Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study

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Abstract

***Objectives*—To determine prospectively the rates of change in bone mineral density in elderly people and to examine the relation between lifestyle and demographic factors and these rates of change.**

***Design*—Longitudinal population based study.**

***Setting*—Dubbo, New South Wales, Australia.**

***Subjects*—Representative sample (n=769) of residents aged ≥60 on 1 January 1989.**

***Main outcome measure*—Rates of change in bone mineral density measured prospectively (mean scan interval 2·5 years) at the femoral neck and lumbar spine by dual energy *x* ray absorptiometry.**

***Results*—Summary rates of loss in the femoral neck were 0·96% per year (95% confidence interval 0·64% to 1·28%) in women and 0·82% per year (0·52% to 1·12%) in men. Importantly, rates of loss at the femoral neck (both percentage and absolute) increased in both sexes with advancing age. No significant loss was evident in either sex at the lumbar spine, probably because of coexistent osteoarthritis. Lifestyle factors had only modest effects on rates of loss at either site.**

***Conclusions*—These data show that bone density of the femoral neck declines at an increasing rate in elderly people, and as this site is predictive of fracture suggest that treatment to minimise bone loss may be important even in very elderly people.**

Introduction

Bone mineral density is a predictor of osteoporotic fracture[1] and is determined by both the peak bone density achieved at skeletal maturity and subsequent bone loss related to age and menopause.[2] Bone loss after the menopause seems to be rapid, and subpopulations of "fast losers" have been identified in some studies.[3,4] Whether bone loss continues in elderly people or stabilises is uncertain. Cross sectional studies have indicated that bone loss diminishes in elderly people,[5-7] although recent studies have suggested considerable loss continues in older age, at least in the femoral neck.[8,9] Cross sectional studies, however, cannot measure the true rate of bone loss. Conflicting results from such studies probably reflect limitations in sample size,[10] cohort effects, or survivor bias, and these can be controlled for only by longitudinal studies in fairly large populations. We report changes in bone mineral density determined by longitudinal measurements at the femoral neck and lumbar spine in a large population of elderly white men and women. We also examined the contribution of lifestyle to these changes.

Methods

The city of Dubbo with a population of about 32 000 people is 400 km north west of Sydney, Australia. The Dubbo osteoporosis epidemiology study started in 1989 with the aims of relating incidence of osteoporotic fracture determined prospectively to clinical risk factors, postural stability, and changes in bone mineral density in men and women aged 60 years and over.[1] At the start (1 January, 1989) the target population comprised about 1600 men and 2100 women identified as previously described.[11] Dubbo is ideally suited to epidemiological research, being relatively isolated with its own centralised health services. By 1 July 1993, 784 of the original target population had died (data provided by Australian Bureau of Statistics), leaving a target population of about 2900, of whom 62% were participating in the study. Subjects were included if they provided informed written consent. They could be living in an institution or the community. The present study examined the rates of change in bone mineral density in the first 769 subjects (27%) who presented for their first and second visit before 1 July 1993. The remainder of the target population participating in the study had not then presented for their second visit.

Bone mineral density was measured by dual energy *x* ray absorptiometry with a Lunar DPX densitometer (Lunar Radiation Corporation, Madison, Wisconsin, United States) as previously described.[1] All scans were analysed by using LUNAR DPX-L software program version 3.4. The average interval between the two scans used to determine rates of change was 2·5 years (range 1 to 4 years). Reproducibility was checked every fortnight with an aluminium spine phantom and was found to have a coefficient of variation of 1·6%. The coefficient of variation of bone mineral density at our institution determined in perimenopausal subjects is 1·5% at the lumbar spine and 1·2% at the proximal femur[1] and for elderly subjects is 1·5% and 2·4%, respectively (unpublished data). Bone mineral density of the lumbar spine is uniformly reported as the value for spinal segments L2-L4.

The contribution of lifestyle factors to changes in bone mineral density was also examined. After informed consent was obtained subjects were interviewed at each visit by a nurse coordinator, who administered a structured questionnaire to collect data including age, anthropometric variables (height, weight), and lifestyle factors such as dietary calcium,[12] past and present use of tobacco, and alcohol consumption. Quadriceps strength (maximum isometric contraction) was measured with a horizontal spring gauge calibrated up to 50 kg force[13] in the dominant (stronger) leg while subjects were seated.

To check for representativeness the incidence of fracture was monitored in the target population as well as in those participating in the study. The methods for determining incidence are described in detail elsewhere.[14] Briefly, the numerator was atraumatic symptomatic fractures which were ascertained by

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reviewing x ray reports for the word "fracture" (supplemented by a clinical history) from the only two providers of radiology in the area for the period 1989-92. The denominator was the mid-term population estimated by an initial 'comprehensive private census with subsequent adjustment for deaths (monitored through the Australian Bureau of Statistics). Thus, it was possible to estimate reliably the incidence of fracture in both the target population and those participating in the study.

STATISTICAL METHODS

The statistical analysis aimed at determining (*a*) the trends in rates of loss of bone mineral density in elderly people and (*b*) the predictors of change in bone mineral density.

To examine the predictors of change in bone mineral density, we initially considered several potential predictors such as age, body mass index, lifestyle factors (tobacco, alcohol, and dietary calcium), and quadriceps strength to formulate a regression model for each sex at each skeletal site. The inclusion of variables in the final equation was based on the results of the backward and stepwise regression search in which the probability for entry into the final equation was set to 0·15 and the significance of a predictor variable was defined as $P<0·05$. Collinearity was also investigated by using previously published methods.[15] Based on our previous hypotheses,[16] we were also interested in assessing the effects of baseline bone mineral density, quadriceps strength, and dietary calcium; thus these variables were included in the model regardless of the results of the selection algorithms. We investigated the changes in bone density in relation to the selected predictor variables in both main effect and interaction models.

Since baseline bone mineral density is subject to measurement error, its coefficient (estimated by the least squares method) would be biased. To alleviate this problem we categorised the bone mineral density at baseline into quarters. Data on quadriceps strength and dietary calcium were logarithmically transformed. Because the predictor variables were measured in different units and to simplify the interpretation we expressed the predictor variables in z scores, and the estimated regression coefficients were presented as standardised coefficients.

To estimate what proportion of subjects experienced a change in bone density above that expected because of measurement error alone we calculated the difference between his or her first and second measurements and the variance of the difference (by making use of the known coefficient of variation at each site) and classified changes in excess of 2 SD of the difference as significant (see figs 1 and 2).

All computations were carried out by using the procedure GLM (general linear model) of SAS.[17]

Considerations of sample size assuming a similar SD (3·7%) to that observed in a previous controlled trial[18] indicated that about 110 subjects would be required to show a significant rate of change in bone density of 1% a year with the significance level of 5% and power of 80%. Given our present observed data, we estimated that the power to detect a change of this magnitude in bone mineral density with the sample size of over 280 men and over 470 women was $>0·95$.

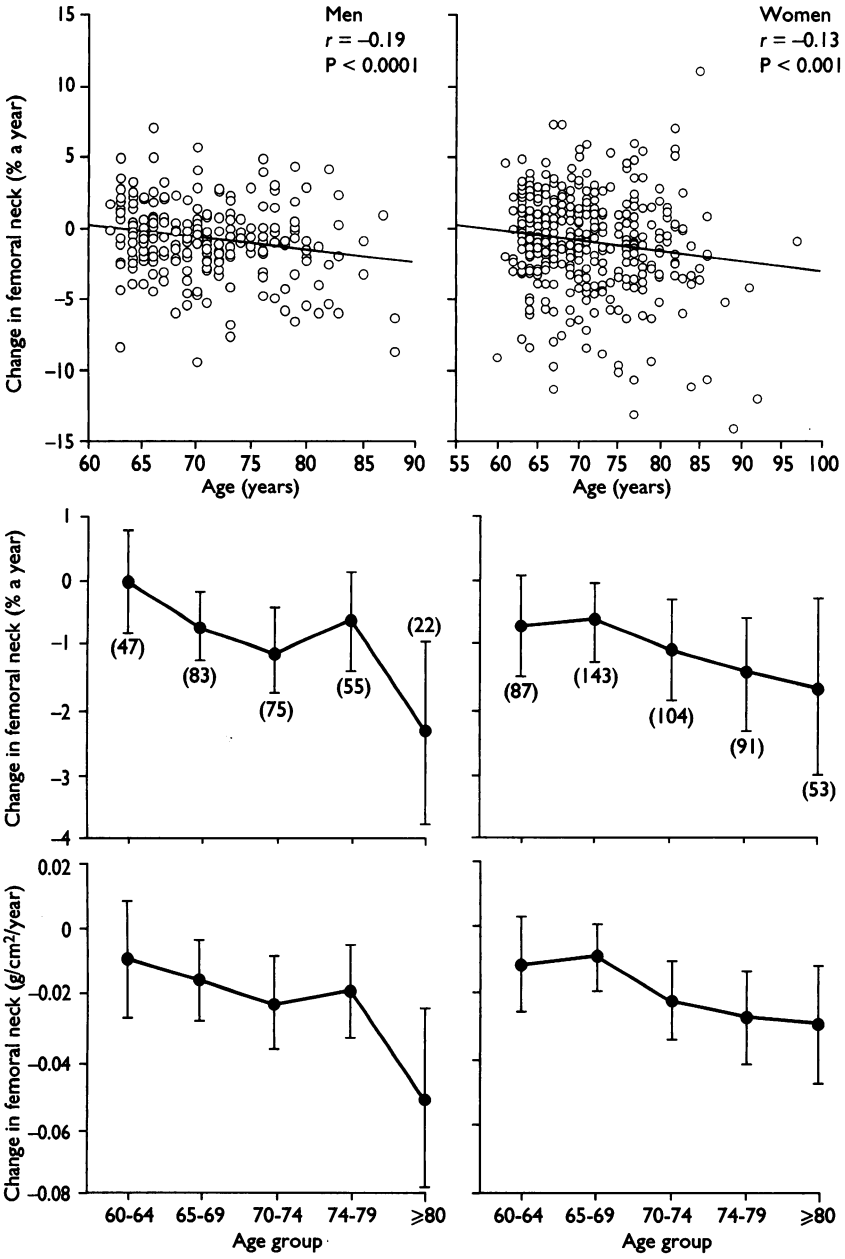

FIG 1—*Increasing rate of loss in bone density of femoral neck with age at baseline. Upper graphs show actual data points with regression line; lower graphs show mean (95% confidence interval) for both percentage and actual change for each age group. In individual subjects, 44% of women and 28% of men had rates of change in excess of that expected because of measurement error alone. Of those with this change, 29% experienced increase and 71% experienced decrease in bone mineral density*

Results

Of the 769 subjects who presented for their second interview and measurement of bone mineral density by 1 July 1993, two subjects declined to have their second scan, and three had had a total hip replacement during the interval between interviews; a small number of scans were unable to be included for technical reasons. This left complete data on 760 lumbar spines and 754 femurs in 763 subjects. A total of 137 subjects were taking one or more drugs with known effects on bone (thiazides 82; oestrogens 25, oral or inhaled corticosteroids, or both, 46; anabolic steroids four). Inclusion of these subjects made little difference to the overall rates of change and statistical modelling, but they were excluded from further analysis, leaving a total of 626 (385 women, 241 men). Table I gives a comparison of incidence of fracture and age and sex structure of this sample compared with the total target population. The incidence of fracture in our sample was lower, but 95% confidence intervals overlapped with that of the original total target population. Table II shows the observed versus expected fractures in this sample broken down by age and sex. Table III shows demographic characteristics in men and women. Rates of loss for each five year age group and by sex are provided in figures 1 and 2.

FEMORAL NECK

The average annual rate of loss at the femoral neck for women was 0·96% (95% confidence interval 0·64%

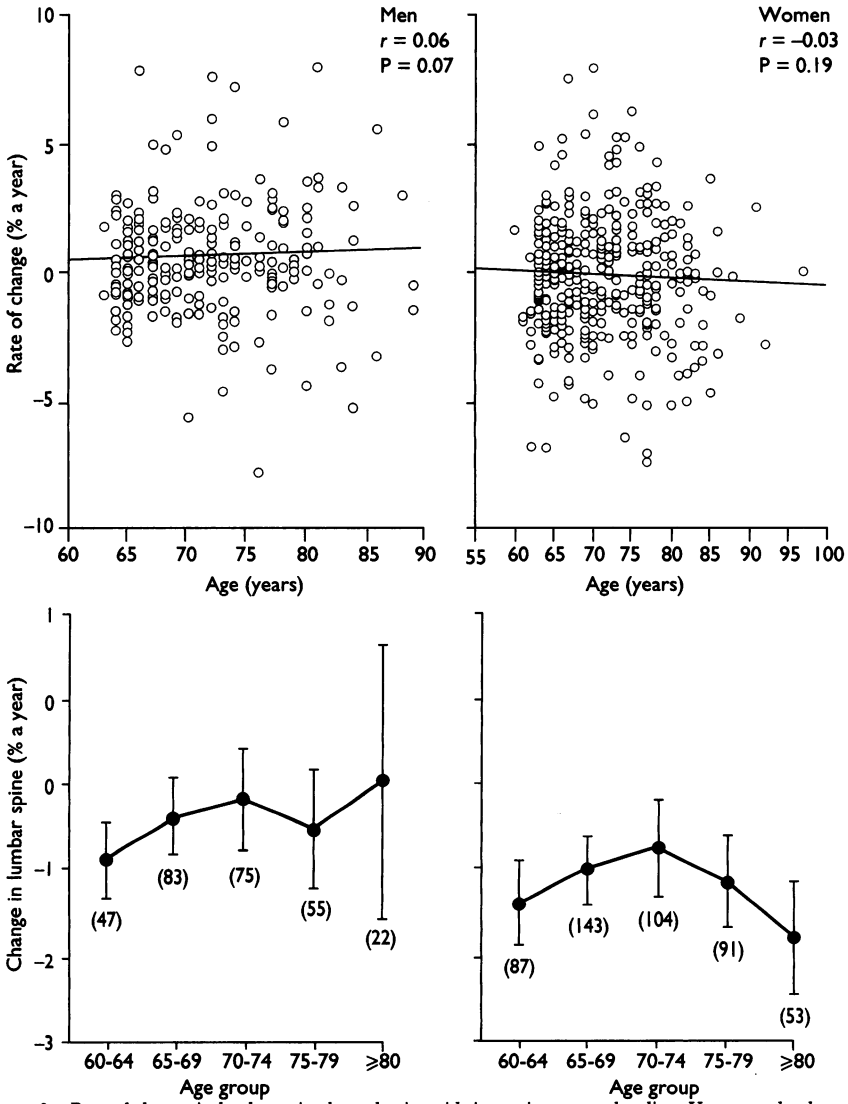

FIG 2—*Rate of change in lumbar spine bone density with increasing age at baseline. Upper graphs show actual data points with regression line; lower graphs show mean (95% confidence interval) for each age group. In individual subjects, 39% of women and 36% of men had rates of change in excess of that expected because of measurement error alone. Of those with this change, men were more likely to experience increase (68%) while marginally more women experienced decrease (54%)*

TABLE I—*Comparison of study sample with total population of Dubbo*

Age (years)	Repeat measurement sample		Target population*	
	Men†	Women†	Men†	Women†
60-64	47 (17)	87 (18)	535 (32)	596 (28)
65-69	83 (29)	143 (30)	414 (25)	498 (23)
70-74	75 (27)	104 (22)	342 (20)	438 (20)
75-79	55 (20)	91 (19)	246 (15)	336 (16)
≥80	22 (8)	53 (11)	153 (11)	293 (13)
Total	282	482	1693	2167
Ratio (women:men)	1·7		1·3	
Incidence of fracture‡	1·1 (0·0 to 2·5)	2·2 (0·9 to 3·5)	1·9 (1·3 to 2·5)	3·2 (2·5 to 3·9)

*As at 1 January 1989.
†Results presented as number (percentage of total).
‡Percentage a year (95% confidence interval based on appropriate formula from binomial distribution). Results derived from previous estimates of incidence of total population of Dubbo aged over 60[14] standardised to that of age structure of total population of Dubbo at start of study.

to 1·28%) and for men 0·82% (0·52% to 1·12%). In both men and women the rate of loss increased with increasing age. In women there was a greater scatter about the regression line, but there was no evidence to support a subpopulation of fast losers apart from some minor skewing to the left. The overall distribution remains normal. In the main effect model rates of change in both sexes were predicted by age, bone mineral density of the femoral neck at baseline, and body mass index (weight (kg)/height (m)^2) (fig 1, table IV). Modelling for interaction showed significant interactions between age and dietary calcium in women

TABLE II—*Incidence of fracture in repeat measurement sample and expected incidence based on incidence in target population*

Age group (years)	No of fractures in men		No of fractures in women	
	Observed	Expected*	Observed	Expected*
60-64	2	2·0	9	5·1
65-69	2	3·5	14	12·5
70-74	2	3·2	5	6·8
75-79	4	6·4	2	11·8
≥80	0	3·4	4	16·0
Total	10	18·5	34	52·2
Observed/expected (%)	54		65	

*Based on numbers in sample and overall incidence in target population.[14]

TABLE III—*Characteristics of study population at time of entry*

Characteristic	Men	Women
Mean (SD) age (years)	70·8 (5·8)	71·1 (6·5)
Mean (SD) weight (kg)	78·3 (12·3)	65·3 (12·2)
Mean (SD) height (cm)	175·0 (6·4)	161·8 (6·6)
Median (range) alcohol intake (g/day)	15·0 (0-140)	4 (0-120)
Median (range) tobacco intake (pack/years)	31 (0-129)	9 (0-1104)
Mean (SD) dietary calcium (mg/day)	627 (365)	645 (345)
Median (range) quadriceps strength	33 (9-50)	20 (3-50)

and quadriceps strength and dietary calcium in men (table V).

LUMBAR SPINE

The average annual rate of change at the lumbar spine for women was −0·04% (−0·26% to 0·18%) while for men there was a significant annual increase in bone mineral density of 0·56% (0·26% to 0·86%). There was no significant relation between rates of change and age at this site. In the main effect model rates of change were weakly predicted by initial bone mineral density in women (P=0·12) and age in men (P=0·08) (fig 2, table IV). Modelling for interaction revealed no significant interactions (table V).

Forty four subjects in our sample who had symptomatic fractures identified from *x* ray reports had higher annual rates of loss (adjusted for age and sex) at the femoral neck and lumbar spine than had those who did not have a fracture (femoral neck −1·40% *v* −0·84%, P=0·26; lumbar spine −0·72% *v* 0·29%, P=0·007). The failure to achieve significance at the femoral neck probably reflects the combination of the fairly small numbers of subjects with fracture and the higher variability of rate of change in the femoral neck in our sample. Cigarette smoking (n=68), as a dichotomous variable or as the number of cigarettes a day or pack years, was not related to the rates of change at either site in both sexes. No other measured variable was significantly related to the rate of change at either site. The rate of change at each site correlated poorly in both men and women (r=0·03 for men and r=0·05 for women), but baseline measures correlated moderately (r=0·55 for men and r=0·62 for women).

Discussion

We observed that considerable bone loss continues at the femoral neck in elderly men and women and that rates of loss increase with age. Previous longitudinal studies in elderly subjects have used the older techniques of single photon absorptiometry[19-21] and dual photon absorptiometry[6 21] to determine the rate of change in elderly people at the radius, calcaneus, and lumbar spine. These studies have suggested that the rate of loss plateaus at all sites apart from the calcaneus[19] and lumbar spine.[21] Three of these studies had small numbers of elderly subjects,[6 20 21] and the other one included women of Japanese ancestry.[19] Ours is the first study reporting rates of change in bone

TABLE IV—*Predictors of change in bone density: standardised estimates of main effect model*

Variable	SD	Femoral neck		Lumbar spine	
		Estimate coefficient	P value	Estimate coefficient	P value
			Men		
Initial bone density*	1·0	−0·15	**0·028**	−0·03	0·657
Age	5·8	−0·22	**0·002**	0·12	0·076
Body mass index	3·5	0·16	**0·018**	0·09	0·156
Dietary calcium†	6·3	0·05	0·364	0·03	0·571
Quadriceps strength†	3·4	0·02	0·783	0·11	0·093
Residual mean square error (250 df)		6·43	**0·002**	4·77	0·128
			Women		
Initial bone density*	1·0	−0·10	0·055	−0·08	0·122
Age	6·5	−0·12	**0·020**	−0·01	0·791
Body mass index	4·6	0·19	**<0·001**	0·03	0·609
Dietary calcium†	0·5	0·01	0·813	0·03	0·508
Quadriceps strength†	0·4	0·03	0·595	0·02	0·723
Residual mean square error (434 df)		11·32	**0·001**	5·26	0·664

*Based on quartile of bone density.
†Based on natural logarithmic transformation.
All other variables are continuous.

TABLE V—*Predictors of change in bone density: standardised estimates of main and interaction effect model*[‡]

Variable	SD	Femoral neck		Lumbar spine	
		Estimate coefficient	P value	Estimate coefficient	P value
			Men		
Initial bone density*		−0·14	**0·031**	−0·03	0·636
Age	5·8	0·29	0·716	−0·53	0·523
Body mass index	3·5	0·16	**0·012**	−0·10	0·143
Dietary calcium†	6·3	−0·88	0·500	−0·22	0·874
Quadriceps strength†	3·4	−1·83	**0·048**	0·61	0·525
Age × dietary calcium	51·4	−0·71	0·541	0·92	0·443
Quadriceps strength × dietary calcium	2·9	2·37	**0·037**	−0·64	0·609
SD		2·51	**<0·001**	3·33	0·186
r^2		0·09		0·04	
			Women		
Initial bone density*		−0·09	0·067	−0·08	0·114
Age	6·5	1·44	**0·008**	−0·40	0·467
Body mass index	4·6	0·19	**0·003**	0·03	0·603
Dietary calcium†	0·5	1·67	**0·020**	−0·50	0·500
Quadriceps strength†	0·4	0·12	0·817	−0·19	0·722
Age × dietary calcium	55·2	−2·12	**0·004**	0·52	0·481
Quadriceps strength × dietary calcium	3·0	−0·19	0·771	0·26	0·695
SD		2·20	**<0·001**	2·30	0·806
r^2		0·06		0·01	

*Because there are interaction terms in model interpretation of main effect should be seen in context of partial derivative with respect to interest variable. For example, in our model for men changes in bone density with respect to quadriceps strength or dietary calcium should simultaneously consider effect of dietary calcium, quadriceps strength, and their interaction term to arrive at overall effect.
†Based on quarters of distribution of bone density.
‡Based on natural logarithmic transformation.

mineral density in elderly white men and women determined longitudinally at the femoral neck and lumbar spine by using dual energy x ray absorptiometry. These findings have important implications for preventing and treating osteoporotic fractures in elderly people.

COMPARISON WITH CROSS SECTIONAL STUDIES

The summary rates of change are similar to those seen in previous cross sectional studies for men and women at the femoral neck and lumbar spine,[5 6 8 9 16 19-23] suggesting that cohort effects were not having a significant influence on these estimates. In contrast with cross sectional studies that have used statistical modelling to estimate the pattern of loss, however, the pattern of loss at the femoral neck (both percentage and actual) was clearly different and increased significantly with increasing age in both sexes. This effect persisted after adjustment for potential confounders such as body mass index, sex, and smoking. Previous cross sectional work has suggested that bone loss at all sites plateaus or is at most linear with age,[5 6 8 9 16 19-23] highlighting the importance of the longitudinal design. Although figures 1 and 2 suggest that a nearly equal number of subjects, especially at the lumbar spine, experienced apparent rises as well as apparent falls in bone density, this was predictable because the coefficient of variation of our measurement instrument in elderly subjects is of the same order of magnitude as the annual rate of change. As has been previously reviewed, different strategies are necessary for detecting changes in individual subjects compared with groups.[24] In the present study there were more individual changes in bone mineral density than could be explained by the 5% expected from measurement error alone, suggesting that a substantial minority experienced real changes in bone density.

CLINICAL IMPORTANCE

The clinical importance of our observations is emphasised by the possibility that the overall effect of aging on bone loss at the femoral neck has been underestimated for several reasons. Firstly, the recent finding that subjects with low bone mineral density have a higher mortality from causes other than trauma indicates that subjects who did not have a second measurement of bone mineral density may have had faster rates of loss than those included in our sample.[25]

Secondly, the elderly subjects reported here, while representative of the total target population in terms of age and sex, had a lower risk of fracture. Although this reduction in risk was not significant, the discrepancy was clearest in those over 75 years of age. Our finding that subjects with fracture have higher rates of loss at the femoral neck and lumbar spine, possibly because of a period of immobilisation, suggests that the relative lack of subjects with fracture over 75 years of age may also underestimate the effect of aging on bone loss.

Body mass index was an important predictor of the rate of change at the femoral neck in both sexes but particularly in women. This suggests that bone loading is particularly important in protecting against bone loss in both sexes. The relative strength of the effect in women suggests also that body mass index may be an indirect measure of postmenopausal production of oestrogen, which largely occurs in adipose tissue.

Current smoking (as a dichotomous variable or measured as number of cigarettes a day or pack years) had no clear effect on the rates of loss in either sex. This finding is in contrast with those from other studies which have suggested that smoking is an important risk factor in both sexes.[26-32] These studies, however, have generally been in younger populations. The other possibility for this finding is the comparative rarity of smokers in our sample (n=68) due to their higher mortality and earlier death. Our cross sectional analysis of this population showed a clear negative effect of smoking,[16] suggesting that smoking may have a more important effect on the attainment of peak bone density rather than subsequent rates of loss. Although rates of loss in the hip were greatest in those with the highest bone mineral density (in both percentage and actual terms) at baseline, this may represent the statistical phenomenon of regression to the mean, whereby outlying measurements are more likely to be closer to the average if measured a second time.

The role of dietary calcium remains controversial. It did not predict rates of change in our sample, although there was evidence of a protective interaction between dietary calcium and quadriceps strength in men despite no apparent effect of each variable alone. We have also found this previously in a cross sectional study of this population.[16] In women, however, there was a negative interaction between age and dietary calcium suggesting that in this overall population those with higher intakes of dietary calcium have greater rates of loss, this being dependent on age. This finding is difficult to explain biologically given the recent controlled evidence of the benefits of calcium supplementation.[33 34] It may be due to selection bias whereby subjects at increased risk of osteoporosis increase their calcium intake.

Clinical implications

- Mineral content of bone is a predictor of osteoporotic fracture
- Bone loss has been thought to slow down with age
- In the femoral neck the rate of loss was seen to increase with age, and no plateau of loss was reached
- Treatment should be initiated to reduce bone loss even in elderly people to lessen the risk of fracture

BONE DENSITIES IN FEMORAL NECK AND LUMBAR SPINE

In direct contrast with findings for the femoral neck, the trend in bone mineral density of the lumbar spine showed no change for women and a significant increase in men. These findings are probably due to coexistent and increasing spinal osteoarthritis with age. Other authors have shown that the degree of osteoarthritis contributes about 27% of the variation in bone mineral density of the spine,[35] and subjects with osteoarthritis have values that are 15% higher on average than those without osteoarthritis.[36] The lack of correlation between the rates of change at each site despite the high correlation between baseline measurements at each site supports this hypothesis with the increasing prevalence of osteoarthritis in elderly people. It is unclear currently whether subjects with osteoarthritis are protected from vertebral fracture or whether osteoarthritis is falsely increasing bone mineral density and acting as a confounder. The lack of effect of lifestyle factors on rates of change at the lumbar spine probably also reflects the presence of coexistent osteoarthritis.

As only a modest, although significant, amount of the variation in the rate of change at the femoral neck and lumbar spine was explained by the combination of demographic and lifestyle factors, it seems likely that other variables also contribute to rates of change in elderly subjects, and these may include genetic influences.[37-39]

CONCLUSIONS

Our findings have important practical implications for reducing the risk of osteoporotic fracture in elderly people. The observation of an increasing rate of bone loss at the femoral neck with age, indicating an exponential or quadratic decline in absolute bone mineral density, suggests therapeutic intervention with agents that prevent further bone loss may be important, even in elderly people. Indeed, because older subjects have the greatest risk of fracture treatment may actually be more cost effective in very elderly people. These findings, in combination with our recent observations of the predictive value of measures of postural instability for symptomatic fractures, including those of the hip, in elderly people[1] provide a rational basis for designing interventions to decrease the burden of osteoporotic fractures.

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