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(Accepted 18 July 1990)

24

Bone mineral loss in young women with amenorrhoea

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Abstract

***Objective*—To examine the impact of amenorrhoea on bone mineral density in women of reproductive age.**

***Design*—Cross sectional study of 200 amenorrhoeic women compared with normally menstruating controls.**

***Setting*—Teaching hospital outpatient clinic specialising in reproductive medicine.**

***Subjects*—200 Women aged 16-40 with a past or current history of amenorrhoea from various causes and of a median duration of three years, and a control group of 57 age matched normal volunteers with no history of menstrual disorder.**

***Main outcome measure*—Bone mineral density in the lumbar spine (L1-L4) as measured by dual energy x ray absorptiometry.**

***Results*—The amenorrhoeic group showed a mean reduction in bone mineral density of 15% (95% confidence interval 12% to 18%) as compared with controls (mean bone mineral density 0·89 (SD 0·12) g/cm^2 *v* 1·05 (0·09) g/cm^2 in controls). Bone loss was related to the duration of amenorrhoea and the severity of oestrogen deficiency rather than to the underlying diagnosis. Patients with a history of fracture had significantly lower bone density than those without a history of fracture. Ten patients had suffered an apparently atraumatic fracture.**

***Conclusions*—Amenorrhoea in young women should be investigated and treated to prevent bone mineral loss. Menopausal women with a past history of amenorrhoea should be considered to be at high risk of osteoporosis.**

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Br Med J 1990;**301**:790-3

Introduction

Osteoporosis is a major cause of morbidity and indirectly of mortality in Western women. It has been estimated that 40% of postmenopausal women sustain at least one osteoporotic fracture[1 2] and that the cost to the NHS of treating hip fractures alone is £160m a year.[3] Loss of bone mineral is a major risk factor for fracture.[4] Demineralisation is related to age, but women have accelerated bone loss with loss of ovarian function at the menopause.[5]

Osteoporotic fractures are rare in young women. Vertebral crush fractures and histologically proved osteoporosis have, however, been reported in young women with anorexia nervosa and amenorrhoea.[6] Stress fractures occur in amenorrhoeic runners with low bone mineral density[7] and in ballet dancers with prolonged lack of oestrogen.[8] Appreciable loss of bone has been recorded in women with hyperprolactinaemic amenorrhoea.[9 10] Cann *et al* found in a series of 38 amenorrhoeic women aged 16-49 that spinal bone mass was reduced when assessed by quantitative computed tomography.[11]

Amenorrhoea is common in women of reproductive age with a reported prevalence of at least 2%.[12 13] Hence any effect on bone mass would have important consequences by predisposing these women to osteoporosis in later life.

Other studies have generally been confined to a single diagnostic group and have been limited by small numbers and comparatively inaccurate techniques of measurement. Measurements have often been confined to peripheral cortical bone whereas loss of trabecular bone is of greater clinical importance. Changes in the lumbar spine seem to be a sensitive indicator of bone loss.[14] We report on a large series of young women with amenorrhoea who were subjected to bone densitometry of the lumbar spine by quantitative digital radiography, which has greater precision than other techniques.

Subjects and methods

The study population consisted of 200 white women of reproductive age (16-40; mean 27·8 years) who had a past or current history of amenorrhoea (defined as absence of menstruation for at least six months). They were an unselected consecutive series of outpatients who attended the reproductive endocrinology clinics at the Middlesex Hospital and Soho Hospital for Women over 18 months. During this period half of all new referrals to the clinics came direct from general practitioners.

The duration of amenorrhoea ranged from six months to 24 years (median 3·0 years). Forty seven patients had primary and 153 secondary amenorrhoea. The cause of amenorrhoea was determined by history, examination, serum hormone estimations, and imaging techniques as appropriate.[15] The diagnostic categories with the largest numbers of patients were weight related amenorrhoea (n=49) and premature ovarian failure (n=48). Twenty two patients had hyperprolactinaemia, 18 polycystic ovarian disease, 17 isolated hypogonadotrophic hypogonadism, and 18

panhypopituitarism. Seventeen patients had gonadal dysgenesis. Eleven were having long term treatment with luteinising hormone releasing hormone analogues.

A group of normal subjects was included as controls. It consisted of 57 healthy volunteers in the same age range as the patients who had no history of menstrual disorder or of medical conditions or treatment that might predispose to osteoporosis.[16]

INVESTIGATIONS

Quantitative digital radiography was performed with a Hologic QDR1000 scanner. This technique uses a dual photon beam from an x ray source[17] giving an absorbed dose of 0·003 mSv and a precision better than 1% in vivo in our unit.[18] Two specially trained radiographers performed all the scans during the study. Measurements were made of vertebral area, bone mineral content, and bone mineral density of the lumbar spine (L1-L4), and the mean bone mineral density was expressed as g/cm^2.

Height and weight were recorded at the time of examination. All patients and volunteers were asked to complete a questionnaire concerning their menstrual history, medical history (including fractures), parity and breast feeding, family history, drug treatment, oral contraceptive use, diet, alcohol intake, smoking habits, and exercise. Details of medical histories were confirmed by reference to hospital case records.

Laboratory investigations were performed in patients for diagnosis and thus were not standardised. Serum concentrations of oestradiol-17β, gonadotrophins, prolactin, thyroxine, and thyroid stimulating hormone were estimated by radioimmunoassay at the Middlesex Hospital. In addition, 58 patients had their serum calcium, phosphate, and albumin concentrations and alkaline phosphatase activities measured by standard procedures in our laboratory. Twenty eight patients provided fasting one hour urine samples[19] for determination of the hydroxyproline to creatinine ratio. Hydroxyproline excretion was measured by colorimetry.[20] Diagnostic ultrasound scanning of the pelvis was performed by experienced radiographers in 120 cases to assess ovarian morphology, uterine cross sectional area, and endometrial thickness.[21]

STATISTICAL ANALYSIS

Preliminary calculation suggested that to achieve a power of 80% in detecting a clinically important (estimated as 5%) difference in bone mineral density between amenorrhoeic and normal subjects significant at the 5% level we would need to have 60 subjects in each group.

Analysis was performed with a statistical package for the social sciences (SPSS-PC). Characteristics of patients and controls were compared by Student's t test, the Mann-Whitney U test, and the χ^2 test as appropriate. Evaluation of bone mineral density in patients and controls was performed by analysis of variance with covariates. Means were adjusted for the influence of covariates. The heterogeneous group of patients was subdivided by diagnosis for further analysis, and relevant variables affecting bone mineral density in the study group (such as weight, height, and oestrogen state) were examined separately. Methods used were analysis of variance for nominal variables, regression analysis for continuous variables (using logarithmically transformed data when appropriate) and calculation of correlation coefficients, and multiple regression analysis with a stepwise method for inclusion of variables.

TABLE I—*Characteristics of patients and normal controls*

	Controls (n=57)	Patients (n=200)	p Value*
Mean age (years) (SD)	29·6 (6·7)	27·8 (6·3)	
Mean height (cm) (SD)	166 (7)	161 (9)	<0·0005
Mean weight (kg) (SD)	61·7 (9·2)	58·6 (11·6)	0·03
Mean body mass index (kg/m^2) (SD)	22·6 (3·8)	22·5 (3·9)	
No (%) parous	10/57 (17·5)	25/191 (13·1)	
No (%) ever smokers	15/57 (26·3)	69/162 (42·6)	0·02
No (%) taking regular exercise	22/55 (40·0)	32/162 (19·8)	0·004
No (%) oral contraceptive users (ever users)	45/57 (78·9)	141/193 (73·1)	
Median duration of oral contraceptive use (years) (range)	3·5 (0-15)	2·0 (0-19)	
Median alcohol intake (units/week) (range)	7 (0-14)	2 (0-42)	
Mean vertebral bone mineral density (g/cm^2) (SD)	1·05 (0·09)	0·89 (0·12)	<0·0005

*For differences significant at 5% level.

Results

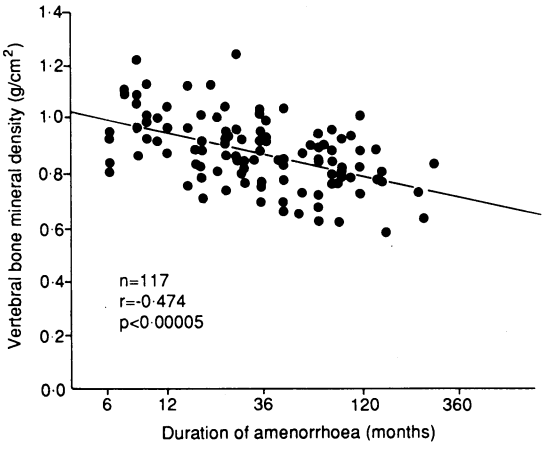
Table I gives the characteristics of the amenorrhoeic patients and normal controls. The groups were comparable in age, body mass index, parity and breast feeding, type of diet and alcohol intake, and previous use of the contraceptive pill. The mean weight of the patients was less than that of the controls (because of the inclusion of patients with weight related amenorrhoea) and their mean height was less (because of the inclusion of patients with longstanding hypopituitarism and Turner's syndrome). More patients were cigarette smokers and fewer took regular strenuous exercise compared with controls.

Vertebral bone mineral density was significantly lower in the amenorrhoeic women than in the controls (0·89 (95% confidence interval 0·88 to 0·91) g/cm^2 v 1·05 (1·02 to 1·07) g/cm^2; p<0·0005) (table I). This difference persisted after correction for height, weight, exercise, and smoking habits (adjusted means 0·90 g/cm^2 and 1·04 g/cm^2; p<0·0005). Bone mineral density was significantly reduced in every diagnostic group except women with polycystic ovarian disease and those being treated with luteinising hormone releasing hormone analogue (table II). Patients with

TABLE II—*Mean vertebral bone mineral densities in various diagnostic groups (SD in parentheses)*

Diagnostic group	No of patients	Bone mineral density (g/cm^2)
Gonadal dysgenesis*	17	0·80 (0·10)
Hypopituitarism*	18	0·83 (0·11)
Hypogonadotrophic hypogonadism*	17	0·87 (0·12)
Weight related amenorrhoea*	49	0·87 (0·10)
Premature ovarian failure*	48	0·91 (0·13)
Hyperprolactinaemia*	22	0·93 (0·10)
Treatment with luteinising hormone releasing hormone analogue	11	0·93 (0·08)
Polycystic ovarian disease	18	0·99 (0·12)
Total	200	0·89 (0·12)

*Groups different from controls at 5% level of significance (analysis of variance with Scheffe's procedure).



Vertebral bone mineral density in relation to duration of amenorrhoea in patients currently amenorrhoeic. In patients with primary amenorrhoea duration was calculated from expected age at menarche (that is, 14 years)

primary amenorrhoea had significantly lower bone mineral density than those with secondary amenorrhoea irrespective of diagnosis (0·81 (SD 0·10) g/cm^2 (n=47) *v* 0·92 (0·11) g/cm^2 (n=153); p<0·00005).

Vertebral bone mineral density was inversely related to the duration of amenorrhoea. This was a logarithmic relation. For all subjects (n=191) regression of bone mineral density on log (duration) gave r=−0·35; p<0·00005. The relation was strongest for subjects currently amenorrhoeic (figure).

The relation between vertebral bone mineral density and indices of oestrogen deficiency was investigated. Bone mineral density was significantly correlated with circulating concentrations of oestradiol-17β measured at the initial outpatient attendance with untreated amenorrhoea (mean oestradiol-17β concentration (n=119) 91 (SD 73) pmol/l; r=0·30, p=0·001). Uterine size assessed by ultrasound scan during the episode of amenorrhoea was significantly correlated with bone mineral density (mean uterine cross sectional area (n=116) 15·7 (6·6) cm^2; r=0·33, p=0·0004). Endometrial thickness was not strongly related (mean (n=120) 3·4 (2·2) mm; r=0·17, p=0·07).

Analysis of the effect of oestrogen treatment on vertebral bone mineral density showed no significant difference between currently treated and untreated patients (table III), nor was any trend discernible with increasing duration of treatment (n=54; r=−0·04, p=0·67). No difference in mean bone mineral density was apparent between patients with a past history of amenorrhoea (n=73; 0·89 (0·11) g/cm^2) and those with current amenorrhoea (n=117; 0·89 (0·12) g/cm^2).

A past history of fracture was related to bone mineral density. Fifty seven patients reported at least one fracture, and their mean bone mineral density (0·85 (0·12) g/cm^2) was significantly lower than that of patients who had never had a fracture (n=102; 0·91 (0·12) g/cm^2) (p=0·003). The fracture history was unknown or doubtful in 41 patients. Most fractures were associated with a clear history of trauma such as riding accidents or falls from skis. No precipitating event was recalled by the patient in 10 cases, and this subgroup had a mean bone mineral density of only 0·80 (0·10) g/cm^2 (NS). Four patients reporting an atraumatic fracture had also suffered at least one previous fracture.

Analysis of factors affecting bone mineral density within the study group yielded significant simple correlations with height (n=195; r=0·22, p=0·002) and weight (n=196; r=0·32, p<0·00005). Multiple regression analysis showed that weight accounted for the variability of bone mineral density determined by height by virtue of the interdependence between these two factors. No relation was detected between age and bone mineral density in this population. Twenty five patients had had at least one full term pregnancy, and their bone mineral density was higher than that of the nulliparous patients (0·93 (0·09) g/cm^2 *v* 0·88 (0·12) g/cm^2; p=0·012). A family history of osteoporosis was reported by 18 patients; no difference in their bone mass was detectable compared with others.

Thirty nine patients were cigarette smokers and a further 30 were ex-smokers. No effect on bone mineral density was detected (table IV), and no trend was discernible with increasing consumption (expressed as lifetime consumption in packs). Thirty two patients undertook regular moderate or strenuous exercise (aerobics, distance running, etc); no difference in bone mineral density was detected compared with sedentary subjects (0·90 (0·10) g/cm^2 *v* 0·89 (0·13) g/cm^2; NS). Detailed dietary assessment was not attempted. Patients were, however, questioned on their intake of dairy products (excluded by two), vegetarian diet (26 were vegetarians), and use of calcium supplements (five took supplements), and no effect of these factors was detected. No correlation was detected between bone mineral density and alcohol consumption. Only five patients, however, reported drinking more than 14 units a week.

Serum calcium measurements (corrected for albumin) were available in 58 cases; no relation to bone mineral density was found. Serum alkaline phosphatase activity, however, was negatively correlated with bone mineral density (n=58; r=−0·39, p=0·003). Measurements of the urinary hydroxyproline to creatinine ratio (28 cases) showed a weak negative relation (r=−0·32; p=0·047).

TABLE III—*Effect of oestrogen treatment on mean vertebral bone mineral density in 193 patients for whom data were available (SD in parentheses)*

	No of patients	Bone mineral density (g/cm^2)
Treated	60	0·87 (0·12)
Untreated	133	0·90 (0·12)
Previous users of oral contraceptives	81	0·91 (0·12)
Never users of oral contraceptives	52	0·87 (0·11)

There were no differences at 5% level of significance among never users, past users, and current users of oestrogen (analysis of variance)

TABLE IV—*Effect of cigarette smoking on mean vertebral bone density in 162 patients for whom data were available (SD in parentheses)*

	No of patients	Bone mineral density (g/cm^2)
Never smokers	93	0·89 (0·12)
Ever smokers	69	0·89 (0·12)
Ex-smokers	30	0·93 (0·10)
Current smokers	39	0·86 (0·13)

There were no significant differences among the groups.

Discussion

This study examined the effect of amenorrhoea on bone mass in women of reproductive age (16-40). We excluded patients over 40 because a decline in vertebral bone mass has been reported in premenopausal women.[14] The age at which peak bone mass is attained is uncertain, but as we found no correlation between age and bone mass in our normal population we included 20 patients below the age of 20. All subjects in the study were white. There are racial differences in bone mass,[22,23] and no normal range has been established for women from other ethnic groups living in the United Kingdom.

Amenorrhoeic subjects differed from controls in three respects: they were smaller; they smoked more; and they took less exercise. These three factors would be expected to have a negative effect on bone density. Analysis of the data with allowance for these variables, however, confirmed a highly significant reduction in bone mass associated with amenorrhoea. Moreover, separate analyses showed no difference in bone mass between the exercisers and the sedentary or between smokers and non-smokers. Thus amenorrhoea is associated with demineralisation.

We hypothesise that amenorrhoea affects bone mass through the mechanism of oestrogen deficiency,[24] analogous to the effect of loss of ovarian function at the menopause. This study provides several pieces of evidence to support this. Primary amenorrhoea was associated with particularly low bone mass, which reflects the duration and severity of oestrogen deficiency in this setting. All diagnostic groups showed a reduction in bone mass, which was greatest in the group with gonadal dysgenesis—that is, women with no ovarian function. The effect was least in patients with polycystic ovarian disease, in which anovulatory amenorrhoea occurs without lack of oestrogen. A single measurement of the serum oestradiol-17β concentration would be expected to be a crude index of

oestrogen deficiency, yet it was significantly related to bone mass. Uterine size is also an indicator of oestrogen state[25] and was also found to be related to bone mineral density. The mechanism of the effect of oestrogen on bone is not fully understood, but oestrogen receptors have been detected on osteoblasts.[26] We were surprised to find no effect of oestrogen treatment on bone mineral density, but this may have been due to the cross sectional design of the study or to patient selection. We noted, however, that untreated patients who had previously used the contraceptive pill had a slightly higher bone mineral density, suggesting a protective effect of the pill, but this was not significant at the 5% level.

The logarithmic relation between duration of amenorrhoea and bone density indicates that the most rapid bone loss occurs at the onset of amenorrhoea and the rate of loss slows with increasing duration of amenorrhoea.

We noted a surprisingly high incidence of fracture in our study population and found an association between fracture and demineralisation. Hence even among the young, those with lower bone mass seem more likely to incur fracture.[27] Worryingly, apparently atraumatic fractures had occurred in some subjects.

Smoking was not found to affect bone density, although other workers have found a detrimental effect of smoking, which is believed to be mediated through altered oestrogen metabolism.[28] A positive effect of weightbearing exercise has also been reported[29] but was not found in this study. The effect of childbearing is not clearly established.[30] We found that parous subjects had a higher bone density, but this probably reflected the likelihood of fertility in different diagnostic groups. No effect of a positive family history of osteoporosis was detected in this study. Nevertheless, many subjects did not know whether relatives were affected, so that this was likely to be underreported.

Thus in summary, these results show that bone mineral loss occurs in young women with amenorrhoea and that this is related to the duration and degree of oestrogen deficiency rather than to the specific diagnosis. The results imply that even a moderate degree of demineralisation may predispose to fracture.

Amenorrhoea in young women is a common condition and is frequently underinvestigated and untreated. Our findings contradict the common assumption that treatment is necessary only if the patient desires pregnancy; untreated oestrogen deficiency may be damaging her future health. The patients we studied who had lost appreciable bone mass during prolonged amenorrhoea were at high risk of osteoporosis in later life. Indeed, the lowest bone mineral density recorded during the study was 0·60 g/cm^2 in a patient aged 28; this would be considered an "osteoporotic" result in a woman of 70.

Much research has concentrated on secondary prevention of osteoporosis by giving oestrogens at around the time of the menopause.[31] Our study indicates an opportunity for primary prevention. Restoration of menstruation and thus increased endogenous oestrogen would be expected to lead to improvement of bone mass. There is already evidence to support this in the treatment of hyperprolactinaemia[32] and anorexia.[33] When treatment is not possible (in primary ovarian failure caused by gonadal dysgenesis or premature menopause) our results lead us to recommend oestrogen replacement therapy. There is ample evidence for the efficacy of hormone replacement in menopausal patients both in maintaining bone mass and in reducing the risk of fracture.[34,35]

Osteoporosis is a major public health issue in the Western world, and attempts have been made to identify women at greatest risk[19] in order to target the use of hormone replacement therapy. Screening all women at the menopause is as yet far from being a practicable proposition. Nevertheless, this study suggests that we can identify a group of women who are at particular risk.

We thank Professor P J Ell, institute of nuclear medicine; Ms J Ryder and Ms J Heavens for measuring bone density; Dr Olga Rutherford, Rayne Institute, University College London, for recruiting volunteers; Dr Gerry Conway, department of reproductive endocrinology, for statistical help; and Dr Joan Round, department of chemical pathology, for measurements of urinary hydroxyproline.

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(Accepted 10 July 1990)