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Clinical Investigations

Effects of Lifestyle and Risk Factors on Bone Mineral Density in a Cohort of Italian Women: Suggestion for a New Decision Rule

P. D'Amelio,[1] C. Tamone,[1] F. Pluviano,[2] M. Di Stefano,[1] G. Isaia[1]

[1]Department of Internal Medicine, University of Torino, Corso Dogliotti 14, 10126-Torino, Italy
[2]Department of Imaging, University of Torino, Corso Dogliotti 14, 10126-Torino, Italy

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Abstract. In this study the authors analyzed the role of risk factors in postmenopausal osteoporosis in a cohort of Italian women and evaluated predictive values of decision rules for early identification of osteoporotic women. Furthermore, the authors investigated the prevalence of secondary osteoporosis in this population. Women who underwent bone densitometry were asked to answer a questionnaire about the common risk factors for osteoporosis. Patients were classified as nonosteoporotic, nonosteopenic, and osteoporotic. Risk factors were compared among the groups by use of analysis of variance (ANOVA). National Osteoporosis Foundation (NOF) recommendation, Osteoporosis Risk Assessment Instruments (ORAIs), Osteoporosis Self-Assessment Tools (OST) score, and weight criterion were applied to this population. The authors proposed a new decision rule based on a new score. A total of 525 women received the questionnaire: 47.4% women were osteoporotic, 32.2% were osteopenic, and 20.4% nonosteoporotic. Risk factors that differed significantly between these groups were: age, age at menarche, postmenopausal period, and body mass index (BMI); the aforementioned risk factors appear to be significant predictors of bone density (BMD) in linear regression model. The incidence of secondary osteoporosis was 13%.In conclusion, the authors (1) confirmed the role played by nonmodifiable risk factors in determining BMD; (2) showed that the use of NOF guidelines, ORAI, OST score, and weight criterion is not satisfactory in our cohort; (3) suggested a new score, based upon the features that were significantly different between patients and controls; and (4) demonstrated the relatively high prevalence of secondary osteoporosis and suggest a primary screening for secondary osteoporosis in all patients with low BMD.

Key words: Bone mineral density — Decision rules — Osteoporosis — Risk factors — Score

Correspondence to: P. D'Amelio; E-mail: patriziadamelio@netscape.net

Postmenopausal osteoporosis has been defined by the 1984 National Institutes of Health Consensus Development Conference as a "systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture." More recently the Consensus Development Conference stated that clinical risk factors-have an important, but, as yet, poorly validated, role in determining who should have bone mineral density (BMD) measurement, in assessing risk of fracture, and in determining who should be treated [1].

Clinical osteoporosis manifestations are fragility fractures and much literature investigates the incidence of fractures most commonly linked to osteoporosis, for example, distal forearm fractures ([2, 3], femoral fractures [4, 5], or vertebral fractures [6–8], whereas there are few data in the literature about osteoporosis prevalence as diagnosed by bone densitometric techniques [9, 10]. In fact, dual energy X-ray absorptiometry (DXA) is accepted as the most accurate clinical method for identifying those with low BMD ("National Institutes of Health Consensus Development Conference, 1984).

Several risk factors, both modifiable or not, are implied in favoring postmenopausal bone loss. Among nonmodifiable factors, important predictors of bone demineralization are age, sex, and period of amenorrhea [11, 12]. Important modifiable factors are dietary calcium intake [13–18], low body mass index (BMI) [11, 19, 20], smoking [21–23], physical activity [24, 25], parental history of fracture [26], and high alcohol intake [27, 28].

There is a well-established relationship between BMD and the ability of bone to withstand trauma, such that 60% to 70% of the variance in bone strength depends on BMD [29]. Fracture risk increases 1.5 to 3-fold for each standard deviation (SD) decrease in BMD [29]. The early identification of women at higher risk for developing osteoporosis, and, hence, fragility fractures could

Table 1. Selection criteria suggested from the National Osteoporosis Foundation (NOF) and four clinical decision rules for bone mineral density testing among peri- and postmenopausal women

Guideline/rule	Selection cutpoint	Scoring system
National Osteoporosis Foundation (NOF)	Score equal or more than 1	1 point each for: Age ≥ 65 years Weight < 57.6 Minimal trauma fracture > 40 years Family history of fractures Currently 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 (y): 15 if 75+, 9 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 (y): 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.

reduce the economic and social cost of osteoporosis in terms of mortality and morbidity linked to fractures. The need for early and correct prescription for bone densitometry led to the research for decision rules useful for clinicians to address women to bone densitometry. The National Osteoporosis Foundation (NOF) 1998 practice guideline (revised in 1999) [30] recommended BMD testing in women aged 65 years or older, and in younger postmenopausal women who have one or more risk factors for osteoporotic fractures other than menopause. On the basis of this guideline, other decision rules have been published in recent years [31-38].

The aim of the present study is to detect the prevalence of postmenopausal and secondary osteoporosis among a cohort of women that came to our department to undergo bone densitometry. The authors analyzed the role of modifiable and non-modifiable risk factors in the development of postmenopausal osteoporosis, and assessed the diagnostic properties of NOF recommendations and of other three decision rules; furthermore, the authors suggested a new decision rule based on a new score developed on the basis of their population features.

Materials and Methods

Women in the postmenopausal period who consequently came to the Department of Internal Medicine of our institution to undergo bone densitometry with DXA from 10 August 2003 to 15 September 2003, were asked to answer a questionnaire on the most relevant risk factors for osteoporosis.

Women in the premenopausal period, men, and in-hospital and day-hospital patients did not receive the questionnaire. Our Bone Metabolic Unit is located in Turin in the north of Italy and the women who reach the center are almost entirely Italian caucasian women whose health issues are addressed by their own physicians, by their gynecologists or by our ambulatory care facility. We performed a median of 1,100 densitometric scans monthly at the center. The patients were asked to sign an informed consent form, the study was approved by a scientific committee, since Italian law does not require ethics committee approved for studies without drugs administration.

A total of 525 caucasian women who agreed to be included were recruited for the study; the questionnaire was administered and the densitometric examination measurements were recorded. We considered those patients as osteoporotic with a BMD T score value of −2.5 standard deviation (SD) or less, the patients with a BMD T score value of −1.0 SD as normal, and the patients with a BMD T score value between −1.0 and −2.5 SD as osteopenic, according to the World Health Organization (WHO) [39]. BMD was measured by DXA by means of a Hologic QDR 4500 at lumbar spine or at femoral neck according to the clinical features of each patient.

The questionnaire administered was the one validated by the ESOPO study [40, 41]. Routine physical activity was anamnestically recalled and defined less than half an hour, between half an hour and an hour, and more than 1 hour daily. Smokers were classified as current or past. Women were considered to be postmenopausal if they had a period of amenorrhea of at least 1 year. To avoid a possible bias caused by drugs active on bone metabolism, a separate analysis excluding patients treated was done.

NOF recommendation, Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Self-Assessment Tools (OST) scores, and weight criterion have been applied to this population. Receiver-operating characteristic (ROC) curves were plotted for each method to determine the area under the ROC curve (AUROC) at each threshold score [38]. Because the AUROC seems to be unsatisfactory, the authors propose a new decision rule called AMMEB. It was developed on the basis of the variables predicting BMD at linear regression model, age, years after menopause, age at menarche, BMI, scores were assigned at age using ORAI scores [38], whereas for postmenopausal period, age at menarche and BMI scores were assigned by rounding the odds ratios estimated to the nearest integer and assigning a score of zero to the reference group [38]. ROC were plotted for each threshold score to determine the AUROC, to ensure that few subjects with a BMD T score of 2 or more SDs below the mean would be missed, threshold score for recommending BMD testing with DXA was chosen to yield 90% sensitivity. Table 1 summarizes

Table 2. Results of analysis of variance (ANOVA) with mean and standard deviations for age, age at menarche, postmenopausal period, years of estrogen exposition, body mass index (BMI), number of pregnancies, number of deliveries, alcohol intake (daily), calcium intake (weekly), lumbar bone mineral density (BMD) and femoral BMD as distributed according to densitometric parameters (osteoporotic, normal, and osteopenic)

	Normal	Osteopenic	Osteoporotic	*P*
Age (yr)	57.3 ± 6.6	60.2 ± 7.8	62.2 ± 6.7	0.000
Age at menarche (yr)	12.3 ± 1.6	12.9 ± 1.7	13 ± 1.6	0.002
Postmenopausal period (yr)	8.4 ± 7.7	11.3 ± 8	13.2 ± 7.9	0.000
Estrogen exposition (yr)	41 ± 43.8	35.7 ± 5	36 ± 4.6	NS
BMI	25.8 ± 4	24.7 ± 3.9	23.5 ± 3.1	0.000
Weight (kg)	66.8 ± 1.6	63.3 ± 11	59 ± 8	0.000
Number of pregnancies	1.8 ± 1.2	1.83 ± 1.5	1.7 ± 1.4	NS
Number of deliveries	1.5 ± 0.9	1.6 ± 1.5	1.4 ± 1	NS
Alcohol intake (mg/day)	11.1 ± 13	10.2 ± 12.5	11.5 ± 13.4	NS
Calcium intake (mg/week)	6525.2 ± 3760.8	5460.9 ± 2798.6	5900.8 ± 3372.2	NS
BMD lumbar (g/cm^2)	1.06 ± 0.1	0.876 ± 0.05	0.717 ± 0.06	0.000
BMD femoral neck (g/cm^2)	0.767 ± 0.08	0.689 ± 0.05	0.583 ± 0.09	0.000

the criteria recommended for use by clinicians in deciding which women should undergo bone densitometry under the NOF guidelines, the above-mentioned decision rules, and AMMEB. In a subpopulation of 132 osteoporotic women not receiving pharmacologic treatment who came to our attention at our outpatient care department, anamnesis, physical examination, and common laboratory studies for calcemia, phosphoremia, serum protein electrophoresis, bone alkaline phosphatase [BAP], parathyroid hormone (PTH), and 25 OH vitamin D were performed to identify secondary osteoporosis; also measurement of bone Gla protein (BGP) and urinary cross-links were performed.

Statistical Analyses

The statistics were performed by using SPSS 8.0 for Windows and Graph Pad PRISM version 3.0. Osteoporotic, osteopenic, and healthy patients were compared according to age, postmenopausal period, age at menarche, period of estrogen exposition, number of pregnancies and deliveries, BMI, number of cigarettes per day, dietary calcium (weekly), and alcohol (daily) intake by one way ANOVA.

The distribution of categorical variables (smoking habit, family history of osteoporosis, use of drugs active on bone metabolism, presence of pathologic conditions that could affect bone metabolism, presence of fragility fracture [anamnestically recalled], and physical activity) among the three categories of women (osteoporotic, osteopenic, and normal) was analyzed by χ^2 test. Association between variables significant at ANOVA test and BMD was assessed by a stepwise linear regression model. The variables that resulted as independent predictors of BMD were used to suggest the new decision rule called AMMEB. In order to evaluate a possible difference in the distribution of the type of fractures according to other parameters, an one-way ANOVA was run. NOF guidelines, ORAI, OST score, weight criterion, and AMMEB score were applied to our population. ROCs were plotted for each method to determine the AUROC at each threshold score.

In all the statistical analyses performed, the result was considered statistically significant if the *P* value was equal to or lower than 0.05.

Results

Participation rate was 95%

In the population analyzed, 249 (47.4%) women were osteoporotic, 169 (32.2%) were osteopenic, and 107 (20.4%) were normal. The percentage of first diagnosis of osteoporosis was 48.5%, whereas percentage of first diagnosis of osteopenia was 51.5%.

Table 3. Percentage distribution of use of drugs active on bone metabolism according to densitometric parameters (osteoporotic, normal and osteopoenic)

	Normal	Osteopenic	Osteoporotic
No drugs	77.4%	50%	57.2%
Calcium and vitamin D	5.7%	31%	27%
Bisphosphonates	0.9%	0.6%	18.8%
Raloxifene	0%	0.6%	35%
Corticosteroids	0.9%	3%	0.4%
L-Thyroxine	11.3%	9.5%	3.9%
Others	3.8%	3.6%	0.9%

Considering the population divided according to densitometric parameters, the only features significantly different were age, age at menarche, period of amenorrhea after menopause, weight, and BMI (Table 2). Mean weekly calcium intake did not differ significantly among the three groups: 5900.8 ± 3372.2 in osteoporotic patients, 6525.2 ± 3760.8 in normal, and 5460.9 ± 2789.6 in osteopenic. As regards the categorical variables, namely, smoking habit, family history of osteoporosis, presence of pathologic conditions that could affect bone metabolism, presence of fragility fracture (anamnestically recalled), and physical activity, there were no statistically significant differences among the three categories analyzed (data not shown); whereas the use of drugs active on bone metabolism in the three categories differed significantly ($P < 0.0001$, Table 3). The site of fragility fractures according to densitometric parametres is described in Table 4. To evaluate possible differences in the type of fractures according to age and/or BMD at the lumbar spine and femoral neck, an ANOVA was run (Table 5). It is interesting to note than only 56.7% of patients with a previous diagnosis of osteoporosis (111 patients) were receiving treatment, in particular 74.6% of those treated patients assumed only

Table 4. Distribution of fragility fractures in percentage according to densitometric features, namely: osteoporosis, osteopenia and normality

	Normal	Osteopenic	Osteoporotic
No fractures	92.5%	88.7%	84.3%
Wrist	2.8%	2.9%	5.7%
Vertebrae	0.9%	2.4%	4.8%
Femoral neck	0.9%	0.6%	0%
Ribs	0%	0%	3%
Others	2.8%	6.5%	5.2%

calcium and vitamin D. As regards osteopenia, 55% of patients with a previous diagnosis were treated. Furthermore, only 14.3% of patients taking bisphosphonates or raloxifene were treated in association with calcium and vitamin D.

The linear regression model between age, postmenopausal period, age at menarche, and BMI showed that the predictors of lumbar BMD are age, postmenopausal period, age at menarche, and BMI ($R^2 = 0.45$). With respect to femoral neck BMD, only age and BMI are predictors ($R^2 = 0.38$, Table 6).

The comparison of the AUROCs between the methods to select women with osteoporosis (T score < -2.5 SD) or with osteopenia (T score between -1.5 and -2.5 SD) plus osteoporosis is presented in Table 7.

As regards the incidence of secondary osteoporosis, 17 patients (13% of the osteoporotic population) were found to be affected by a secondary osteoporosis (64.7% hypovitaminosis D, 17.6% primary hyperparatyroidism, and 17.6% osteomalacia); in 3 patients, a high turnover osteoporosis was diagnosed (elevated level of BAP without other abnormalities). Mean cross-links were found to be elevated, whereas BGP was normal in our osteoporotic subject.

Discussion

From a methodologic point of view it is important to underscore that this is not a population-based study; infact, prescreening of subjects at higher risk for osteoporosis was probably done by the physicians who encountered the women in our center to perform bone densitometry. This could lead to an overestimation of well-known risk factors for osteoporosis and of the prevalence of osteoporosis and osteopenia; nevertheless, our data on the use of common clinical scores do not confront this observation and lead us to consider that in common clinical practice physicians do not use clinical rules in recommending BMD testing. Few studies have been performed to estimate the cumulative incidence of modifiable or nonmodifiable risk factors in determining osteoporosis as diagnosed by bone densitometric techniques [9, 10]. The aim of our study was to find early predictors of postmenopausal bone loss, by comparing well-known risk factors in a cohort of women with respect to densitometric features.

Our data demonstrate that osteoporotic women are significantly older, have a longer postmenopausal period, and are older at menarche with respect to osteopenic and normal subjects whereas their BMI is lower. These data confirm those in the previous literature [11, 19, 20]. Furthermore, it is interesting to point out that BMI is not pathologically lower in patients with osteoporosis higher

Table 5. One-way analysis of variance (ANOVA) between type of fragility fractures and bone mineral density (BMD) at lumbar spine, BMD at femoral neck and age with mean and standard deviations

	BMD lumbar (g/cm^2)*	BMD femoral neck (g/cm^2)	Age (yr)†
No fractures	0.857 ± 0.16	0.656 ± 0.12	60.12 ± 7.2
Wrist	0.740 ± 0.14	0.628 ± 0.09	62.57 ± 6.3
Vertebrae	0.766 ± 0.20	0.609 ± 0.09	63.47 ± 8.3
Femoral neck	—	0.819 ± 0.0	68 ± 0.0
Ribs	0.647 ± 0.0	0.520 ± 0.04	73.5 ± 2.12
Others	0.869 ± 0.14	0.677 ± 0.11	62.546 ± 8.2

*$P = 0.033$
†$P = 0.012$

Table 6. Stepwise linear regression models for lumbar BMD and femoral neck BMD

Lumbar BMD	Beta	Standard error	T	*P*
Age (yr)	−0.35	0.001	−6.9	0.000
BMI	0.24	0.002	4.9	0.000
Years after menopause	−1.56	0.002	−2.16	0.031
Age at menarche	−0.11	0.005	−2.14	0.033
Femoral neck BMD	**Beta**	**Standard error**	**T**	**P**
BMI	0.3	0.06	7.24	0.000
Age (years)	−0.004	0.001	−3.5	0.001

Table 7. Comparison between the AUROCs of NOF, OST, ORAI, weight criterion and AMMEB for the identification of osteoporotic or osteoporotic plus osteopenic women

	AUROC osteoporotic	AUROC osteoporotic plus osteopenic
NOF	0.60	0.60
OST	0.33	0.34
ORAI	0.32	0.27
Weight	0.13	0.17
AMMEB	0.71*	0.73†

AMMEB, Age, years after menopause, age at MEnarche, BMI, Body Mass Index; NOF, National Arthritis Foundation; ORAI, Osteoporosis Risk Assessment Instrument; OST, Osteoporosis Self-Assessment Tools
*$P = 0.37$
†$P = 0.34$

than 1P and that the mean age of this group is younger than 65 years (age proposed as the cutoff point for DXA examination [30]). When considering other risk factors linked to lifestyle, there are no significant differences among the three categories of patients in ferus of smoking habits, family history of osteoporosis, dietary calcium intake, presence of pathologic conditions that could affect bone metabolism, presence of fragility fracture (anamnestically recalled), and physical activity. These data disagree with those in the previous literature [13, 21, 27], whereas, they could reflect the characteristics of our population in which the aforementioned conditions had low incidence and, as regards calcium intake, it is generally lower for all of the analyzed women. It is interesting to note that calcium intake, as obtained from the questionnaire, is clearly under the recommended level for postmenopausal women both in osteoporotic and normal subjects (1,200 mg/day). The difference among the two groups in the use of any drug results from the administration of therapy for osteoporosis and not the administration of drugs that could negatively affect bone metabolism, such as corticosteroids or L-thyroxine. It seems important to point out that only 56.7% of patients with a previous diagnosis of osteoporosis were treated and that only 26.3% of those treated used bisphosphonates or raloxifene (i.e., the only drugs supported by the rules of evidence-based medicine). Furthermore, it is noteworthy that only14.3% of patients receiving bisphosphonates or raloxifene were correctly treated in association with calcium and vitamin D.

The analyses of risk factors potentially useful for an early diagnosis of low BMD demonstrate that age, years after menopause, age at menarche, and BMI are important predictors of bone demineralization of the lumbar spine, whereas only age and BMI are predictors of BMD at the femoral neck. Lumbar BMD is explained (45%) by these factors, whereas age and BMI account for only 38% of femoral BMD. As regards the prevalence of fragility fractures, it is interesting to note that their distribution according to age and BMD measured at lumbar spine, but not at the femoral neck, even if not according to the cutoff for BMD indicated by WHO; in particular the patients with ribs fractures had a significantly lower BMD at lumbar spine and were significantly older.

In recent years, the availability of new drugs for treatment of patients with osteoporosis [42] has put new pressures on primary care physicians to screen patients at risk of fragility fractures with BMD testing. The goal is to identify those with low BMD, and, hence, to limit unnecessary screening healthy patients that is why in the present study we use some of the proposed decision rules.

The validation of NOF guidelines, ORAI, OST score, and weight criterion in our population is unsatisfactory because of the AUROC as compared to AMMEB in detecting both osteoporotic and osteoporotic plus osteopenic subjects (Table 7). It is also important to consider that although patients in our population are prescreened by their own physician or gynecologist, the anagraphic and anthropometric characteristics are clearly not suitable with the well-known guidelines (our population is younger with higher BMI); that is why we decided to propose a new score developed on the basis of our data.

The use of our score may be useful for identifying osteoporotic and osteopenic patients with respect to healthy patients and, hence, to address BMD testing for those patients at higher risk for osteoporosis, thereby reducing the cost efficacy ratio for bone densitometry.

Our data on the prevalence of secondary osteoporosis substantially reflects the literature on the topic [43–45].

In conclusion, our study (1) does not confirm the role of lifestyle risk factors in determining postmenopausal bone loss, whereas it confirms the role played by nonmodifiable risk factors such as age, postmenopausal period, age at menarche, and BMI; (2) indicates as predictors of BMD of the lumbar spine age, years after menopause, age at menarche, and BMI, whereas at the femoral neck only age and BMI are predictors of BMD; (3) shows that the use of NOF guidelines, ORAI, OST score, and weight criterion in this population are not completely satisfactory in detecting osteopenic and osteoporotic subject, and lead to high medical costs; (4) suggests a new score that will be validated on the Italian population; and (5) demonstrates the relatively high prevalence of secondary osteoporosis and suggests a primary screening for secondary osteoporosis in all patients with low BMD.

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