Bone Mineral Status in Turner Syndrome

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Abstract  Bone mineral density (BMD) was studied in 22 young girls with Turner syndrome (5–22 year) in relation to pubertal status and karyotype. BMD of trabecular and cortical bones were evaluated by dual-energy X-ray absorptiometry of the lumbar spine (L2-4 BMD) and II metacarpal bone microdensitometry ($\Sigma$GS/D), respectively. Furthermore, 6 patients treated with growth hormone (GH) were analyzed longitudinally.

The mean Z scores of L2-4 BMD and $\Sigma$GS/D were -1.485 and -1.613, respectively. The mean Z scores of L2-4 BMD and $\Sigma$GS/D corrected for bone age were -1.199 and -1.104, respectively. There was no significant difference in BMD between those who eventually developed puberty and those who did not. No difference in either L2-4 BMD or $\Sigma$GS/D was found between the 14 patients with karyotype monosomy X and the 7 patients with other karyotypes. GH treatment improved the BMD of cortical bone; improvement was marked in patients treated from an early age.

These findings show that mineralization of both trabecular and cortical bone is impaired and that estrogen deficiency is not the only cause of osteopenia in this disease. Moreover, GH may be an effective treatment for osteopenia as well as for short stature.

Key words: Turner syndrome, bone mineral density, dual energy X-ray absorptiometry, II metacarpal bone microdensitometry, growth hormone therapy

Introduction

Turner syndrome is associated with multiple skeletal anomalies, including osteoporosis (1–3). Ovarian failure and consequent lack of the normal pubertal estrogen surge theoretically contribute to insufficient acquisition and maintenance of bone mass. However, some reports have shown that estrogen deficiency per se does not cause osteoporosis in this disease(2, 3). As most patients fail to initiate or complete puberty, estrogen replacement for the purpose of secondary sexual development is usually begun. The optimal age to initiate estrogen therapy remains controversial, because sex steroids have the potential to accelerate skeletal maturation and reduce final height. On the other hand, GH has been increasingly used to treat short stature in this disease. However, the effects of estrogen or GH upon bone mineralization have not been adequately determined. It is therefore critical from a scientific and therapeutic perspective to
establish what causes bone mineral deficiency in this disease.

In this study, we evaluated the BMD of trabecular and cortical bones in girls with Turner syndrome to determine what induces demineralization in this disease. We also obtained longitudinal data for GH-treated patients.

**Subjects and Methods**

BMD was studied in 22 girls with Turner syndrome, aged 5 to 22 years, in relation to pubertal status and karyotype. Of the 22, 11 patients eventually developed puberty, while 4 others did not. The remaining 7 were too young to determine at the time of writing. The karyotype was monosomy X in 16 subjects and various mosaic patterns in the remaining 6. No patients had received sex hormone replacement. BMD of trabecular bones was evaluated by dual X-ray absorptiometry (DXA) of the L2-4 BMD using Hologic QDR-1,000 and that of cortical bones by ΣGS/D using Teijin Bonalyzer (computed X-ray densitometry; CXD). We also studied longitudinal data of six patients receiving GH, administered at a dose of 0.5 IU/kg/ week. All subjects had normal GH values before initiation of therapy. Age-matched Japanese girls were used as normal controls (4, 5). Comparisons between Turner syndrome subjects and control populations used a mean Z score; comparisons between pubertal status and karyotype used the unpaired t-test. Significance was defined as P<0.05. In skeletal age comparisons, bone age was evaluated by the method of Greulich and Pyle (6).

**Results**

1) **BMD in relation to chronological age** (Fig. 1, 2)

Fig. 1 shows L2-4 BMD in relation to chronological age (CA). L2-4 BMD was below the mean value in all the subjects, although

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**Fig. 1** L2-4 BMD vs CA in Turner syndrome (DXA). L2-4 BMD was below the mean value in all subjects. Mean Z score was -1.485. CA: chronological age.

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**Fig. 2** ΣGS/D vs CA in Turner syndrome (CXD). ΣGS/D was below the mean value in most of the subjects and 64.3 % were below -2 SD. Mean Z score was -1.613. Demineralization is severer in cortical bone than in trabecular bone (compare with Fig. 1).
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most were within ±2 SD. Mean Z score was -1.485. Fig. 2 shows ΣGS/D in relation to CA. Z score values were lower than those of L2-4 BMD and 64.3% of the cases were below -2 standard deviation (SD). Mean Z score was -1.613. Z scores of both L2-4 BMD and ΣGS/D tended to become lower with increasing age.

2) BMD in relation to bone age (Fig. 3, 4)

Females with Turner syndrome commonly have a typical lag of 1–3 years in bone age (BA) relative to CA. As this delay in BA may lead to underestimation of BMD in this disease, BMD was adjusted for bone age. As shown in Figs. 3 and 4, both L2-4 BMD and ΣGS/D values corrected for bone age were still below the mean. Mean Z scores of L2-4 BMD and ΣGS/D were -1.199 and -1.104, respectively.

3) BMD in relation to pubertal status (Fig. 5, 6)

As pubertal status strongly influences bone mineral acquisition in normal females, BMD was evaluated in relation to this parameter. The subjects were divided according to Tanner breast stage at age 13; Tanner stage I was regarded as without signs of puberty and Tanner stages II-V as various stages of puberty. Neither L2-4 BMD nor ΣGS/D showed statistically significant differences between subjects who eventually developed puberty and those who did not in L2-4 BMD.
Fig. 6 ΣGS/D and pubertal status. There were no statistically significant differences between subjects who eventually developed puberty and those who did not in ΣGS/D.

Fig. 7 Longitudinal data during GH therapy. GH initiated at an early age improved the rate of bone mineral acquisition. Note the insufficient improvement in those who were started on GH during or after adolescence.

Discussion

It has been documented that BMD is lower in Turner syndrome (2, 3). There have also been reports suggesting that osteopenia associated with this disease is not analogous to postmenopausal osteoporosis (3).

We measured trabecular and cortical BMD in Turner syndrome subjects and found them to be lower than in normal controls. Cortical bone showed severer demineralization. As females of Turner syndrome commonly have a typical lag in skeletal age of about 1–3 years relative to chronological age, BMD was adjusted for bone age. However, this did not completely eliminate the difference. Bone mineral acquisition in normal females is also strongly correlated with pubertal status, possibly due to the effects of estrogen on bone. However, in these subjects, BMD did not differ significantly between sub-

who eventually developed puberty and those who did not.

4) BMD in relation to karyotype

Turner syndrome is said to result from the absence or deletion of the short arm of the second X chromosome. Analysis similar to that described above was performed by dividing the subjects into Xp monosomy and mosaic groups. There were no statistically significant differences between the two groups in either L2-4 BMD or ΣGS/D (data not shown).

5) Longitudinal data during GH therapy (Fig. 7)

Second metacarpal bone microdensitometry was studied longitudinally in 6 subjects. The arrows indicate initiation of GH therapy. Our results showed that this therapy, if initiated at an early age, improved the rate of bone mineral acquisition. However, the rate did not improve sufficiently in those beginning GH therapy during or after adolescence.
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jects who eventually developed puberty and those who did not. Up to now, the effects of estrogen upon BMD are not clear in Turner syndrome. Although there is some evidence that BMD in adults with Turner syndrome is related to estrogen therapy (7), estrogen replacement in Turner syndrome adolescents has not been clearly associated with bone mineral accretion (8). Considering that estrogen affects trabecular bone more than cortical bone (9), and that estrogen strongly affects bone age, our results show that estrogen deficiency is not the only cause of osteopenia in this disease. Although they showed no statistically significant difference between karyotype monosomy X and other types, the osteopenia in Turner syndrome may represent an independent effect of the chromosome constitution (2). Further evaluation with bone mineral turnover markers is required.

Clinical management of children and adolescents with Turner syndrome has focused on growth therapy, and many patients now receive recombinant human GH. It is well known that GH and insulin-like growth factor-I (IGF-I) enhance bone growth per se, and several in vitro studies support the role of GH & IGF-I in bone accretion. However, there is little definite evidence that GH increases bone mineralization in vivo. Our results show that GH therapy, if initiated at an early age, improves the rate of bone mineral acquisition. Previous reports of bone mineral deficiency in Turner syndrome subjects have led to the suggestion that estrogen replacement should begin early in adolescence to prevent this complication. However, because there is serious concern that estrogen stimulates acceleration of bone age and consequently reduces final height, early estrogen replacement cannot be justified on the basis of bone mineral status during GH therapy (10).

In summary, 1) children with Turner syndrome have a decreased BMD, 2) demineralization is not always analogous to postmenopausal osteoporosis, and 3) GH may be an effective treatment for osteopenia as well as for short stature (11).

References

7. Stepan JJ, Musilova J, Pacovsky V. Bone demineralization, biochemical indices of bone remodeling, and estrogen replacement


