Determinants of forearm bone density in premenopausal women: a study in one general practice

MARIA L COX

S A KHAN

D W GAU

S A L COX

H M HODKINSON

SUMMARY. Predictors of distal and proximal forearm bone density, measured by photon absorbtiometry, were investigated in 248 premenopausal women aged 39–56 years. Only one strong predictor of lower bone density was found — history of previous fracture at any site (P<0.001). Two other factors showed a weaker association with density, but only at the distal site — history of diuretic use showed a positive association (P<0.02) whereas alkaline phosphatase level was inversely correlated with density (P<0.01). Other factors were not significant predictors: these included age, calcium intake, level of exercise, anthropometric measures of obesity, serum calcium level, parity, lactation history, a menopausal symptom history, use of the contraceptive pill, smoking and alcohol intake. These results contrast with the far stronger predictors found for postmenopausal women and suggest that genetic endowment rather than lifestyle may be the major determinant of bone density before the menopause.

Introduction

THE peak bone mass achieved before the menopause is clearly an important factor in determining bone density levels after the menopause when osteoporosis becomes a major health problem. However, though there have been many studies of postmenopausal osteoporosis, far less attention has been paid to bone density before the menopause.

In this study potential factors determining bone density have been examined in a general practice setting in premenopausal women who have been recruited for a longitudinal study across the menopause. Bone density was measured at the wrist only as this measurement could easily be carried out in the practice surgery, was highly acceptable to patients and ensured a high rate of participation.

Method

The longitudinal study took place in a general practice in Beaconsfield, Buckinghamshire, with a list of 12 000 patients. Eight hundred women aged 39 years and above were identified from the practice age–sex register and asked to join the study if they were still having menstrual periods. A total of 560 women attended the practice for an examination and interview with a research nurse (response rate 70%). The first 302 women who attended were included in this study of bone density. However, women with thyrotoxicosis, Cushing's syndrome or hyperparathyroidism, or receiving systemic corticosteroid therapy or hormone replacement therapy were excluded leaving 248 women aged 39–56 years in the study.

The bone density of the women's non-dominant forearm was measured using the ND1100B bone scanner (Nuclear Data Inc) which employs a photon absorbtiometric technique using an I^{125} source with a reported coefficient of variation of 1–2% for measurements.

The bone scanner averages four measurements at the distal and six at the proximal wrist and these are corrected for soft tissue effect (fat being more transradiant than water or non-fat tissue). Results can be expressed as total mineral in the cross section or can be corrected for total bone width. The latter method was used in the analyses described here as it is independent of body size. Results are calculated in arbitrary computer units based on proportional absorption but can be converted into grams of calcium per centimetre by an internal standard.

A venous blood sample was taken in order to determine serum calcium, total protein, albumin and alkaline phosphatase levels using standard autoanalyser methodology. The women's height was measured using a stadiometer, their weight in light clothing by beam balance, the skin fold thickness of the triceps and the back of the hand by Harpenden callipers and mid-arm circumference by tape measure. A dietary recall questionnaire was used to assess the women's weekly calcium intake from dairy products. This correlates strongly with total calcium intake. The women's alcohol intake during the past week was recorded in units (1 unit = 10 g alcohol).

All women were asked if they had experienced the following symptoms never, rarely, sometimes or often during the preceding three months: hot flushes, cold sweats, blind spots in front of the eyes, a crawling feeling of the skin, a feeling of suffocation, pain or discomfort of the breasts, cold hands or feet, headaches, crying spells, irritability, excitability, depression and inability to concentrate. Parity, breast feeding history, history of fracture before and after 25 years of age, relevant drug therapy, use of the contraceptive pill and current smoking experience were also recorded. The women's grip strength in the non-dominant arm was measured using a semi-inflated bag connected to an anaeroid barometer.[1] The women's activity level was measured using a digital pedometer attached to the waist for a period of exactly 24 hours.

Owing to logistic difficulties not all women had pedometry and venepuncture performed so that analyses for pedometry and biochemical parameters are on a smaller number of women (92 and 89, respectively).

The significance of association was tested by Pearson's correlation or, where categories were compared, the unpaired *t*-test.

M L Cox, MRCP, honorary research fellow; S A Khan, MRCP, honorary research assistant; H M Hodkinson, FRCP, Barlow professor of geriatric medicine, Department of Geriatric Medicine, University College and Middlesex School of Medicine, London. D W Gau, FRCGP; S A L Cox, MRCGP, general practitioners, Beaconsfield, Buckinghamshire.
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Results

The mean age of the 248 women was 47 years (range 39–56 years, standard deviation three years). Their mean bone density was 1.45±0.14 units for the proximal wrist and 1.09±0.14 units for the distal wrist (corresponding to 0.48±0.05 g(Ca) cm^{-1} and 0.36±0.05 g(Ca) cm^{-1}, respectively).

Predictors of bone density

In univariate analyses, only two factors showed statistically significant relationships to forearm density — history of fracture and history of diuretic use.

Of the 248 women 86 (34.7%) reported a history of fracture at any site and at any age. These women had a significantly lower mean bone density at both the distal forearm (−7.4%, $t = 4.47$, $P<0.001$) and the proximal forearm (−4.2%, $t = 3.45$, $P<0.001$) than the group as a whole. These significant relationships were also found for the subgroups of women reporting fractures before the age of 25 years (24.2% of women) (−5.7%, $P<0.01$ for distal and −2.9%, $P<0.05$ for proximal forearm) and aged 25 years or over (14.9% of women) (−8.0%, $P<0.001$ for distal and −4.5%, $P<0.01$ for proximal forearm).

A positive history of diuretic use was reported by only seven women (2.8%) but their mean bone density at the distal forearm was significantly higher (+12.5%, $t = 2.48$, $P<0.02$ than for the group as a whole). However, the difference for proximal density (+5.1%) was not significant.

Correlations of borderline significance were found for grip strength and density ($r = 0.111$ for distal and $r = 0.121$ for proximal forearm, both $P<0.1$) and for serum alkaline phosphatase level (logarithmically transformed to correct for skewness) and distal density ($r = -0.181$, $P<0.1$). Although correlations between pedometry mileage (mean 5.3 miles in 24 hours) and density were of the same order as for grip strength, because of the smaller number of women involved ($n = 92$) they were not significant ($r = 0.106$ for distal and $r = 0.128$ for proximal forearm). There was also a non-significant trend for increasing density with increasing parity.

There was no association between age and density at either the distal or proximal forearm ($r = 0.003$ and $r = -0.060$, respectively). Similarly, no significant relationships were found for anthropometric measures — height, weight, Quetelet's index (weight in kilograms/height in metres squared), skin fold thickness of the triceps and the back of the hand, mid-arm circumference, and calculated arm muscle circumference — nor for history of breast feeding, or use of the contraceptive pill (1.9% of women current users, 6.4% users at some time), sleeping tablets, steroid creams, steroid inhalers or antacids. Calcium intake from dairy produce (mean 684 mg over 24 hours), smoking (13% of women current smokers), alcohol intake (mean 4.9 units per week), and serum total protein, albumin and calcium levels (corrected for serum albumin) also showed no significant relationships.

Presence of menopausal symptoms did not show a significant correlation with either proximal or distal bone density for any of the symptoms.

Multivariate analyses

Multivariate analyses (multiple linear regression) using all the significant and borderline predictors were carried out to attempt to find models which would improve on the prediction of density given by fracture history alone. The combination of history of fracture before the age of 25 years and history of fracture since reaching 25 years of age did not improve on the prediction given by history of fracture at any age alone.

Prediction of distal forearm density was significantly improved by addition of either serum alkaline phosphatase level or history of diuretic use, the former being the more powerful combination though still only explaining 17.8% of variance (compared with 7.6% for fracture history alone and 9.8% for fracture and diuretic histories together). These models could not be significantly improved by the addition of further predictors.

No significant improvement in prediction of proximal forearm density could be achieved by adding a further predictor to fracture history, although pedometer mileage, grip strength and parity did achieve improvements of borderline significance ($P = 0.12$, 0.11 and 0.09, respectively). The proportion of explained variance remained low, however, for these models involving two predictors (10.3%, 5.8% and 5.7% respectively compared with 4.6% for fracture history alone).

Discussion

The finding that a history of previous fracture at any site is the only useful predictor of forearm bone density in premenopausal women is a surprising one. Densities were normally measured in the non-dominant arm but, where subjects had had a previous fracture of the non-dominant arm, measurements were taken from the dominant arm. As the dominant arm usually has a higher density, any bias this procedure might introduce would be against the association of fracture and lower density found here.

There would appear to be two ways in which fracture history could be linked to bone density. Bone density might decrease after fracture because of changes in activity, or a fracture may merely identify those who have more lightly constructed skeletons for genetic or other reasons. Fractures both before and after the age of 25 years were found to be significant independent predictors of bone density and it would be surprising if changed activity levels influencing bone density persisted from before the age of 25 years to the average age of 47 years of the women studied here. The genetic explanation seems more plausible and is in accord with a recent report showing that daughters of osteoporotic mothers have lower than average bone densities.[2]

The association between higher bone density and diuretic use found here should be interpreted cautiously as it is based on only seven diuretic users. However, thiazide diuretics are known to decrease renal calcium excretion and appear to have a positive effect on skeletal density.[3]

Serum alkaline phosphatase level was found to be inversely correlated with the bone density of the distal forearm (where trabecular bone predominates) though not of the proximal forearm (where cortical bone predominates). This association is of borderline significance but in conjunction with fracture status it reaches full significance. Alkaline phosphatase levels are related to bone turnover and normally rise after the menopause[4] when accelerated bone loss occurs. The average age of the women in this study (47 years) is only three years below the average age of the menopause. Raised alkaline phosphatase levels may be identifying women who are very close to the menopause and who have already entered the phase of more rapid bone loss.

The findings of borderline associations between bone density and grip strength and pedometer mileage as a measure of exercise levels agree with previous work. Animal work shows a clear relationship between bone density and peak loading of the bone[5] and exercise regimens have been shown to increase bone density generally[6] and locally at the forearm.[1] The non-

significant association between parity and forearm bone density is also in agreement with previous studies, for example that of Goldsmith and Johnston in premenopausal women[7] while other studies have found this protective effect in postmenopausal women.[8,9]

The failure to find the reported association between low bone density and smoking and alcohol consumption[10] is unsurprising given that only 13% of the study group were smokers, none of whom smoked heavily, and that average alcohol intake was only 4.9 units per week. Stevenson and colleagues,[10] like ourselves, failed to find any association between calcium intake and bone density in premenopausal women.

That neither height, weight, Quetelet's index nor triceps skinfold thickness correlated with forearm density in this study is in agreement with previous findings that the protective effect of obesity is confined to postmenopausal women[10] and is in accord with the postulated mechanism of protection, that fat tissue is responsible for the main production of oestrogen from the conversion of adrenal androstenedione in postmenopausal women.

Perhaps the most noteworthy finding of this study is the poor prediction of bone density from the factors studied in contrast with far stronger predictions, for example, from grip strength and exercise, which result from studies involving postmenopausal women.[1] The measures of exercise and of calcium intake used in this study are admittedly crude, although this is true of many studies with similar sample size which found significant associations in postmenopausal women. It is possible that more sensitive measures, or a far larger study, would have demonstrated significant associations in premenopausal women, but the results presented here indicate that any such associations are unlikely to be as strong as those in postmenopausal women.

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Address for correspondence

Dr M L Cox, Watford General Hospital, Vicarage Road, Watford, Herts WD1 8HB.