Original Article

Screening Procedure for Women at Risk of Developing Postmenopausal Osteoporosis

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Abstract. The present study includes 70 healthy, immediately postmenopausal women stratified according to future rate of bone loss. The stratification was performed by means of four parameters of bone turnover: serum alkaline phosphatase, fasting urinary calcium and hydroxyproline, and body weight, used in an equation developed in a previous study. After the stratification the women were followed without intervention for the next 24 months, with bone mass measurements every 3 months. The bone loss estimated at baseline by means of the equation correlated with the bone loss measured in the forearm (y=0.72x−1.52; r=0.61; P<0.001). Plasma bone gla protein (BGP, osteocalcin), which is a new specific marker of bone formation, was now added to the model (replacing body weight). This increased the diagnostic validity (y=x; r=0.76; P<0.001).

From the present study we conclude that the postmenopausal bone loss can be predicted by means of four biochemical parameters determined in plasma and urine in women just after the menopause.

Keywords: Osteoporosis; Prediction; Biochemical markers

Introduction

Osteoporosis is characterized by a reduction in bone mass that often results in fracture, particularly of the vertebrae, proximal femur, and lower forearm [1]. Loss of bone with advancing age is universal, but progresses more rapidly in women than in men, with a five- to tenfold acceleration just after the menopause [2,3].

Many attempts have been made to establish a preventive treatment for postmenopausal bone loss, but for many years estrogen either alone or in combination with a gestagen has proved to be the only known effective treatment [4–7]. Unfortunately, it may have some side effects [8–10]. Recent studies indicate that calcitonin (now available as a nasal spray) may be effective [11,12]. Used nasally, calcitonin is apparently without side effects, but it is expensive and the long-term effect on the fracture rate is unknown. The cost–benefit ratio for preventive treatment of postmenopausal osteoporosis would therefore be considerably improved if the women at highest risk of osteoporosis could be identified.

New technology has made it possible to determine bone mass in vivo, but the changes over years in the bone mass of postmenopausal women are of the same magnitude as the precision of the methods, all of which necessitate repeated measurements after several years to detect the women at risk [13,14]. On the other hand, the changes in biochemical estimates of bone turnover around the menopause are in the order of 30%–100%, with a precision error of the methods in the order of 5%–10% [3,15]. Theoretically, a biochemical approach could provide a simple and reliable screening procedure. We have thus demonstrated in a retrospective analysis of a prospective study (performed from 1977–1979) that fast bone losers could, to some extent, be separated out from normal bone losers by one blood and one urine sample [16] (‘1977 predictor’). The optimum scientific approach to a screening procedure of this nature is to repeat it in a new independent series of

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postmenopausal women to test whether the analysis holds true. In the present study we therefore investigated our ‘1977 predictor’ in an independent new ‘1983 study group’. We have recently reported that plasma bone gla-protein (BGP) is a reliable predictor of bone loss in postmenopausal women [15]. Therefore, we examined also the diagnostic validity when BGP was included in the calculations.

Participants

The present study (1983) was a large trial performed at Glostrup Hospital from June 1983 to January 1986. The study was designed to cover several problems occurring in the postmenopausal period [4,14]. The participants were selected by questionnaires and medical screening examination. They were 45–54 years old, had passed a natural menopause 6 months to 3 years before the study, had taken no sex hormones or other drugs known to influence calcium metabolism, and were free of past or present diseases known to influence calcium metabolism or to contra-indicate the trial medications. All participants were thoroughly informed about the trial, and gave their written consent to participate (Helsinki Declaration II). The study also includes data from 29 healthy premenopausal women.

By means of the screening procedure developed in our first study (1977) [16], 70 women (1983 population) were divided into three groups: fast bone losers, slow bone losers, and borderline. The women were then followed up for 2 years, with examinations every 3 months. A part of the data has been presented previously [17].

The 1983 population was comparable to the 1977 population, which consisted of 178 healthy postmenopausal women of the same age. Details of this population are given elsewhere [5].

Methods

Bone mineral content (BMC) of the forearms was measured every third month by single-photon absorptiometry, using a 125I source. The method includes software developed in our laboratory and determines BMC in a proximal region of the forearm with predominantly cortical bone (BMCprox), and in an ultradistal part of the forearm with a higher content of trabecular bone (BMCdist). The long-term in vivo precision of BMCprox is 1% and of BMCdist 1.5% [18]. Bone mineral content of the lumbar spine (BMCSpine) was measured at baseline and after 1 and 2 years by dual-photon absorptiometry on a Lunar Radiation Corporation DP3 scanner using a Gd153 source. The long-term in vivo precision is 4% after corrections for the variation due to changes of sources [19]. Total body bone mineral (TBBM) was similarly measured at baseline and after 1 and 2 years by dual-photon absorptiometry with a Gd153 source on a whole body scanner developed in our laboratory. The long-term in vivo precision of TBBM is 2% [20].

Height and the weight were measured in all the participants without shoes and wearing indoor clothing. Lean body mass (LBM) and fat mass (FM) were calculated according to the formula of Boddy et al. [21], which is comparable to the LBM and FM measured by dual-photon absorptiometry [22]. Blood samples were taken and urine collected in the morning after an overnight fast and tobacco abstinence. Serum alkaline phosphatase (AP) was measured enzymatically according to Scandinavian recommendations. The intra- and interassay variations were 3% and 5%. Plasma BGP was measured by radioimmunoassay. The intra- and interassay variations were 7% and 12% [23]. Fasting urinary calcium and creatinine were measured on an SMA 6/60 autoanalyzer, and calcium excretion was corrected for creatinine excretion (A u-Ca). Fasting urinary hydroxyproline was measured by a spectrophotometric method [24] and corrected for creatinine excretion (A u-Hpr). The intra- and interassay variations were 10% and 12%.

Statistical Evaluations

Baseline clinical values were compared using student’s t test for unpaired data. The bone mass measurement values (9 forearm measurements, 3 spine and total body measurements) were expressed in percent values of the initial measurement value (= 100%). The individual percentage of bone loss in the forearms was expressed as the slope estimated by linear regression using the nine BMCprox measurements (zBMC). The bone loss in BMCdist was calculated in the same way. The bone loss in the spine and total body (BMCSpine and TBBM) was calculated using the percent values after 1 and 2 years of treatment, thus using all three data points:

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\text{Bone loss} = \left( \frac{\text{1 year value} + \text{2 year value}}{2} \right) \times 4/3
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The 1977 predictor equation was at that time derived by multiple regression analysis of the biochemical parameters and the measured BMCprox bone loss [16]. The new 1983 predictor equation including BGP was derived in the same way. The estimated bone loss (calculated from the 1977 predictor equation) and the measured bone loss (zBMC) was related by linear regression analysis (Fig. 1).

The diagnostic validity of the biochemical models including either FM or BGP was compared by a receiver operating characteristic analysis (ROC-analysis). The number of true positive was plotted against the number of true negative at different cut-off levels. The cut-off level used to calculate the sensitivity and specificity was similar to the one used in 1977 to separate the true fast and slow bone losers (2.7% per year).