Bone Mineral Density in Turner Syndrome: Relation to GH Treatment and Estrogen Treatment

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Abstract. The bone mineral density (BMD) of the second metacarpal bone of the left hand was measured in 57 patients with Turner syndrome by the digital image processing (DIP) method to study the relations between the treatment regimen and their bone mineral density. BMD SD score in the patients who had started the GH treatment before 10 years old was within ±2SD of the standard before 14 years, but the score decreased to below −2SD after 14 years. In the patients who had started GH treatment after 10 years old, BMD score were significantly lower than −2SD, although there was tendency to increased. In the patients who had estrogen after 15 years old, BMD did not increase with GH alone and slowly increased after estrogen replacement. In the other two patients who had started sex steroid hormone replacement treatment before 15 years old, BMD maintained ±2SD. In patients who received combined GH and LH-RH analog treatment, their BMD score did not increase during LH-RH analog treatment. It slowly increased but was still below −3SD after stop of LH-RH analog and start of estrogen treatment. In Turner syndrome, GH may play a role in maintaining prepubertal BMD levels [4], and estrogen plays an important role in pubertal BMD increment. It is recommended that estrogen treatment is started before 15 years of age for maintenance of normal BMD level.

Key word: Bone mineral density, Turner syndrome, GH treatment, Estrogen replacement treatment, LH-RH analog

SHORT stature and gonadal dysgenesis are common features of Turner syndrome. It has been reported that growth hormone and estrogen influence bone maturation and solidity, and that bone mineral density (BMD) levels in Turner girls is lower than normal girls [1–3]. In this study, we measured BMD in patients with Turner syndrome to study the effects of their treatment regimens on BMD.

Subjects

Subjects were 57 patients with Turner syndrome who had been followed longitudinally at the National Children's Hospital, aged between 3 and 42 years. Nine patients received no treatment, 19 patients received only GH treatment, 10 patients received combined GH and sex hormone replacement treatment, 5 patients received only sex hormone replacement treatment, and 14 patients received combined GH and LH-RH analog treatment.

Method

The bone mineral density (BMD) of the 2nd metacarpal bone of left hand was measured by the digital image processing (DIP) method [4].
Results

Fig. 1 shows BMD in patients without any treatment. In the patients without spontaneous puberty, BMD SD score was within \( \pm 2SD \) of standard before 14 years, but the score was below \(-2SD\) after 14 years. In three patients with spontaneous puberty,

![Figure 1](image1.png)

Fig. 1. BMD in patients without any treatment \((n=9)\). Circle symbols indicate spontaneous puberty, square symbols indicate no spontaneous puberty.

![Figure 2](image2.png)

Fig. 2. BMD in patients with only GH treatment \((n=19)\). Square symbols indicate the patients who started GH treatment before 10 years of age, and Circle symbols indicate the patients who started GH treatment after 10 years old. Open symbols represent no GH treatment period, and closed symbols represent the GH treatment period.
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Fig. 2 shows BMD in patients who had received GH only. BMD score in patients who had started GH treatment before 10 years was within ±2SD of the standard before 14 years, but it became lower than −2SD of normal girls after 14 years. In

Fig. 3. BMD in patients with combined GH and sex steroid hormone replacement treatment (n=10). Circle symbols indicate the patients who started sex steroid hormone replacement treatment before 15 years old; square symbols indicate the patients who started sex steroid hormone replacement treatment after 15 years old. Open symbols represent no estrogen treatment period, and closed symbols represent the estrogen treatment period.

Fig. 4. BMD in patients who received only sex steroid treatment (n=5).
the patients who had started GH treatment after 10 years old, BMD scores were significantly lower than −2SD, although there was a tendency to increase. In the patients with combined GH and sex steroid hormone replacement therapy, who had started estrogen treatment after 15 years old, BMD did not increase with GH alone but slowly increased after sex hormone replacement began. In another two patients who had started sex steroid replacement therapy before 15 years old, BMD had been maintained within ±2SD (Fig. 3). BMD in patients who had received only sex steroid was between −1SD and −3SD (Fig. 4). In the patients who had received combined GH and LH-RH analog treatment, BMD did not increased during LH-RH analog treatment. In patients who stopped LH-RH analog and started estrogen treatment, their BMD score slowly increase but still was below −3SD (Fig. 5).

Discussion

There are several reports about the relationship between GH treatment and bone mineral density [1, 2]. Nimura et al. has reported that the mean BMD score in complete GHD before GH treatment was significantly lower than that of normal children, and after start of GH treatment, it significantly increased before puberty. These data demonstrated that GH treatment influences BMD [4].

Nelly et al. has found no reduction in lumbar spine and whole body bone mineral measurement in Turner adolescents receiving GH compared with the normal adolescent population, and concluded that early estrogen replacement is not necessary for adequate bone mineral status in Turner adolescents receiving GH [5]. However in our study although BMD scores in Turner syndrome on GH treatment started before 10 years were maintained within ±2SD before 14 years, they decreased below −2SD after 14 years. The fact that BMD did not increase during pubertal age even on GH treatment demonstrates that estrogen plays an important role in pubertal BMD increment. However, it is difficult to normalize BMD levels when estrogen treatment is started after 15 years.

Significant loss of vertebral bone density was demonstrated in premenopausal women treated with GnRH analog, and bone mineral density did not recover to pretreatment values six months after the
discontinuation of the treatment [6]. There is no study to evaluate the effect on bone mineral density of LH-RH analog in Turner syndrome. We have demonstrated that BMD did not increased during pubertal age in the patients who received combined GH and LH-RH analog treatment; and although their BMD score slowly increased after the discontinuation of LH-RH analog and the commencement of estrogen therapy, it was still below −3SD. Therefore LH-RH analog treatment should be stopped before 15 years for maintenance of a normal BMD level.

Lisslulla et al. has reported that bone mineral density in middle-aged women with Turner syndrome depended on the period of estrogen replacement treatment for maintenance of normal BMD [7]. But in our study, there was no relation between the period of estrogen therapy and BMD (data not shown). Since the observation period was short in our study, longer observation might be necessary to draw a conclusion.

Zseli et al. reported that a decreased basal level of calcitonin was reported in 11 untreated subjects with Turner syndrome [8]. Turner women may need not only estrogen replacement but also other treatments (intake of calcium, other medication etc.) to maintain normal BMD.

**Conclusion**

BMD in patients with Turner syndrome should be carefully followed by longitudinal observation especially after pubertal age.

It is recommended that estrogen treatment is started before 15 years of age for the maintenance of normal BMD levels.

**References**