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Original Article

Bone Mineral Density in Young Women with Long-Standing Amenorrhea: Limited Effect of Hormone Replacement Therapy with Ethinylestradiol and Desogestrel

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Abstract. To assess bone mineral density (BMD) at different skeletal sites in women with hypothalamic or ovarian amenorrhea and the effect of estrogen–gestagen substitution on BMD we compared BMD of 21 amenorrheic patients with hypothalamic or ovarian amenorrhea with that of a control population of 123 healthy women. All amenorrheic patients were recruited from the outpatient clinic of the Division of Gynecological Endocrinology at the University of Berne, a public University Hospital. One hundred and twenty-three healthy, regularly menstruating women recruited in the Berne area served as a control group. BMD was measured using dual-energy X-ray absorptiometry (DXA). At each site where it was measured, mean BMD was lower in the amenorrheic group than in the control group. Compared with the control group, average BMD in the amenorrheic group was 85% at lumbar spine ($p < 0.0001$), 92% at femoral neck ($p < 0.02$), 90% at Ward's triangle ($p < 0.03$), 92% at tibial diaphysis ($p < 0.0001$) and 92% at tibial epiphysis ($p < 0.03$). Fifteen amenorrheic women received estrogen–gestagen replacement therapy (0.03 mg ethinylestradiol and 0.15 mg desogestrel daily for 21 days per month), bone densitometry being repeated within 12–24 months. An annual increase in BMD of 0.2% to 2.9% was noted at all measured sites, the level of significance being reached at the lumbar spine ($p < 0.0012$) and Ward's triangle ($p < 0.033$). In conclusion BMD is lower in amenorrheic young women than in a population of normally menstruating, age-matched women in both mainly trabecular (lumbar spine, Ward's triangle, tibial epiphysis) and mainly cortical bone (femoral neck, tibial diaphysis). In these patients, hormone replacement therapy resulted in a limited recovery of BMD. Therefore, early hormone replacement therapy is mandatory for young amenorrheic women to minimize bone loss.

Keywords: Amenorrhea; Bone mineral density; Densitometry; Desogestrel; Ethinylestradiol; Hormone replacement therapy

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Introduction

Osteporosis is a major cause of morbidity and mortality of the aging population and has become an important public health issue in industrialized societies. In 1940 Albright [1] was the first to recognize that the pathophysiological pathway of osteoporosis was a lack of estrogens in postmenopausal women. There have been numerous reports on postmenopausal osteoporosis and its prevention by adequate hormone substitution since the first controlled studies by Lindsay et al. [2] and Christiansen et al. [3]. Early postmenopausal bone loss due to lack of estrogens occurs primarily in trabecular bone at the spine and forearm [4]. There is, however, some conflicting evidence on the estrogen dependence of the mineral content of the proximal femur [4,5]. Moreover, almost no information is available about the effect of estrogen deficiency on peripheral weight-bearing bones such as the tibia.

In addition to the extent of postmenopausal bone loss, peak bone mass reached at the end of adolescence and premenopausal bone loss are important factors in the pathogenesis of osteoporosis [6]. Several studies

have focused on the influence of primary ovarian failure on peak bone mass or of hypothalamic amenorrhea on early bone loss, with consecutive early osteoporosis [7–9]. Hypothalamic amenorrhea is well known in patients with hyperprolactinemia [10] and anorexia [11,12], but is also seen in young athletes, such as long distance runners [13,14].

Recently, Prior et al. [15] observed loss even in young women with luteal insufficiency but regular menstruation, which suggests that progestins may also play a role in maintaining an optimal bone mass. Prevention of osteoporosis remains a priority as long as there is no adequate treatment to restore mineral loss completely. Adequate calcium intake, abstinence from nicotine and excessive alcohol, non-excessive physical activity and early hormone substitution of hypoestrogenic states are the mainstay of oesteoporosis prevention.

Dual-energy X-ray absorptiometry (DXA) allows precise and accurate measurements of bone mineral density (BMD) [16]. The aim of the present study was: (1) to investigate bone mineral content applying this technique at different sites of the skeleton (lumbar spine, femoral neck, distal tibia) with various bone structures (cortical, trabecular) in amenorrheic young women and to compare the results with those of a control group of regularly menstruating women, and (2) to quantify BMD changes after 12–24 months of hormone replacement therapy in these patients.

Patients and Methods

Twenty-one young women with primary ovarian failure or hypothalamic amenorrhea (aged 18–45 years) were studied at the outpatient clinic of the Division of Gynecological Endocrinology, University of Berne. Athletes, patients on steroid medication or on hormone substitution within the previous 12 months and women with a family history of osteoporosis were excluded from the study. Three of the amenorrheic patients had received hormone substitution in the past. Up to 12 months prior to the first densitometry no patient was taking sex steroids in any form.

Two patients were classified as suffering from primary hypothalamic amenorrhea, 13 patients from secondary hypothalamic amenorrhea, 4 patients from primary ovarian failure with secondary amenorrhea and 2 patients from ovarian dysgenesis. All amenorrheic subjects had normal prolactin, testosterone and dihydroepiandrosterone sulfate levels. Median duration of amenorrhea for the 17 women with secondary amenorrhea was 36 months (range 12–144 months).

All amenorrheic patients were informed that estrogen substitution would be necessary to prevent further bone loss. Therefore an oral contraceptive preparation providing 0.03 mg ethinylestradiol and 0.15 mg desogestrel daily for 21 days per month was prescribed. After 12–24 months BMD was measured for a second time. Fifteen patients accepted hormone substitution and took it as prescribed, 4 patients did not accept it and 2 women were lost to follow-up. Changes in BMD were expressed as annual rates of change as a percentage of the initial value for each patient. One hundred and twenty-three healthy, regularly menstruating women (aged 19–45 years) recruited in the Berne area served as controls.

There were no significant differences in mean weight (56 ± 11 v 58 ± 7 kg), mean height (166 ± 9 v 165 ± 7 cm), and body mass index (20.5 ± 4.1 v 21.5 ± 3.1 kg/m^2) between patients and controls. Mean age was 26 ± 7.2 years in amenorrheic patients (range 18–45 years) and 36.1 ± 7.8 years in controls (range 19–45 years) ($p < 0.001$), a difference which we regarded as irrelevant for the present study in view of the lack of correlation between bone density and age in our group of healthy controls aged between 19 and 45 years. Lack of correlation between age and bone mass in this age group was also reported by others [7,8].

All scans were performed using a dual-energy X-ray absorptiometer (Hologic QDR 1000, Waltham, MA) and analyzed by the same physician (J.-P.C.). The coefficient of variation (CV) was 0.35% in vitro for the spine anthropomorphic phantom supplied by the manufacturer. In vivo, CV was 1% at the lumbar spine, 1.5% at the proximal femur, 3.5% at Ward's triangle, 2.1% at the tibial diaphysis and 1.9% at the tibial epiphysis. In all patients and controls bone density was measured at the lumbar spine (L2–4) and proximal femur (femoral neck and Ward's triangle). The tibia was scanned in all patients and in 74 of the 121 controls: the non-dominant leg was slipped into a soft tissue simulator to compensate for heterogeneity of soft tissue thickness around the tibia and immobilized at 20° of internal rotation (J.-P. Casez et al., unpublished data). Scans were performed using the standard spine program (resolution 1 × 1 mm) and started just below the ankle joint. Analysis was performed on an area 130 mm high and 129 mm wide, the bottom of which was positioned on the top of the ankle joint space. The fibula was excluded from analysis. Two sections of the tibia were analyzed individually (spine subregion analysis program, version 4.47), i.e. epiphysis (mm 12–52) and diaphysis (mm 91–130).

Statistical analysis was performed using SPSS software (Statistical Software for Social Sciences; SPSS, Inc., Chicago, IL). Characteristics and BMD of amenorrheic patients and controls were compared by two-tailed Student's *t*-test and the Mann–Whitney *U*-test as appropriate. Correlation between duration of amenorrhea and BMD was calculated using logarithmically transformed duration of amenorrhea. Data are presented as mean ± SD.

Results

Baseline Investigation

Serum levels of estradiol were below normal values for fertile women (0.22 nmol/l) in all but 2 patients (0.29 and 0.27 nmol/l, respectively), but in all patients the

Table 1. Bone mineral density (BMD), in g/cm^2 measured at different skeletal sites in amenorrheic patients and in the control group

Localization	*n*	Amenorrhea	% of control	*n*	Control	*p*
Lumbar spine L2–4	21	0.89 ± 0.12	85.2	121	1.05 ± 0.13	<0.0001
Femoral neck	21	0.74 ± 0.12	92.4	103	0.8 ± 0.11	<0.02
Ward's triangle	21	0.64 ± 0.15	90.1	103	0.71 ± 0.13	<0.03
Tibial diaphysis	20	1.29 ± 0.12	91.9	74	1.4 ± 0.11	<0.0001
Tibial epiphysis	20	0.70 ± 0.11	92.0	73	0.76 ± 0.1	<0.03

Table 2. Bone mineral density (BMD, in g/cm^2) at first and second densitometry and annual BMD changes as percentage of initial values in 15 amenorrheic patients receiving hormonal substitution with 0.03 mg ethinylestradiol and 0.15 mg desogestrel daily for 21 days a month

Localization	First Densitometry	Second Densitometry	Total change as % of initial value	Mean change as % of initial value per year (*p*)
Lumbar spine L2–4	0.897 ± 0.132	0.972 ± 0.119	3.7 ± 0.9	2.5 (<0.0012)
Femoral neck	0.736 ± 0.131	0.747 ± 0.119	2.1 ± 1.7	1.6 (NS)
Ward's triangle	0.623 ± 0.157	0.643 ± 0.144	2.4 ± 1.8	2.9 (<0.033)
Tibial diaphysis	1.286 ± 0.139	1.291 ± 0.138	0.5 ± 0.8	0.2 (NS)
Tibial epiphysis	0.701 ± 0.119	0.701 ± 0.117	0.3 ± 1.2	0.2 (NS)

progestin challenge test gave a negative result, thus pointing to estrogen deficiency.

Mean BMD was lower in amenorrheic patients than in healthy controls at each of the sites where it was measured (Table 1). Comparison of BMD in the amenorrheic group, expressed as percentage of BMD in controls, revealed no statistically significant difference between the various skeletal sites (one-way ANOVA: $p = 0.44$).

For patients with secondary amenorrhea ($n = 17$) there was a highly significant correlation between the log of the duration of amenorrhea and BMD (expressed as a percentage of normal values) for lumbar spine ($r = -0.84$, $p < 0.0001$), femoral neck ($r = -0.49$, $p < 0.045$), tibial epiphysis ($r = -0.63$, $p < 0.007$) and tibial diaphysis ($r = 0.53$, $p < 0.03$). There was no significant correlation for Ward's triangle ($r = -0.37$, $p = 0.15$).

Follow-up

Twelve to 24 months after enrolment, a second BMD measurement was carried out in 15 women receiving hormone substitution. The results are presented in Table 2. In patients who received the estrogen–gestagen preparation, a significant rise in BMD was noted at the lumbar spine and Ward's triangle, and no significant change at the femoral neck, tibial diaphysis and tibial epiphysis.

Discussion

The present study confirms that chronic amenorrhea is associated with osteopenia and that the latter can be partially reversed by hormone replacement therapy. It shows, however, that the magnitude of this bone loss and of its recovery varies according to the skeletal site taken being considered. Indeed, in the present study, bone mass of amenorrheic women was more depressed at the lumbar spine than at any other site of the skeleton, although these differences were not statistically significant. In fact it was expected that the lumbar spine, a mainly trabecular bone, would be more prone to early bone loss than predominantly cortical bones such as the femoral neck or tibial diaphysis. However, the tibial epiphysis, which consists mainly of trabecular bone, appears to be best preserved, with only an 8% decrease versus controls as compared with 15% at the lumbar spine.

The fact that the tibia is a weight-bearing bone whereas lumbar spine acts as less of one offers an explanation for the heterogeneity in bone loss. Indeed, according to Frost's mechanostat theory, mechanical use of a skeletal site leads to conservation of spongiosa and cortical–endosteal bone [17]. Such discrepancies in degree of severity of oesteopenia between axial and peripheral skeleton have already been noted in metabolic bone diseases of various origins. For instance, bone loss is predominantly axial in corticosteroid-induced osteoporosis whereas the converse is true for hyperparathyroidism and hyperthyroidism [18]. During hormone replacement therapy, however, no sign of recovery could be detected at the tibia whereas a gain in BMD of 2.5% per year was noted at the lumbar spine, suggesting that the lower the degree of osteopenia, the smaller the recovery.

There is no evidence that any therapeutic intervention may lead to full restoration or preservation of bone mass. Wolman et al. [14] in a study on 46 amenorrheic athletes demonstrated that the loss of bone mass at the lumbar spine could be reduced but not completely prevented by specific physical exercise. Rigotti et al. [11] studied 27 patients with anorexia

nervosa and observed that even after a change of dietary habits with subsequent normalization of body weight, the mineral loss of trabecular bone at the radius was not reversible. On the other hand, it has been shown in 35 young amenorrheic women that the mineral loss of cortical bone at the forearm (radius) could be stopped by combined estrogen–progestin substitution. However, in the same patients trabecular bone mass of the vertebrae appeared to decline further [19].

Reduced mineral content is associated with the development of stress fractures. In a case–control study, Myburgh et al. [20] observed a decreased BMD, a higher incidence of irregular menstrual cycles, a lower dietary calcium intake and a rarer use of hormonal contraceptives in 25 young athletes with stress fractures as compared with healthy controls. A low BMD is obviously also associated with frank osteoporotic fractures. Davies et al. [8] compared 200 amenorrheic women aged between 16 and 40 years with healthy controls and found a 15% lower BMD in the lumbar vertebrae (L1–4). Ten of these women suffered from spontaneous fractures. Women with a history of spontaneous fractures showed a significantly reduced BMD. It is interesting that analysis of bone loss revealed a logarithmic correlation between BMD and duration of amenorrhea, an observation that our data confirm. This implies that the most significant bone loss occurs at the beginning of the amenorrheic period. Thus, early hormone substitution appears mandatory for young women with amenorrhea.

In addition to estrogens, gestagens also appear to play a role in the maintenance of skeletal homeostasis. Prior et al. [15], for instance, recently observed a significant decrease in BMD at the lumbar spine in 28 patients with a short luteal phase in more than 1 of 12 cycles and in 13 women who had anovulatory but regular cycles. In the two subgroups of 13 normally ovulating women with a luteal phase of normal length and 12 women with a short luteal phase during only 1 of 12 cycles, no significant change in BMD could be seen.

Most studies on hormone replacement therapy show a 2%–4% gain in BMD after 1–2 years of treatment. In the present study bone gain of similar magnitude was obtained at the lumbar spine and upper femur with hormone substitution given as an oral contraceptive preparation providing 0.03 mg ethinylestradiol and 0.15 mg desogestrel daily for 21 days per month. The mean annual increase in BMD ranged from 0.2% to 2.5% depending on the skeletal site. The largest two increments at the lumbar spine were 11.2% and 7.9%, after 21 and 26 months on therapy, respectively, whereas the mean increment was much lower, i.e. 3.7% after a mean duration of therapy of 18 months.

It is noteworthy that the data obtained by Metka et al. [9] are at variance with all these results. Indeed, these authors obtained increases in BMD of about 20% at the distal forearm after 30 months on hormone replacement therapy and by 12–26% at the lumbar spine after 18 months. The reason for these discrepancies are not readily apparent: 0.625 mg conjugated estrogens used by these authors might be more potent than the 0.03 mg ethinylestradiol and 0.15 mg desogestrel used in this study, but this is unlikely. Indeed, Williams et al. [21] showed in a randomized study in early postmenopausal women that 0.01 or 0.02 mg ethinylestradiol plus 0.5 or 1 mg norethindrone acetate daily provided the same protective effect on bone as did cyclic substitution with conjugated estrogens in a dose of 0.625 mg daily plus 10 mg medroxyprogesterone acetate for 10 days a month.

In conclusion, careful evaluation and early estrogen–progestin substitution is strongly recommended in young amenorrheic women to prevent or reduce a further decrease in bone mass. Women with a history of amenorrhea are at high risk for postmenopausal osteoporosis and spontaneous stress fractures. However, because bone loss can only be partially reversed by late hormone substitution or spontaneous resumption of the menstrual cycle [22], secondary amenorrhea of more than 6 months' duration or primary amenorrhea have to be considered an absolute indication for combined oestrogen–progestin substitution.

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