Bone Mineral Density in Primary and Secondary Amenorrhea

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Abstract

Amenorrhea in young women is one of the best clinical indicators for estrogen deficiency, except in the presence of gynecological structural pathology. This study aimed at investigating bone mineral density (BMD) in patients with primary and secondary amenorrhea. Thirty-six patients were enrolled in the study, seven with primary amenorrhea (mean age 24.3± 4.5 yrs.) and twenty-nine with secondary amenorrhea (mean age 31.1±6.9 yrs.). Eighteen regularly menstruating women (mean age 31.8±3.7 yrs.) served as controls. BMD was measured at lumbar spine, femoral neck, Ward's triangle and trochanter. Results : BMD was significantly decreased in both primary and secondary hypoestrogen amenorrheic patients. Primary amenorrheic patients were more severely affected with a BMD mean Z score below 80 per cent (osteopenia) at all sites measured. The age of primary amenorrheic women also strongly correlated with degree of demineralization. This should emphasize the importance of early diagnosis and treatment of young amenorrheic patients.

Key word : Primary and Secondary Amenonorrhea, Bone Mineral Density

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Osteoporosis is the major cause of morbidity and mortality in aging women especially in western countries. It has been estimated that 40 per cent of postmenopausal women sustain at least one osteoporotic fracture(1). Peak bone mass is one of the major determinants of the subsequent development of postmenopausal osteoporosis. Women usually reach their peak bone mass at 20-35 years old. Recent studies even found that maximum trabecular lumbar spine bone mass may be reached by the age of 15-16 years(2). Factors affecting peak bone mass and causing bone loss in young women are receiving increased attention. Osteoporotic fractures are rare in young women, however, these

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have been reported in young women with anorexia nervosa and amenorrheic runners[3,4]. Amenorrhea in young women is, except in the presence of gynecological structural pathology, one of the best clinical indicators for estrogen deficiency[5,6]. This study aimed at examining the extent of primary and secondary amenorrhea on bone mineral density and also the relationship between duration of amenorrhea and bone mineral density.

MATERIAL AND METHOD

Thirty-six amenorrheic patients were studied between January 1997 and April 1998. Primary amenorrhea was defined as no period by age 14 with absence of secondary sexual characteristics or no period by age 16 and secondary amenorrhea as the absence of menstruation for at least 6 months. Patients with structural pathology were excluded. None of these patients had been treated with sex steroids in the last six months. The cause of amenorrhea was determined by history, examination, progesterone challenge test, serum hormone measurement, imaging techniques and other tests as appropriate. Seven patients had primary amenorrhea (mean age 24.3±4.5 years, range 18-30). Four out of this group presented with gonadal dysgenesis, two patients suffered from hypothalamic dysfunction and the other one from macroprolactinoma. Twenty-nine patients had secondary amenorrhea (mean age 31.1±6.9 years, range 17-40). Mean duration of amenorrhea was 29.3±44.6 months (range 6-240 months). Fourteen of them were premature ovarian failure. Seven patients had prolactinoma with negative progesterone challenge test. Six patients had chronic anovulation and the other two were hypothalamic amenorrhea. The control group consists of 18 healthy regular menstruating women who had no history of medical conditions or treatment that might predispose to osteoporosis.

Bone mineral densities of the spine (lumbar vertebrae 2-4) and femur (femoral neck, Ward's triangle and trochanter) were measured with dual energy X-ray absorptiometry (Lunar Co., Madison, WI). Osteopenia was defined as a Z-score of 80 per cent or less, corresponding to a bone mineral density of more than two standard-deviations below the mean of healthy age and sex-matched controls[1]. Data are presented as their mean±SEM. Statistical analysis was performed by analysis of variance (ANOVA) and by linear regression analysis with a significance level of $P<0.05$.

RESULTS

Table 1 gives the clinical data of the controls and studied group. Patients with secondary amenorrhea were divided into 2 groups according to progesterone challenge test result. (Group I with negative progesterone challenge test which means hypoestrogenic condition while anovulation was the one with positive progesterone challenge test). The age of patients with primary amenorrhea was statistically significant lower than the other groups as expected, while age of the other groups was not statistically different. Height, weight and body mass index (BMI) were not statistically different between the groups. No correlation between body mass index and bone mineral density was found.

Bone mass measurements from the various amenorrheic groups at 4 sites are shown in Table 2 and 3 along with the control values from 18 women in this study. Bone mineral densities in primary amenorrheic patients were significantly lower than controls at all four sites ($P<0.05$). Mean bone mineral densities at all four sites were also

Table 1. Clinical data.

	n	Age (yrs)	Duration of Amenorrhea (mo.)	BMI (kg/m^2)
1° Amenorrhea	7	24.3±4.5*	NA	20.6±2.0
2° Amenorrhea				
- Hypoestrogen	23	32.2±6.6	32.8±49.4	21.6±3.6
- Anovulation	6	27.0±7.1	15.7±10.8	22.9±4.3
Controls	18	31.8±3.7	NA	21.2±2.6

* $p<0.05$ compared with controls
NA = Not applicable

Table 2. Bone mineral densities (g/cm^2)

	n	BMD (g/cm^2)			
		Lumbar	Femoral Neck	Ward's triangle	Trochanter
1° Amenorrhea	7	0.83±0.14 a,b	0.72±0.10 a	0.61±0.14 a	0.57±0.08 a
2° Amenorrhea					
- hypoestrogen	23	0.98±0.10 a	0.82±0.12 a	0.69±0.11 a	0.65±0.10 a
- anovulation	6	1.17±0.08	0.97±0.15	0.90±0.15	0.83±0.14
Controls	18	1.17±0.14	0.96±0.15	0.85±0.14	0.76±0.11

a $p<0.0.5$ compared with controls
b $p<0.05$ compared with hypoestrogen 2° amenorrhea

Table 3. Bone mineral densities (Z-score %).

	n	BMD (Z-score %)			
		Lumbar	Femoral Neck	Ward's triangle	Trochanter
1° Amenorrhea	7	72.7±12.4	79.0±10.3	68.9±15.6	76.6±11.1
2° Amenorrhea					
- hypoestrogen	23	87.8±9.9	91.7±13.7	79.2±12.9	86.7±13.7
- anovulation	6	101.2±12.6	107.8±16.5	103.2±15.8	110.0±18.5
Controls	18	105.0±12.6	106.4±16.9	96.7±15.6	101.5±15.1

below 80 per cent of Z-score. The two most affected sites were Ward's triangle and lumbar spine which were mainly trabecular bones. Bone mineral densities in secondary amenorrhea with hypoestrogen were significantly lower than controls at all four sites ($P<0.05$), however, they were more than 80 per cent of Z-score, except at Ward's triangle. Bone densities of the latter group were higher than the primary amenorrheic group, but significant only at lumbar spine. Bone densities of patients with chronic anovulation were similar to the control group at all sites.

In the primary amenorrheic group, there was a strong negative linear correlation between the age of patients and bone mineral densities at all four sites, except femoral neck ($r = -0.729$, $P = 0.063$). (Fig. 1) There was no linear or loglinear correlation between duration of amenorrhea and bone mineral densities in secondary amenorrhea.

DISCUSSION

Estrogen deficiency is well known to be the major cause of osteoporosis or bone loss in menopausal women. The effect of estrogen on the bone is not fully understood but it generally acts by reducing overall bone turnover and bone resorption rather bone formation[7]. However, why resorption is increased in estrogen deficiency is still unknown. The bone of elderly women, who manifest osteoporotic fractures, depends on both the rate of loss and the initial bone mass, namely peak bone mass, which is the highest value that an individual attains during her lifetime. Previous studies found that maximum bone mass is reached by age 30-35 years with 90 per cent accumulating before 20[8]. However, recent studies in adolescents suggest that the maximum trabecular lumbar spine bone mass may be reached by the age of 15-16 years[2]. Moreover, a recent longitudinal study using dual photon absorptiometry indicates that accumulation rate in area bone mineral density at both the lumbar spine and femoral neck levels increases by 4-6 folds over a 3 year period in females (from 11-14 years)[9]. Therefore, the bone mass attained during childhood and adolescence is one of the major determinants of bone mass content in the peri-menopausal female and the susceptibility to fractures later in life and prevention of osteoporosis has to start in adolescents or at least before the age of 20[8].

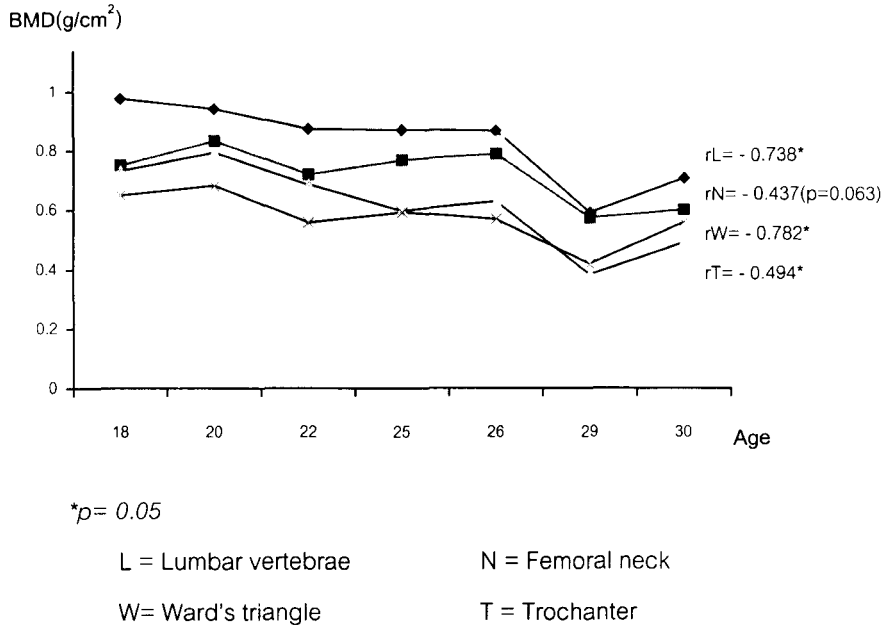

Fig. 1. Age of 1° amenorrhea patient and BMD.

This study investigated the effect of amenorrhea on bone mass at four sites : lumbar spine, femoral neck, Ward's triangle and trochanter in women of reproductive age. Amenorrhea with hypoestrogen was strongly associated with significant bone loss at both cortical and tracecular bones.

In primary amenorrhea, bone mineral densities were significantly lower than controls at all four sites measured. Mean bone mineral densities at all four sites were also below 80 per cent of Z-score, corresponding to a bone mineral density of more than two standard deviations below the mean of healthy age and sex matched controls[7]. Ward's triangle and lumbar spine which were mainly trabecular bone were the two most affected sites. There was also a strong negative linear correlation between the age of primary amenorrheic patients and Bone mineral densities at all four sites except at the femoral neck which was nearly significant. In other words, the longer the duration of hypoestrogenic state is, the lower the bone mineral densities will be. Low bone density in primary amenorrheic patients seems to be a result of reduced bone formation rather than of uncoupling with increased bone resorption. If hormonal replacement therapy is not commenced at the age of normal puberty for these patients, they inevitably develop bone mineral deficit later in life. In our study, primary amenorrheic patients who were only 18 years old already had 13-17 per cent decrease in bone mineral densities and at the age of 22, bone mineral densities at all four sites were below 80 per cent of Z-score.

In secondary amenorrhea, two groups of patients were identified. One with hypoestrogen and the other with chronic anovulation. Bone mineral densities of the hypoestrogenic group were significantly lower than controls at all four sites ($P<0.05$), however, they were more than 80 per cent of Z-score, except at Ward's triangle. Bone mineral densities of this group were higher than that of the primary amrnorrheic group, but significant only at the lumbar spine. In other words, the degree of demineralization in primary amenorrheic patients was higher than those with secondary amenorrhea with hypoestrogen. This seems to be due to demineralization of secondary amenorrheic patients occurring from a higher initial bone mineral density than in the young with primary estrogen deficiency who have never had adequate bone mineralization. Ward's triangle which is mainly trabecular bones was the most affected site. However, we didn't find correlation between the duration of amenorrhea and

bone mineral densities in this secondary amenorrheic group. This result is in contrast with the results of Park and Song who reported that there was no decrease in bone mineral densities within the first year of amenorrhea but rapidly decreased during the subsequent 2 years and thereafter the bone loss slowed down[8]. The different results could be due to our small sample size and the fact that we didn't know the initial bone mass of each amenorrheic patient before they had hypoestrogenic states.

In chronic anovulation, bone densities were not significantly different from controls at any site. This is in contrast with other forms of amenorrhea. Women with chronic anovulation are not in hypoestrogenic states and frequently have hyperandrogen with the expected positive effect on bone mineral densities[10].

Although osteoporotic fractures are rare in young women, they do occur[3,4]. This risk of fractures was found to be associated with the overall degree of demineralization. Hormonal replacement therapy by means of estrogens and progestogens has been shown to increase bone densities in amenorrheic as well as postmenopausal patients. However, a substantial gain in bone mass by oral hormonal replacement therapy has not been shown in amenorrheic, osteopenic patients. Most studies show a 2-4 per cent gain in bone densities after 1-2 years of treatment[11-15]. There is no evidence that any therapeutic intervention may lead to full restoration or preservation of bone mass[11-13]. Moreover, it is not clear whether the bone mass deficit of these patients can ever be compensated for in later life and physiological replacement doses of ovarian steroids are sufficient. This emphasizes the importance of early diagnosis and initiation of hormonal replacement therapy in these amenorrheic patients. Further investigations are needed to conclude about the doses and forms of estrogens and progestogens required for reconstitution of bone densities in these osteopenic patients.

In conclusion, significant bone loss was found in both cortical and trabecular bone in patients with primary nonanatomical amenorrhea and secondary hypoestrogenic amenorrhea. This should increase the risk of osteoporotic fractures in young amenorrheic women as well as later in life. Thus, careful evaluation and early hormonal replacement therapy is strongly recommended in young amenorrheic women to prevent further bone loss and restore bone mass.

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ความหนาแน่นของกระดูกในสตรีที่ขาดระดูชนิดปฐมภูมิและทุติยภูมิ

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การขาดระดูในสตรีอายุน้อยที่มิได้มีสาเหตุจากความผิดปกติทางกาย เป็นตัวบ่งชี้ที่สำคัญที่สุดอันหนึ่งในการบ่งบอกถึงภาวะการขาดเอสโตรเจน การศึกษานี้มีวัตถุประสงค์ เพื่อหาผลของการขาดระดูทั้งชนิดปฐมภูมิและทุติยภูมิที่มีต่อความหนาแน่นของกระดูก ที่ระดับไขสันหลังส่วนเอว และกระดูกต้นขา มีผู้ป่วยจำนวนทั้งสิ้น 36 คน เป็นผู้ป่วยขาดระดูชนิดปฐมภูมิ 7 คน อายุเฉลี่ย 24.3 ± 4.5 ปี และผู้ป่วยขาดระดูชนิดทุติยภูมิ 29 คน อายุเฉลี่ย 31.1 ± 6.9 โดยมีสตรีที่มีระดูปกติ 18 คน อายุเฉลี่ย 31.8 ± 3.7 ปี เป็นกลุ่มควบคุม ผลการศึกษาพบว่า ความหนาแน่นของกระดูกทุกตำแหน่งลดลงอย่างมีนัยสำคัญทั้งในผู้ป่วยขาดระดูชนิดปฐมภูมิและทุติยภูมิ โดยชนิดปฐมภูมิมีความรุนแรงกว่ามาก และผู้ป่วยขาดระดูชนิดปฐมภูมิจะมีความรุนแรงของภาวะกระดูกบางมากขึ้นตามอายุขณะได้รับการวินิจฉัย ข้อมูลเหล่านี้เน้นให้เห็นถึงความสำคัญของการให้การวินิจฉัยภาวะขาดระดูทั้งสองชนิดและให้การรักษาแต่เนิ่น ๆ

คำสำคัญ : ความหนาแน่นของกระดูก, สตรีที่ขาดระดูชนิดปฐมภูมิและทุติยภูมิ

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