Prevalence of postmenopausal osteoporosis in Italy and validation of decision rules for referring women for bone densitometry.

Prevalence of post menopausal osteoporosis in Italy and validation of decision rules for referring women for bone densitometry.

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Running title: screening tests for osteoporosis.

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Mini abstract: This paper reports the prevalence of osteoporosis, osteopenia and fractures in 995 healthy women: osteoporotic were 33.67%, osteopenic 46.63% and 19.7% normal at bone density test. The prevalence of fractures was 21.9%, clinical guidelines used for referring women to bone density test performed poorly.

ABSTRACT

Purpose. This paper reports the prevalence of osteoporosis, osteopenia and fractures in a cohort of Italian women randomly recruited amongst the general population and validates the use clinical guidelines in referring women to bone density test.

Methods. We enrolled in the study 995 healthy women (age range: 45-92 years). A bone density test at lumbar spine and femur was performed and a questionnaire on osteoporosis risk factors was performed in all the patients.

Results. The prevalence of osteoporosis was 33.67%, osteopenia 46.63% whereas 19.7% were normal at bone density test. Osteoporotic women were generally older, thinner with a shorter period of estrogen expositions. The prevalence of fractures was 21.9%, fractured women have a lower bone density, were older with longer post-menopausal period.

Clinical guidelines for referring women to bone density test performed poorly (the best performance was 68%).

Conclusions. 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 influences bone density and risk of fractures.

The role of screening test in detecting women with postmenopausal osteoporosis is far from optimal.

Key words: osteoporosis, fracture, risk factors, screening test.

INTRODUCTION

Primary osteoporosis is a skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with an increased fracture risk. Major osteoporotic fracture are a social and economic burden, in developed countries, the lifetime risk for osteoporotic fractures at the wrist, hip or spine is 30% to 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 4000 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 UK, this will be associated with an increase in the number of fractures 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 1.5-3 fold for each standard deviation (SD) fall in BMD [4]; osteoporosis was defined on the basis of bone mineral density (BMD) assessment by the WHO 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 literature about osteoporosis prevalence as diagnosed by bone densitometry [8-12].

Several risk factors, both modifiable or not, are implied in favouring postmenopausal bone loss. Among non-modifiable 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 over treatment. It has been showed that screening post-menopausal osteoporosis is cost effective, but, until now, it is not clear which is the best strategy to screen women at risk for osteoporosis [26].

The evaluation of risk factors is important in predicting bone loss and various algorithms implying the assessment of risk factors have been used to define patients to screen for osteoporosis [27]. We developed a score named AMMEB to screen patients at risk for osteoporosis [28], in this paper we analyse the prevalence of osteoporosis and osteopenia in a cohort of Italian women randomly recruited amongst the general population and validated 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, Torino, and all patients signed an informed consent statement prior to recruitment.

Subjects enrollement.

We enrolled the patients from the general practitioner list, in particular we asked each physician enrolled in the study (32 doctors participates) to send to the centre their patients according to a randomization list sent from the centre.

Each doctor was required to send a number of patients that corresponds to 15% of their cohort of patients, if the adhesion was lower than 85% the general practitioner was dropped from the study.

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

The exclusion criteria were:

-use of drugs active on bone metabolism as calcium and vitamin D, bisphosphonates, SERMs, PTH (1-84 or 1-34), glucocorticoids, antiepileptics, estrogens, chemotherapies, etc

-illness that influences bone turnover as hyperthyroidism, diabetes, celiac disease, hyperparathyroidism, Cushing disease, cancer, etc.

-mental inability to give the consent

-inability to perform bone densitometry (no consent, obesity, inability to walk, etc).

We enrolled in the study 1030 women, 35 women (3.9%) were dropped because of violation of inclusion/exclusion criteria.

Risk factors for osteoporosis and general health.

All the 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]. Routinary physical activity was anamnestically recalled and defined as inferior to half an hour, between half an hour and an hour and more than one hour daily. Smokers were classified as: current (number of cigarettes recorded) or past.

The eating habits were evaluated using a semi-quantitative Food Frequency Questionnaire (FFQ) [29, 30] and weekly calcium intake was recorded.

Presence of fractures was anamnestically recalled, fragility fractures were defined as fractures that occur as 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. Body mass index (BMI) was calculated as usual as weight in kg divided by height in m^2.

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

Bone density and screening tests.

Bone mineral density was measured by Dual energy X-ray Absorptiometry (DXA) by means of a Hologic QDR 4500 at lumbar spine and femoral neck.

We considered osteoporotic those patients with a BMD T-score value of -2.5 S.D. or less, normal those patients with a BMD T-score value of –1.0 S.D. and osteopenic those patients with a BMD T-score value between –1.0 to –2.5 S.D., according to WHO [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 manufacturer instruction. The in vitro coefficient of variation calculated during a year (295 measurement) ranged between 3.1 to 3.3% intra observer, and was 3.0% inter observer.

NOF recommendation, Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Self-Assessment Tools (OST) scores and weight criterion have

been applied to this population [31-34]. In order to validate the AMMEB score we have previously proposed [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

The statistics were performed using SPSS 17.0 for Windows and graphs were drawn by Graph Pad PRISM version 3.0.

Osteoporotic, osteopenic and normal patients were compared for age, postmenopausal period, age at menarche, period of estrogen exposition, 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 were analyzed by 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 area under the AUROC at each threshold score.

In all the statistical analyses performed the result was considered significant if the p value was equal or lower than 0.05.

RESULTS

A total of 1030 women were sent to the centre by their physicians, of which 995 (96.6%) were enrolled in the study and included in the analyses, the

mean age was not significantly different amongst the women included (65±8, years) and excluded (63±9, years) from the study.

The age of included women ranges between 45 and 92 years.

Prevalence of osteoporosis and osteopenia and patients' characteristic.

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

Screening tests and bone density.

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

The comparison between the AUROCs of the 5 scored applied showed that all the applied scores performed poorly in finding osteoporotic patients (AUROCs ranged between 0.32 to 0.68), the two more performant scores were ORAI and AMMEB scores (Fig.1).

Prevalence of fractures and patients' characteristic.

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

Fractured patients were on average older, had a longer post-menopausal period and lower femoral density (Table 4).

Screening tests and fractures.

All the screening tests applied except for weight criterion are significantly different in fractured as respect to non fractured patients, nevertheless the comparison between the AUROCs of the 5 scored applied showed that AMMEB and ORAI scores (both 0.55) have the best performance, the other scores performed poorly. NOF score was not applied for the presence of fracture evaluation within the score.

ADL and general health.

There was not a significant difference in perceived health status nor in the level of ADL amongst the different densitometric categories, nor in fractured and non fractured patients (data not shown)

DISCUSSION

Osteoporosis and osteoporotic fractures represent a social and economic burden; several studies 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 the postmenopausal women older than 50 yr [36], resulting in considerable mortality, morbidity [37], and cost [38]. The early identification of women at higher risk to develop 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 find out rapid and low cost screening tests to address women to 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 asses weather commonly used screening tests and the one previously proposed by our group could be useful to address women to bone density tests.

Amongst the 995 women enrolled 33.67% were osteoporotic, 46.63% osteopenic and 19.7% 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%), higher of osteopenia (62%), and similar of normal bone density (21%) as respect to the present study, this discrepancy may be

due to the site of bone scan chosen, we measured both lumbar spine and femoral neck whereas Pedrazzoni and colleagues measured only femoral neck; thus site-specific differences in BMD may explain the different data obtained [40].

Osteoporotic and osteopenic were generally older, with longer post-menopausal period and shorter period of exposition to estrogens and had lower BMI as compared to normal subjects; calcium and alcohol intake, number of smoked cigarettes, physical activity and familiar history of fractures were not significantly different in the three categories.

As respect to our previous study in a smaller cohort [28] we do not find significant difference in the age of menarche amongst the different densitometric categories, nor amongst fractured and non fractured patients, nevertheless we find a significant difference in the years of exposition to estrogens.

The prevalence of fractures in our cohort was 21.9%, we do not find a higher prevalence of fractures in women diagnosed as osteoporotic/osteopenic according with standard reference values, even though fracture patients have significantly lower values of femoral BMD, this observation confirms the importance of a decrease in BMD together with the presence of other risk factors as age and post menopausal period.

As regards the fracture site there was a significant difference according with the presence/absence of osteoporosis/osteopenia, in patients with low BMD it is more likely to find typical osteoporotic fractures as wrist, lumbar spine and proximal femur fractures, whereas in osteopenic and normal subjects it is

more likely to find fractures in other sites. These fractures are probably due to higher impact energy. The only risk factors significantly different between fractured and non fractured patients were age and post-menopausal period. The main study pitfall is the probable underestimation of vertebral fractures, as we detect only clinical fractures (by anamnesis) and do not performed spine X-ray. 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 under estimation of vertebral fracture in our cohort.

The use of the clinic guidelines to address women to bone density test performed poorly in detecting osteoporotic women AUROCs ranged between 0.32 and 0.68, however the better scores were ORAI and AMMEB (AUROC 0.68 and 0.63 respectively). The performance of these score in detecting fractures is even poorer.

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

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TABLES.

Table 1. Clinical decision rules for bone mineral density testing among postmenopausal women.

Guideline/rule	Selection cut point	Scoring system
National Osteoporosis Foundation (NOF)	Score equal or more than 1	1 point each for: Age > or =65 Weight < 57.6 Minimal trauma fracture > 40 years Family history of fractures Currently cigarette smoking
Osteoporosis Self-Assessment Tools (OST)	<2	Equation = 0.2x (weight in Kg x – 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 equal or lower than 55 Weight (Kg): 9 if <60, 3 if 60-69.9 Estrogen: 2 if not current taking
Weight criterion	Body weight < 70 Kg	High risk if body weight < 70 Kg
Age, years after Menopause, age at MEnarche, BMI (AMMEB)	Score equal or more than 10	Age (years): 15 if 75+, 9 if 65-74, 5 if 55-64, 0 if equal or lower than 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.

Table 2. Subjects characteristics in the three densitometric categories. 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 $\chi 2$ Test.

	Osteoporotic (335)	**Normal** (196)	**Osteopenic** (464)	**p**
Age (yrs)	67±9	62±7	64±8	0.000
Post menopausal period (yrs)	18±10	11±8	15±9	0.000
Menarche (yrs)	13±2	13±1	13±2	NS
Period of exposition to estrogens (yrs)	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 (yrs)	13±2	13±1	13±2	NS
Calcium intake (mg/day)	902.9±482.7	1544.1±620.3	2529.1±1593	NS
Cigarettes/day	12±6	12±5	11±6	NS
Alcohol (gr/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 exposition (%)	70.2	74	76	NS
Physical activity inferior to 30'/day	28	18.3	20.1	NS
Physical activity between 30' and 1 hour day	40.4	45	42.5	NS
Physical activity between 1 and 2 hours day	21.3	25.7	24.5	NS
Physical activity higher than 2 hours day	10.3	11	12.9	NS

Table 3. Clinical decision rules for bone mineral density testing among the three densitometric categories. Variables are expressed as mean and SD, p values were obtained by one way ANOVA and considered significant if lower than 0.05.

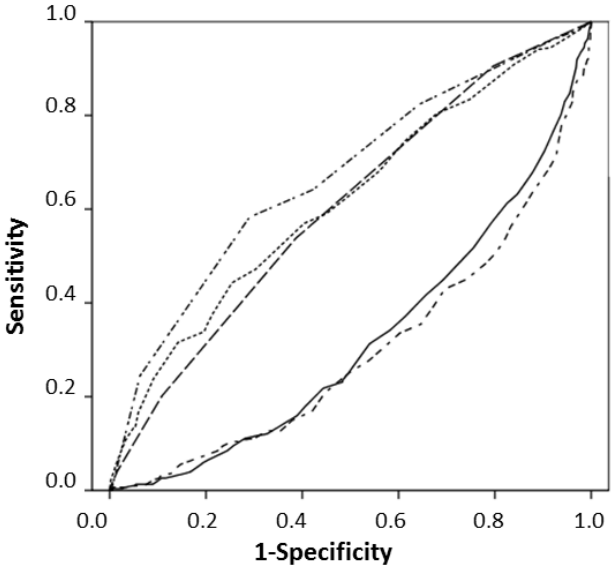
	Osteoporotic (335)	**Normal** (196)	**Osteopenic** (464)	**P**
NOF guidelines	1.76±1.1	1.12±0.9	1.5±0.98	0.000
ORAI score	18.48±5.8	12.96±4.87	15.6±5.37	0.000
OST score	-1.99±4.01	0.96±3.8	-0.44±3.99	0.000
Weight criterion	60.3±9.7	70.11±11	66.12±11.4	0.000
AMMEB score	15.95±7.38	10.92±6.28	13.37±6.5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

Table 4. Subjects characteristics amongst fractured and non fractured. 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 $\chi 2$ Test

	Non fractured (725)	**Fractured** (211)	**p**
Age (yrs)	64±8	66±9	0.001
Post menopausal period (yrs)	14±9	17±10	0.003
Period of exposition to estrogens (yrs)	36±5	38±5	NS
BMD total femur (g/cm2)	0.782±0.128	0.737±0.119	0.001
Age at menarche (yrs)	13±2	13±1	NS
BMD femoral neck (g/cm2)	0.650±0.106	0.610±0.101	0.000
BMI	25.6±4.7	25.3±5	NS
Calcium intake (mg/day)	2102.3±1037.4	902.7±419.8	NS
Cigarettes/day	12±6	12±6	NS
Alcohol (gr/day)	8.13±10.5	9.3±11.8	NS
Familiar history of fractures (%)	39.8	46.11	NS
Active smokers (%)	16.3	13.1	NS
Sun exposition (%)	74	73	NS
Physical activity inferior to 30'/day	22.1	23.5	NS
Physical activity between 30' and 1 hour day	43.3	39	NS
Physical activity between 1 and 2 hours day	22.6	28.6	NS
Physical activity higher than 2 hours day	12	8.9	NS

Figure legends.

Figure 1. ROC curves for the clinical decision rules for bone mineral density testing; AUROCs are indicated in the table.



	AUROC
ORAI	0.68
AMMEB	0.63
NOF	0.60
OST	0.32
Weight	0.32

Figure 2. Graphs shows the prevalence of fractures as distributed according to densitometric test.

Panel A. Prevalence of fractures in the three categories according to the energy of the impact sustained.

Panel B. Prevalence of fractures in the three categories according to the site of fractures. P value is calculated with $\chi 2$ test.