhomocysteinemia is associated with inflammation, bone resorption, vitamin B12 and folate deficiency and MTHFR C677T polymorphism in postmenopausal women with decreased bone mineral density. Int J Environ Res Public Health 2020;17:4260.
14. Bliuc D, Alarkawi D, Nguyen TV, Eisman JA, Center JR. Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: the Dubbo osteoporosis epidemiology study. J Bone Miner Res 2015;30:637-46.
15. Dy CJ, Lamont LE, Ton QV, Lane JM. Sex and gender considerations in male patients with osteoporosis. Clin Orthop Relat Res 2011;469:1906-12.
16. Bor A, Matuz M, Gyimesi N, Biczók Z, Soós G, Doró P. Gender inequalities in the treatment of osteoporosis. Maturitas 2015;80:162-9.
17. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al.; Endocrine Society. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:1802-22.
18. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929-36.
19. Ginaldi L, De Martinis M. Osteoimmunology and beyond. Curr Med Chem 2016;23:3754-74.
20. Siris E, Delmas PD. Assessment of 10-year absolute fracture risk: a new paradigm with worldwide application. Osteoporos Int 2008;19:383-4.
21. Puth MT, Klaschik M, Schmid M, Weckbecker K, Münster E. Prevalence and comorbidity of osteoporosis: a cross-sectional analysis on 10,660 adults aged 50 years and older in Germany. BMC Musculoskelet Disord 2018;19:144.
22. Sirufo MM, Suppa M, Ginaldi L, De Martinis M. Does allergy break bones? Osteoporosis and its connection to allergy. Int J Mol Sci 2020;21:712.
23. Irelli A, Sirufo MM, Scipioni T, De Pietro F, Pancotti A, Ginaldi L, et al. mTOR links tumor immunity and bone metabolism: What are the clinical implications? Int J Mol Sci 2019;20:5841.
24. Irelli A, Sirufo MM, Scipioni T, De Pietro F, Pancotti A, Ginaldi L, et al. Denosumab in breast cancer patients receiving aromatase inhibitors: a single-center observational study of effectiveness in adjuvant setting. Indian J Cancer 2020. doi: 10.4103/ijc.IJC_16_20 [Epub].
25. Irelli A, Sirufo MM, Scipioni T, De Pietro F, Pancotti A, Ginaldi L, et al. Breast cancer patients receiving denosumab during adjuvant aromatase inhibitors treatment: Who are the "inadequate responders" patients to denosumab? J BUON 2020;25:648-54.
26. Alswat K, Adler SM. Gender differences in osteoporosis screening: retrospective analysis. Arch Osteoporos 2012;7:311-3.
27. Adler RA. The need for increasing awareness of osteoporosis in men. Clin Cornerstone 2006;8 Suppl 3:S7-13.
28. US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, et al. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. JAMA 2018;319:2521-31.
29. Lewiecki EM, Compston JE, Miller PD, Adachi JD, Adams JE, Leslie WD, et al. Official positions for FRAX® bone mineral density and FRAX® simplification from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®. J Clin Densitom 2011;14:226-36.
30. Nuti R, Brandi ML, Checchia G, Di Munno O, Dominguez L, Falaschi P, et al. Guidelines for the management of osteoporosis and fragility fractures. Intern Emerg Med 2019;14:85-102.
31. De Martinis M, Sirufo MM, Ginaldi L. Osteoporosis: current and emerging therapies targeted to immunological checkpoints. Curr Med Chem 2019. doi: 10.2174/0929867326666190730113123 [Epub].
32. Salamanna F, Giardino R, Fini M. Spontaneous osteoclastogenesis: hypothesis for gender-unrelated osteoporosis screening and diagnosis. Med Hypotheses 2017;109:70-2.
33. De Martinis M, Sirufo MM, Suppa M, Di Silvestre D, Ginaldi L. Sex and gender aspects for patient stratification in allergy

prevention and treatment. Int J Mol Sci 2020;21:1535.
34. Sirufo MM, Ginaldi L, De Martinis M. Bone health risks associated with finasteride and dutasteride long-term use. World J Mens Health 2020. doi: 10.5534/wjmh.200138 [Epub].
35. Papaioannou A, Kennedy CC, Cranney A, Hawker G, Brown JP, Kaiser SM, et al. Risk factors for low BMD in healthy men age 50 years or older: a systematic review. Osteoporos Int 2009;20:507-18.
36. Irelli A, Sirufo MM, D'Ugo C, Ginaldi L, De Martinis M. Sex and gender influences on cancer immunotherapy response. Biomedicines 2020;8:232.