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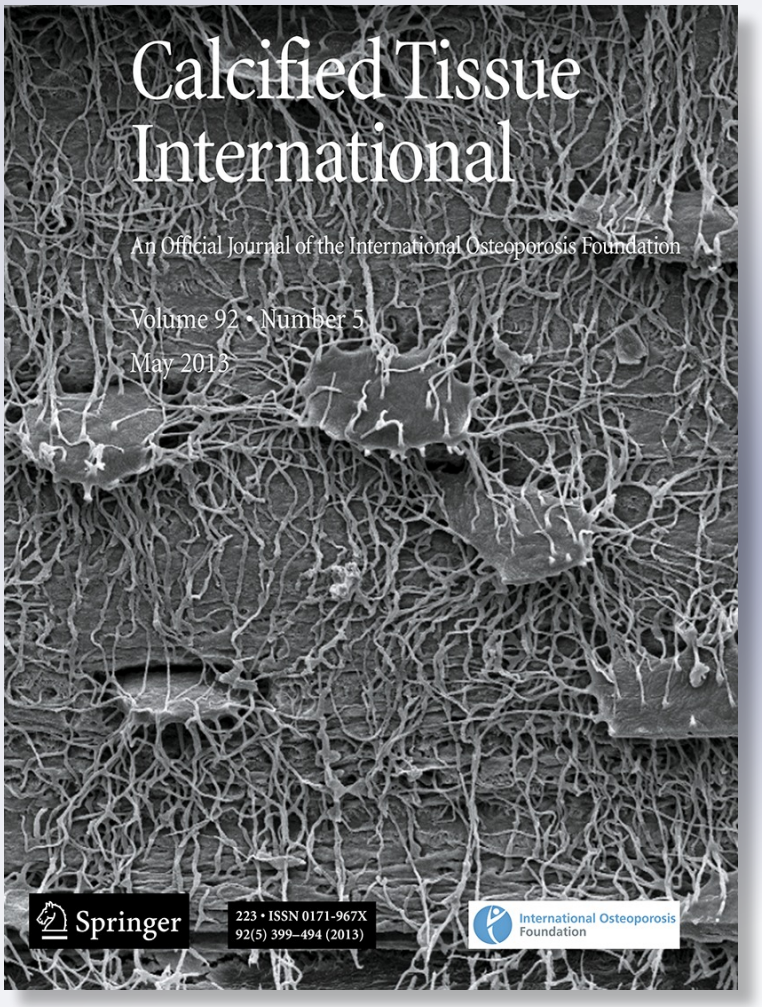

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ORIGINAL RESEARCH

Prevalence of Postmenopausal Osteoporosis in Italy and Validation of Decision Rules for Referring Women for Bone Densitometry

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Abstract We report the prevalence of osteoporosis, osteopenia, and fractures in a cohort of Italian women randomly recruited among the general population and validate the use of clinical guidelines in referring women for bone density testing. We enrolled in the study 995 healthy women (age range 45–92 years). A bone density test at the lumbar spine and femur was performed and a questionnaire on osteoporosis risk factors completed for all patients. The prevalence of osteoporosis was 33.67 %, that of osteopenia was 46.63, and 19.7 % were normal at bone density testing. Osteoporotic women were generally older and thinner, with a shorter period of estrogen exposure. The prevalence of fractures was 21.9 %, and fractured women had a lower bone density, were older, and had a longer postmenopausal period. Clinical guidelines for referring women for bone density testing performed poorly (the best performance was 68 %). This is the first study providing data on the prevalence of osteoporosis/osteopenia and of fractures in a cohort of healthy postmenopausal women. Known risk factors influence bone density and risk of fractures. The role of screening in detecting women with postmenopausal osteoporosis is far from optimal.

Keywords Osteoporosis · Fracture · Risk factor · Screening test

The authors have stated that they have no conflict of interest.

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Primary osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with an increased fracture risk. Major osteoporotic fractures are a social and economic burden; in developed countries, the lifetime risk for osteoporotic fractures at the wrist, hip, or spine is 30–40 %, very close to that for coronary heart disease. It has been estimated that, in the year 2000, there were some 9.0 million osteoporotic fractures worldwide [1]; in Italy we reported recently a prevalence of major osteoporotic fractures of about 34 % in a cohort of 4,000 women [2]. The number of postmenopausal women living with osteoporosis was predicted to increase from 1.8 million in 2010 to 2.1 million in 2020 (+16.5 %) in the United Kingdom; this will be associated with an increase in the number of fractures of between 16 and 18 % [3].

There is a well-established relationship between bone mineral density (BMD) and the ability of bone to withstand trauma, such that 60–70 % of the variance in bone strength depends on BMD [4–6]. Fracture risk increases 1.5- to 3-fold for each standard deviation (SD) fall in BMD [4]; osteoporosis was defined on the basis of BMD assessment by the World Health Organization in 1994 [7], so the assessment of this parameter is still a crucial point for the diagnosis of osteoporosis. Nevertheless, there are poor data in the literature about osteoporosis prevalence as diagnosed by bone densitometry [8–12].

Several risk factors, both modifiable and not, are implicated in favoring postmenopausal bone loss. Among the nonmodifiable factors important predictors of bone demineralization are age, sex, period of amenorrhea [8, 9], and parental history of fracture [10]. Important modifiable factors are dietary calcium intake [11–16], low body mass index [8, 17, 18], smoking [19–21], reduced physical activity [22, 23], and high alcohol intake [24, 25];

nevertheless, their role in determining who should have BMD measurement is yet poorly validated.

The indiscriminate application of bone densitometry to a wide number of women causes an important increase in costs and may produce overtreatment. It has been shown that screening postmenopausal osteoporosis is cost-effective, but until now the best strategy to screen women at risk for osteoporosis has not been clear [26].

The evaluation of risk factors is important in predicting bone loss, and various algorithms for the assessment of risk factors have been used to define patients to screen for osteoporosis [27]. We developed a score named AMMEB (Age, Years after Menopause, Age at Menarche, Body Mass Index [BMI]) to screen patients at risk for osteoporosis [28]. In this article we report the prevalence of osteoporosis and osteopenia in a cohort of Italian women randomly recruited among the general population and validate the use of AMMEB as a reliable tool in prescribing BMD testing.

Methods

The study was approved by the Clinical Study Review Committee of the San Giovanni Battista Hospital (Turin, Italy), and all patients signed an informed consent statement prior to recruitment.

Subject Enrollment

We enrolled patients from a general practitioner list; in particular, we asked each physician enrolled in the study (32 doctors participated) to send to the center their patients according to a randomization list sent from the center. Each doctor was required to send a number of patients that corresponded to 15 % of their cohort of patients; if the adherence was lower than 85 %, the general practitioner was dropped from the study.

The inclusion criteria were female sex and menopause (defined as absence of the menstrual cycle for at least 1 year).

The exclusion criteria were as follows: use of drugs active on bone metabolism such as calcium and vitamin D, bisphosphonates, SERMs, PTH (1–84 or 1–34), glucocorticoids, antiepileptics, estrogens, and chemotherapies; illness that influences bone turnover such as hyperthyroidism, diabetes, celiac disease, hyperparathyroidism, Cushing disease, cancer; mental inability to give consent; and inability to perform bone densitometry (no consent, obesity, inability to walk, etc.).

We enrolled in the study 1,030 women, of whom 35 (3.9 %) were dropped because of violation of inclusion or exclusion criteria.

Risk Factors for Osteoporosis and General Health

All patients answered a questionnaire on risk factors for osteoporosis. Age, years since menopause, smoking habits, regular alcohol consumption, weekly exercise, prevalent illnesses, and drug consumption were recorded during a personal interview on a questionnaire previously used [28–30]. Routine physical activity was anamnestically recalled and defined as less than 30 min, 30–60 min, and more than 1 h daily. Smokers were classified as current (number of cigarettes recorded) or past.

Eating habits were evaluated using a semiquantitative food-frequency questionnaire [29, 30], and weekly calcium intake was recorded.

Presence of fractures was anamnestically recalled; fragility fractures were defined as fractures that occurred as a result of normal activities, such as a fall from standing height or less.

The weight and height of women wearing light indoor clothing and no shoes were measured to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as usual as weight in kilograms divided by height in square meters.

In order to evaluate general health, activities of daily living (ADL) and perceived health status were recorded.

Bone Density and Screening Tests

BMD was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic (Bedford, MA) QDR 4500 at the lumbar spine and femoral neck. We considered osteoporotic those patients with a BMD *T* score of −2.5 SD or less, normal those patients with a BMD *T* score of −1.0 SD, and osteopenic those patients with a BMD *T* score between −1.0 and −2.5 SD, according to the World Health Organization [7].

Bone scans were performed by three operators; stability of the DXA scanner was ensured by daily quality control performed by means of a phantom, according to the manufacturer's instructions. The in vitro coefficient of variation calculated during a year (295 measurements) ranged 3.1–3.3 % intraobserver and was 3.0 % interobserver.

National Osteoporosis Foundation (NOF) recommendation, the Osteoporosis Risk Assessment Instrument (ORAI), and the Osteoporosis Self-Assessment Tools (OST) scores and weight criterion were applied to this population [31–34]. In order to validate the AMMEB score [28], we applied also this score (Table 1). Receiver operating characteristic (ROC) curves were plotted for each method to determine the area under the ROC curve (AUROC) at each threshold score [31].

Statistics

Statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL), and graphs were drawn by GraphPad (La Jolla, CA) Prism, version 3.0.

Table 1 Clinical decision rules for BMD testing among postmenopausal women

Guideline/rule	Selection cut point	Scoring system
National Osteoporosis Foundation (NOF)	Score ≥1	1 point each for:
		Age ≥65
		Weight <57.6
		Minimal trauma fracture >40 years
		Family history of fractures
		Current cigarette smoking
Osteoporosis Self-Assessment Tools (OST)	<2	Equation: 0.2 × (weight in kg − age in years) truncated to yield an integer
Osteoporosis Risk Assessment Instrument (ORAI)	>8	Age (years): 15 if 75+, 9 if 65–74, 5 if 55–64, 0 if 5–55
		Weight (kg): 9 if <60, 3 if 60–69.9
		Estrogen: 2 if not currently taking
Weight criterion	Body weight <70 kg	High risk if body weight <70 kg
Age, Years after Menopause, Age at Menarche, BMI (AMMEB)	Score ≥10	Age (years): 15 if 75+, 9 if 65–74, 5 if 55–64, 0 if ≤55
		BMI: 6 if <20, 2 if 20–23, 1 if 24–26, 0 if >26
		Age at menarche: 0 if <11, 1 if 11–13, 6 if >13
		Postmenopausal period: 5 if >16, 3 if 12–16, 1 if 5–11, 0 if <5

Osteoporotic, osteopenic, and normal patients were compared for age, postmenopausal period, age at menarche, period of estrogen exposure, number of pregnancies and deliveries, BMI, number of cigarettes per day, dietary calcium, and alcohol intake by one-way ANOVA.

The distribution of categorical variables (smoking habit, family history of fragility fractures before the age of 75, presence and type of fractures) was analyzed by the χ^2 test.

NOF guidelines, ORAI, OST score, weight criterion, and AMMEB score were applied to our population; ROC curves were plotted for each method to determine the AUROC at each threshold score.

In all statistical analyses the result was considered significant at $p \leq 0.05$.

Results

A total of 1,030 women were sent to the center by their physicians, of whom 995 (96.6 %) were enrolled in the study and included in the analyses; the mean age was not significantly different among the women included (65 ± 8 years) and excluded (63 ± 9 years) from the study. The age of included women ranged 45–92 years.

Prevalence of Osteoporosis and Osteopenia and Patient Characteristics

Three hundred and thirty-five subjects were osteoporotic (33.67 %), 464 were osteopenic (46.63 %), and 196 were normal (19.7 %). Osteoporotic and osteopenic patients were generally older, with a longer postmenopausal period, a shorter period of exposure to estrogens, and lower BMI compared to normal subjects; calcium and alcohol intake, number of cigarettes smoked, physical activity, and family history of fractures were not significantly different in the three categories (Table 2).

Screening Tests and Bone Density

All applied screening tests were significantly different among the three categories (Table 3).

Comparison between the AUROCs of the five scores showed that all performed poorly in finding osteoporotic patients (AUROCs ranged between 0.32 and 0.68), the two best-performing scores were ORAI and AMMEB (Fig. 1).

Prevalence of Fractures and Patient Characteristics

Nine hundred and thirty-six women answered the question on previous fractures, with 211 reporting a fracture (21.9 %). There were no significant differences in the incidence of fractures (due to high- or low-energy trauma) according to different densitometric features (Fig. 2a), but there was a significant difference in the site of fracture (Fig. 2b). The most frequent fracture site was the wrist (46 % of all fractures).

Fractured patients were on average older and had a longer postmenopausal period and lower femoral density (Table 4).

Table 2 Subject characteristics in the three densitometric categories

	Osteoporotic ($n = 335$)	Normal ($n = 196$)	Osteopenic ($n = 464$)	p
Age (years)	67 ± 9	62 ± 7	64 ± 8	0.000
Postmenopausal period (years)	18 ± 10	11 ± 8	15 ± 9	0.000
Menarche (years)	13 ± 2	13 ± 1	13 ± 2	NS
Period of exposition to estrogens (years)	36 ± 5	38 ± 5	36 ± 5	0.002
BMI	23.8 ± 4.4	27.3 ± 5	25.9 ± 4.8	0.000
Age at menarche (years)	13 ± 2	13 ± 1	13 ± 2	NS
Calcium intake (mg/day)	902.9 ± 482.7	1,544.1 ± 620.3	2,529.1 ± 1,593	NS
Cigarettes/day	12 ± 6	12 ± 5	11 ± 6	NS
Alcohol (g/day)	8.68 ± 0.6	8.9 ± 0.8	7.95 ± 0.52	NS
Familiar history of fractures (%)	41.7	33.1	43.12	NS
Active smokers (%)	14.1	16.9	14.2	NS
Sun exposure (%)	70.2	74	76	NS
Physical activity <30 min/day (%)	28	18.3	20.1	NS
Physical activity 30–60 min/day (%)	40.4	45	42.5	NS
Physical activity 1–2 h/day (%)	21.3	25.7	24.5	NS
Physical activity >2 h/day (%)	10.3	11	12.9	NS

Numerical variables are expressed as mean and SD, p values were obtained by one-way ANOVA; categorical variables are expressed as percentage, p values were obtained by χ^2 test

NS nonsignificant

Table 3 Clinical decision rules for BMD testing among the three densitometric categories

	Osteoporotic ($n = 335$)	Normal ($n = 196$)	Osteopenic ($n = 464$)	p
NOF guidelines	1.76 ± 1.1	1.12 ± 0.9	1.5 ± 0.98	0.000
ORAI score	18.48 ± 5.8	12.96 ± 4.87	15.6 ± 5.37	0.000
OST score	−1.99 ± 4.01	0.96 ± 3.8	−0.44 ± 3.99	0.000
Weight criterion	60.3 ± 9.7	70.11 ± 11	66.12 ± 11.4	0.000
AMMEB score	15.95 ± 7.38	10.92 ± 6.28	13.37 ± 6.5	0.000

Variables are expressed as mean and SD; p values were obtained by one-way ANOVA and considered significant if <0.05

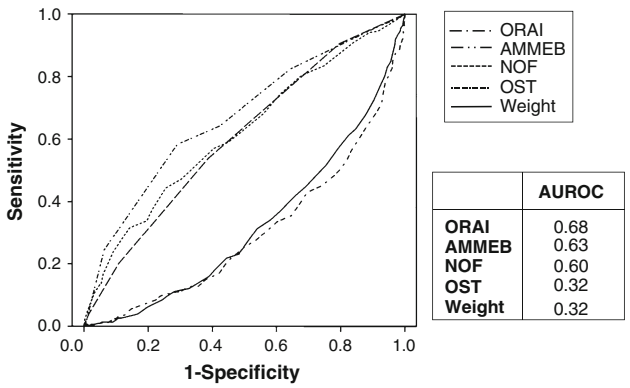

Fig. 1 ROC curves for the clinical decision rules for BMD testing; AUROCs are indicated at *right*. *ORAI* Osteoporosis Risk Assessment Instrument; *AMMEB* Age, Years after Menopause, Age at Menarche, BMI; *NOF* National Osteoporosis Foundation; *OST* Osteoporosis Self-Assessment Tools

Screening Tests and Fractures

All of the screening tests applied except for weight criterion were significantly different in fractured versus nonfractured patients; nevertheless, comparison between the AUROCs of the five scores showed that AMMEB and ORAI (both 0.55) had the best performance, with the other scores performing poorly. The NOF score was not applied because of the presence of fracture evaluation within the score.

ADL and General Health

There was no significant difference in perceived health status or in the level of ADL among the different densitometric categories or between fractured and nonfractured patients (data not shown).

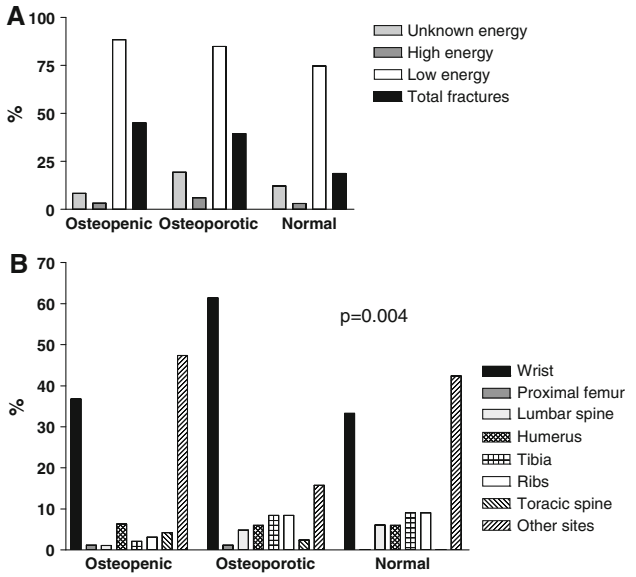

Fig. 2 Graphs showing the prevalence of fractures as distributed according to densitometric testing. **a** Prevalence of fractures in the three categories according to the energy of the impact sustained. **b** Prevalence of fractures in the three categories according to the site of fractures. *p* value was calculated with the χ^2 test

Discussion

Osteoporosis and osteoporotic fractures represent a social and economic burden; several studies have suggested that the incidence of osteoporosis is increasing due to the increase in the aging population. It is estimated that about 75 million people in Europe, the United States, and Japan are affected by osteoporosis; and by the year 2050 this number is expected to increase by 240 % [35]. Osteoporotic fractures have been seen to affect up to one-third of postmenopausal women older than 50 years [36], resulting in considerable mortality, morbidity [37], and cost [38]. Early identification of women at higher risk of developing osteoporosis and, hence, fragility fractures could reduce the economic and social cost of osteoporosis in terms of mortality and morbidity due to fractures. Hence, it is important to develop rapid and low-cost screening tests to identify women in need of bone density tests.

Our study was designed to describe the prevalence of osteoporosis, osteopenia, and fractures in a cohort of healthy Italian women and to assess weather commonly used screening tests and the one previously proposed by our group could be useful in referring women for bone density testing.

Among the 995 women enrolled 33.67 % were osteoporotic, 46.63 % were osteopenic, and 19.7 % were normal; these prevalences are very similar to those previously reported by our group [28]. Whereas osteoporosis and osteopenia are more prevalent in our cohort than in eastern countries [10–12], lifestyle as well as cultural and religious practices may explain this difference. A recent study on Italian women from Pedrazzoni et al. [39] showed a lower prevalence of osteoporosis (17 %), a higher prevalence of osteopenia (62 %), and a similar prevalence of normal bone density (21 %) with respect to the present study, these discrepancies may be due to the bone scan site chosen. We measured both the lumbar spine and femoral neck, whereas Pedrazzoni and colleagues measured only the femoral neck; thus, site-specific differences in BMD may explain the different data obtained [40].

Osteoporotic and osteopenic women were generally older, with a longer postmenopausal period and a shorter period of exposure to estrogens, and had lower BMI compared to normal subjects; calcium and alcohol intake, number of cigarettes smoked, physical activity, and family history of fractures were not significantly different in the three categories.

Table 4 Subject characteristics, fractured and nonfractured

	Nonfractured ($n = 725$)	Fractured ($n = 211$)	*p*
Age (years)	64 ± 8	66 ± 9	0.001
Postmenopausal period (years)	14 ± 9	17 ± 10	0.003
Period of exposure to estrogens (years)	36 ± 5	38 ± 5	NS
BMD total femur (g/cm^2)	0.782 ± 0.128	0.737 ± 0.119	0.001
Age at menarche (years)	13 ± 2	13 ± 1	NS
BMD femoral neck (g/cm^2)	0.650 ± 0.106	0.610 ± 0.101	0.000
BMI	25.6 ± 4.7	25.3 ± 5	NS
Calcium intake (mg/day)	2,102.3 ± 1,037.4	902.7 ± 419.8	NS
Cigarettes/day	12 ± 6	12 ± 6	NS
Alcohol (g/day)	8.13 ± 10.5	9.3 ± 11.8	NS
Family history of fractures (%)	39.8	46.11	NS
Active smokers (%)	16.3	13.1	NS
Sun exposure (%)	74	73	NS
Physical activity <30 min/day (%)	22.1	23.5	NS
Physical activity 30–60 min/day (%)	43.3	39	NS
Physical activity 1–2 h/day (%)	22.6	28.6	NS
Physical activity >2 h/day (%)	12	8.9	NS

Numerical variables are expressed as mean and SD, *p* values were obtained by one-way ANOVA; categorical variables are expressed as percentage, *p* values were obtained by χ^2 test

NS nonsignificant

With respect to our previous study in a smaller cohort [28], we did not find a significant difference in age at menarche among the different densitometric categories or between fractured and nonfractured patients; nevertheless, we found a significant difference in years of exposure to estrogens.

The prevalence of fractures in our cohort was 21.9 %. We did not find a higher prevalence of fractures in women diagnosed as osteoporotic or osteopenic according to standard reference values, even though fracture patients had significantly lower values of femoral BMD. This observation confirms the importance of a decrease in BMD together with the presence of other risk factors such as age and postmenopausal period.

Regarding the fracture site, there was a significant difference according to the presence or absence of osteoporosis or osteopenia; in patients with low BMD it is more likely to find typical osteoporotic fractures, such as wrist, lumbar spine, and proximal femur fractures, whereas in osteopenic and normal subjects it is more likely to find fractures at other sites. These fractures are probably due to higher-impact events. The only risk factors significantly different between fractured and nonfractured patients were age and postmenopausal period. The main study pitfall is the probable underestimation of vertebral fractures as we detected only clinical fractures (by anamnesis) and did not perform spinal X-rays. It is known that only one-fourth to one-third of incident, radiographically identified vertebral fractures are clinically diagnosed [41]; hence, it is reasonable to suppose an underestimation of vertebral fractures in our cohort.

The use of clinical guidelines to refer women to bone density testing performed poorly in detecting osteoporotic women (AUROCs ranged 0.32–0.68); the better scores were ORAI and AMMEB (AUROCs 0.68 and 0.63, respectively). The performance of these scores in detecting fractures was even poorer.

In conclusion, this study provides data on the prevalence of osteoporosis, osteopenia, and fractures in a cohort of healthy postmenopausal women. We evaluated the role of risk factors in determining bone density and risk of fractures. We also evaluated the role of screening test in detecting women with postmenopausal osteoporosis. Even though the performance of the screening tests was far from optimal, the use of clinical guidelines to identify patients at higher risk for bone loss may be cost-effective [26, 34].

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