Clinical risk factors as predictors of postmenopausal osteoporosis in general practice

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SUMMARY
Background: Case-finding strategies to identify women with high risk for osteoporotic fractures have recently been proposed, but little information about such an approach in general practice is known.
Aim: To study the validity of the proposed case-finding strategy for osteoporosis.
Design of study: Survey using case-finding strategy.
Setting: Seven hundred and twelve women aged between 55 and 84 years, randomly selected from a general practice in The Netherlands.
Method: Of the 712 randomly selected women, 449 women participated. Information was obtained from a questionnaire, direct questioning, and computerised patients files. Bone mineral density of the femoral neck was measured by dual energy X-ray absorptiometry and vertebral morphometry was performed on lateral X-rays of the spine. Osteoporosis was defined by a bone mineral density T-score of less than 2.5 and/or the presence of severe vertebral deformities. Sensitivity, specificity, and predictive values were calculated for the whole set of risk factors; those significantly associated with osteoporosis and in logistic models.
Results: Clinical risk factors were present in 55% of the women and identified 68% of the women with osteoporosis. Three risk factors — a low body mass index, fragility fractures, and severe kyphosis and/or loss of height — were associated significantly with osteoporosis; they were present in 33% of the women and identified 60% of those with osteoporosis. A logistic model based on age and fragility fractures selected 32% of the women and identified 76%.
Conclusion: No single risk factor could assist in identifying women with osteoporosis. A simplified case-finding strategy using only three risk factors, that is suitable for primary care, reduces the number of women to be evaluated by two-thirds; however, this is at the cost of missing the diagnosis in 40% of the women with osteoporosis. Addition of spine radiographs to the case-finding approach helped to obtain a better risk profile of the women and had also practical consequences for the management of some. We propose that radiographs should be included in any case-finding strategy.
Keywords: postmenopausal osteoporosis; risk factors; case-finding strategy.

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Introduction

POSTMENOPAUSAL osteoporosis is a common disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.[1,2] Fractures are the major clinical outcomes of the disease and are associated with considerable morbidity and mortality.[3,4] In recent years, interventions that effectively reduce fracture risk in postmenopausal women have become available; it is therefore important to develop strategies to identify women most likely to benefit from these interventions.[5-9]

On the basis of available evidence, population-based strategies for prevention and treatment of osteoporosis cannot be recommended and there is no widely accepted policy for general screening to identify patients with the disease. Recently, expert committees of the Royal College of Physicians in the United Kingdom (UK), the Dutch Ministry of Health, the European Commission, and the WHO independently recommended a case-finding strategy aimed at identifing women with the highest risk for osteoporotic fractures.[10-13] According to this strategy, women with strong clinical risk factors can be identified and subsequently subjected to bone mineral density (BMD) measurements to establish or refute the diagnosis of osteoporosis. Those women diagnosed with osteoporosis should be offered appropriate interventions.[10-13]

The importance of these clinical risk factors has been documented in many studies, most often population-based; however, there is little information about the usefulness of this strategy in a population derived from primary care.[14-16] In the present study we examined the validity of this case-finding strategy to identify women with osteoporosis in a cohort of women aged between 55 and 84 years attending a large general practice in The Netherlands.

Method

The study was performed in a primary health care centre in Noordwijk, The Netherlands, and was part of a larger survey examining ways to identify elderly women with osteoporosis in primary care. Within the Dutch health care system, which is similar to that in the UK, practically every individual is registered in a general practice, regardless of their medical condition. The design and some of the outcomes of the study have been published previously.[17]

At the time of the study, 1325 women aged between 55 and 84 years were registered in the centre. The women were stratified into five-year age groups and a cohort of 771 was randomly selected for the study. Of these, 44 were excluded because they were bedridden (*n* = 4), wheelchair-bound

HOW THIS FITS IN

What do we know?

Postmenopausal osteoporosis is common, and interventions that reduce the risk of fractures are available. To identify women with high fracture risk case-finding strategies using clinical risk factors are recommended.

What does this paper add?

The present study proposes a simplified, conservative case-finding approach that uses three risk factors (low body mass index, previous fragility fracture, severe kyphosis and/or loss of height) suitable to identify women with osteoporosis in general practice.
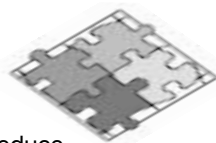
(n = 11), not competent enough to participate (n = 12) or had a concurrent serious illness (n = 17). An additional eight women had moved from the area and seven women were deceased when the selection was made. The remaining 712 women were sent a postal invitation to participate in the study, which included a questionnaire. If there was no response then a reminder was sent after three weeks. In total, 494 (69%) women (mean age = 67.6 years; standard deviation [SD] = 8.2 years) responded to the invitation and attended the clinic. This response rate might have resulted in selecting a more fit population at lower risk for osteoporosis. However, a non-response analysis using data from the patients' computerised files on fractures and other risk factors for osteoporosis did not reveal any difference between the responders and non-responders. At this stage, another 45 women were excluded from the study for the following reasons: no informed consent for radiographs (n = 17), no suitable hip for BMD measurement (n = 10), inability to measure height or armspan (n = 15), non-Caucasian (n = 3). Thus, spinal radiographs and dual energy X-ray absorptiometry (DXA) of the hip were finally performed in 449 women (mean age = 67.4 years, SD = 8.2). All women gave informed consent and the study was approved by the Medical Ethics Committee of the Leiden University Medical Centre.

Clinical risk factors

The clinical risk factors evaluated were those recommended by the Royal College of Physicians (UK) and the Advisory Committee of the Dutch Ministry of Health (Table 1).[10-13] Information about loss of height, hip, wrist and/or vertebral fractures after the age of 50 years, hysterectomy or oophorectomy, and any maternal history of hip fracture were obtained from a questionnaire, while the age at menopause and any history of a prolonged period of secondary amenorrhoea were obtained by direct questioning during the visit to the clinic. Chronic use of oral glucocorticoids (up to six months prior to the visit to the clinic) and concomitant diseases, including malabsorption syndromes and transplant surgery, were obtained from the computerised patient files. In addition, the presence of other conditions was identified by the specific code of the International Classification of Primary Care (ICPC).[18] As not all clinical risk factors examined have a specific code, ICPC-code U99 ('other disease urinary system') and T99 ('other endocrine metabolic and nutritional disease', including hyperparathyroidism and Cushing's syndrome) were also assessed, as these are mostly used in daily practice to record chronic renal failure and hypogonadism. Finally, height, weight (with clothes, without shoes), and armspan were measured and the spine was examined for the presence of kyphosis.[17]

Radiological investigations

BMD of the right (or, if unsuitable, the left) femoral neck was measured by a Lunar DPX-L bone densitometer (Lunar Radiation corporation, Madison WI, USA) with an OsteoDyne hip positioning system.

Lateral radiographs of the spine, including the fourth thoracic and the fifth lumbar vertebrae were made and vertebral morphometry was assessed using the method of Eastell *et al*.[19] Twenty-one radiographs (4.7%) were disqualified for technical reasons. The morphometric analysis was done by the same technician who had analysed the Rotterdam study, which was a population study using the same equipment and reference values.[17,20]

Analyses

Osteoporosis was diagnosed by a BMD value of 2.5 SDs below the mean of premenopausal healthy women using the manufacturer's reference data (<0.680 g cm²; this value is comparable to a Dutch reference population[21]) and/or the presence of a severe (grade II) vertebral deformity as defined by Eastell *et al*[19] confirmed by visual inspection of the films. Relative risk (RR) of each clinical risk factor was calculated for the presence of osteoporosis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for any clinical risk factor, but also for a limited set of risk factors, i.e. those that were found to be significantly associated with osteoporosis. Forward stepwise logistic regression analysis was performed in a randomly selected group of 300 women using age and the applied risk factors (unless their prevalence was lower than 1%) as independent variables. Age was used as a continuous variable. Testing characteristics of the logistic regression model were calculated after obtaining the optimal cut-off value using ROC analysis. The predictive value of the logistic model was evaluated in a cross validation of the remaining 149 women. The statistical program used was SPSS for Windows.

Results

Clinical risk factors for osteoporosis were present in 55% (n = 247) of all women (95% confidence interval [CI] = 50–60%) and the prevalence rose from 43% in the age group 55 to 64 years, to 70% in the age group 75 to 84 years. Seventy-two women (16%) had osteoporosis. Of these, 33 (7%) had a low BMD at the femoral neck (<-2.5 T-score) and 44 (10%) had at least one severe vertebral deformity, five of whom also had a low BMD.

At least one clinical risk factor was present in 68% (n = 49) of the women with osteoporosis and in 53% (n = 198) of the women without osteoporosis (Table 1). The positive predic-

Table 1. Number of women with clinical risk factors and the relative risk (RR) for osteoporosis.

	Osteoporosis (n)			
	No (n = 377)	Yes (n = 72)	RR	95% CI
Clinical risk factor				
Premature menopause (<45 years of age)	69	12	0.9	0.5–1.6
Prolonged secondary amenorrhoea (>1 year)	1	1	5.2	0.3–83
Corticosteroid within the past six months	7	3	2.2	0.6–8.5
Maternal family history of hip fracture	34	2	0.3	0.1–1.3
Low body mass index (<19 kg m^{-2})	1	2	11	1.0–114[a]
Anorexia nervosa (ICPC-code T06)	15	1	0.3	0.1–2.6
Malabsorption	0	0	–	–
Other disease urinary system (ICPC-code U99)	1	0	–	–
Prolonged immobilisation (>6 months)	12	1	0.4	0.1–3.3
Post-transplantation	0	0	–	–
Hyperthyroidism (ICPC-code T85)	4	2	2.6	0.5–14
Other endocrine metabolic and nutritional disease (ICPC-code T99) (includes hypogonadism, hyperparathyroidism and Cushing's syndrome)	3	0	–	–
Reported hip and/or wrist fracture	25	18	3.8	2.2–6.5[a]
Hip fracture	4	3	3.9	0.9–17
Wrist fracture	22	15	3.6	2.0–6.5[a]
Reported loss of height (≥4 cm) and/or severe thoracic kyphosis	88	29	1.7	1.2–2.4[a]
Any clinical risk factor present	198	49	1.3	1.1–1.6[a]

[a]Confidence interval associated with osteoporosis.

tive value (PPV) of having osteoporosis with any clinical risk factor present was 0.20, while the negative predictive value (NPV) was 0.89 (Table 2).

Three clinical risk factors were statistically significant associated with the presence of osteoporosis: a low body mass index (BMI), previous hip and/or wrist fracture (no-one reported a vertebral fracture), and a reported loss of height of 4 cm or more and/or the presence of severe thoracic kyphosis. These were present in 33% (n = 148) of all women, and identified in 60% (n = 43) of the women with osteoporosis, while in only 28% (n = 105) of the women without osteoporosis, any of these three risk factors was present (Table 2). The PPV and NPV on having osteoporosis on the presence of any of these three risk factor was 0.29 and 0.90 respectively (Table 2). This means that the number of investigated women could be reduced by 67%. However, this is at the cost of not accounting for 40% of the cases with osteoporosis.

Logistic analyses showed that, when age was included, only one risk factor, namely a reported hip and/or wrist fracture, was associated with osteoporosis. In this analysis risk factors with a prevalence lower than 1% were not included (see Method). The odds ratio and 95% CI for age was OR = 1.5 (95% CI = 1.2–1.8) for five-yearly increases and OR = 3.8 (95% CI = 1.7–8.7) for a reported fracture. Based on the ROC analysis of this model, the optimal cut-off level for age was 71 years. The model obtained was tested in the remaining 149 women and selected 56 (38%) of them. The model identified 76% (n = 19) of the women with osteoporosis and only 30% (n = 37) of the women without osteoporosis; the PPV and NPV were 0.34 and 0.94 respectively (Table 2). With this approach, 62% of women older than 55 years would not require any further investigation, at the expense of missing 24% of those with osteoporosis.

Discussion

In the present study we examined the value of a set of clinical risk factors in identifying women with postmenopausal osteoporosis in primary care. These risk factors form the basis of case-finding strategies in osteoporosis recently proposed by expert committees in various European countries, including the UK and The Netherlands.[10-12] For diagnosing osteoporosis we measured the BMD at the neck of the femur and we used the current WHO task force definition of a value lower than 2.5 SDs below the mean of healthy pre-menopausal women. In addition, lateral X-rays of the spine were obtained in all women, which also allowed the identification of women with grade II vertebral deformities, morphometrically assessed according to the method of Eastell *et al*.[19] The presence of a severe vertebral deformity is admittedly an independent risk factor for osteoporotic fractures but at the same time is a serious clinical expression of the disease.[22-23] Vertebral deformities do not generally give rise to clinical symptoms and none of the women in our cohort reported such an event.[24] On the other hand, the presence of a vertebral fracture considerably increases the risk of new osteoporotic fractures independently of other risk factors.[22,23] Identification of these women is, therefore, important for therapeutic decisions. The only way to identify women with vertebral fractures is by X-ray of the spine. Our results support this notion. Forty-four of the 72 women with osteoporosis in our study had grade II vertebral deformities radiographically and only five of them had a BMD T-score of lower than -2.5. Because of the presence of deformities additional investigations were performed in this group that helped us to diagnose, in five patients, serious underlying diseases known to affect skeletal integrity, of which the patients themselves were not previously aware. These were: multiple myeloma, leukaemia, Paget's disease, primary hyperparathyroidism, and coeliac disease; none of these

Table 2. Testing characteristics to identify subjects with osteoporosis by using any risk factor, a limited set of three or the logistic model.

	Any risk factor	Limited set of three risk factors	Logistic model [a]
Sensitivity	0.68 (49/72)	0.60 (43/72)	0.76 (19/25)
Specificity	0.47 (179/377)	0.72 (272/377)	0.70 (87/124)
Positive predictive value	0.20 (49/247)	0.29 (43/148)	0.34 (19/56)
Negative predictive value	0.89 (179/202)	0.90 (272/301)	0.94 (87/93)

[a] Model: all women 71 years of age or with a reported hip and/or wrist fracture.

women had a BMD of the femoral neck below -2.5 T-score (manuscript in preparation).

Therefore, the addition of spine radiographs to the case-finding approach not only helped to obtain a better risk profile of our patients but also had serious practical consequences for the management of some of them. These results are directly applicable to clinical practice because we evaluated only patients with severe vertebral deformities that can be recognised by a radiologist, without the need for performing morphometry. We feel, therefore, that lateral X-rays of the spine should be included routinely in any case-finding strategy.

At least one clinical risk factor was present in 55% of the women and the prevalence increased with age so that, in women aged over 75 years, this had risen to 70%. Clearly, no single risk factor could assist in identifying women with osteoporosis as evidenced also by the low PPV (0.20). This is not surprising and is in agreement with numerous reports demonstrating the insufficiency of risk factors in predicting osteoporosis.[14-16] It should be mentioned, however, that risk factors that may be highly predictive for the disease appear to be of little value, because of their low frequency in this community-based cohort. Using this approach we could reduce the number of investigations performed by about one-half while missing at the same time the correct diagnosis of osteoporosis in 32% of those having the disease. However, when taking into consideration only those factors that were significantly associated with osteoporosis in our cohort (previous fracture, low BMI, reported loss of height/thoracic kyphosis), PPV increased to 0.29 while the NVP remained high (0.90). This decreased substantially the number of women needing further investigations, from 55% of the whole cohort if only one risk factor was present to 33% when the three factors were considered. The trade-off for this reduction in the number of evaluated women was that, in 29 out of the 72 (40%) women with osteoporosis, the diagnosis would have been missed. This illustrates the conservative nature of the case-finding approaches, which has also been noted by others (see, for example the report of the Royal College of Physicians[11]) and raises questions about economic and ethical issues in the management of patients with osteoporosis. Is there an acceptable trade-off from a health economic prospective in women with osteoporosis, that may have serious consequences for the individual sufferer who will not be identified with this approach? At present there is no clear answer to these questions. Further analysis of our data can be of some help in addressing these issues in the future.

It is well known that osteoporosis is an age-related disease and that the majority of osteoporotic fractures occur later in life. In addition, all effective antiosteoporotic interventions have been shown to significantly reduce the short-term risk of fractures in women with mean ages of between 63 and 71 years.[5-9] We therefore introduced age as an independent parameter to the logistic regression analysis. The results of the ROC analysis revealed an age of 71 years as a cut-off point for the risk of osteoporosis. This means that serious consideration should be given to devising general screening strategies at this age, while using a set of strong clinical factors for further investigations at younger ages. However, the feasibility and the medical and economic implications of such an approach need to be prospectively evaluated in well-planned studies. For the time being and in view of the very low recognition of osteoporosis in clinical practice, the simplified case-finding strategy described here can be easily implemented and can help in the management of patients.

Apart from helping to clarify issues related to identifying patients with osteoporosis in primary care, our study additionally provides strong evidence against offering pharmacological interventions to postmenopausal women on the basis only of risk factors.

Acknowledgements

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