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NOTE

Low Bone Mineral Density in a Case of Mosaicism Klinefelter Syndrome: Rapid Response to Testosterone Therapy

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Abstract. Male hypogonadism has been recognized as one of the major causes of secondary osteoporosis, but most cases seem to be left undiagnosed. We report a 54-year-old case of mosaicism Klinefelter syndrome lacking typical clinical features such as tall stature or low intelligence, who was found to have marked decrease in lumbar bone mineral density (BMD: 0.686 g/cm^2) during treatment of diabetes mellitus. In investigation for etiologies of secondary osteoporosis, he was diagnosed as having mosaicism Klinefelter syndrome (XXY/XY/XX). Although he was infertile, he lacked typical clinical features of Klinefelter syndrome. Testosterone replacement was started, which resulted in an increase in BMD up to 0.712 g/cm^2 two months after the initiation of therapy. The fact that BMD increased shortly after the initiation of testosterone replacement therapy in the present case supported a beneficial effect of testosterone on BMD, as recently suggested in idiopathic hypogonadotropic hypogonadism. Although the present case was diagnosed as having mosaicism Klinefelter syndrome by investigating etiologies for osteoporosis, it may be stressed that male hypogonadism, in general, should be adequately suspected in the presence of infertility and from the findings of physical examination.

Key words: Klinefelter syndrome, Osteoporosis, Mosaicism, Testosterone treatment, Diabetes mellitus

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HYPOGONADISM has been considered as one of the frequent causes of secondary osteoporosis in man as well as woman [1–4]. However, most of male hypogonadism is left undiagnosed. In particular, Klinefelter syndrome may be difficult to be diagnosed when it lacks typical clinical features such as tall stature or low intelligence. Kleerekoper stated that he made the diagnoses of Klinefelter syndrome in a 79-year-old man referred for evaluation of progressive height loss [4]. Here we describe a case of mosaicism Klinefelter syndrome, which was discovered because decreased BMD was found in the examination of non-insulin-dependent diabetes mellitus. Testosterone replacement therapy was initiated, which resulted in a marked increase of BMD, supporting a beneficial effect of testosterone on BMD, as recently reported in hypogonadotropic hypogonadism.

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Case Report

A 54-year-old man was diagnosed as having diabetes mellitus in 1983. Insulin therapy was started in 1994. Urinary C-peptide level was low (6.6 μg/day). HbA1c was 8.0% under the treatment

Table 1. Endocrinological examinations.

ACTH	27.7 pg/ml (4.4–48)	TSH	0.9 μU/ml (0.4–5.0)
LH	7.8 mIU/ml (1.8–5.2)	T4	7.7μg/dl (5.0–14)
FSH	30.5 mIU/ml (2.9–8.2)	Free T4	1.2 ng/dl (0.8–2.3)
PRL	4.3 ng/ml (<10)	T3	83 ng/dl (80–180)
progesterone	0.4 ng/ml (0.0–0.4)		
DOC	0.070 ng/ml (0.08–0.28)	PTH	191 pg/ml (180–560)
cortisol	12.1 μg/dl (2.7–15.5)	$1,25(OH)_2D_3$	18.3 pg/ml (20–60)
DHEA-S	725 ng/ml (518–2210)		
estradiol	<10 ng/ml (15–60)		
testosterone	0.3 ng/ml (2.7–10.7)		
17-KS	5.9 mg/day (3.0–9.0)		
17-OHCS	3.1 mg/day (2.1–11.5)		

Normal range is shown in parenthesis. DOC, 11-deoxycorticosterone; DHEA-S, dehydroepiandrosterone sulfate; 17-KS, 17-ketosteroids; 17-OHCS, 17-hydroxycorticosteroids; $1,25(OH)_2D_3$, 1,25-dihydroxycholecalciferol.

with 10 units/day of insulin. He was married and had a history of previous consultation with an urologist, who made a diagnosis of untreatable infertility, although further examination was not done. He was 162 cm tall and weighed 46 kg. His intellectual activity was normal. Olfactory sensation was slightly impaired because of sinusitis. The beard, axillary hair and pubic hair were sparse. The penis was normal, but the both testes were soft and small (about 3 ml). BMD of L2–4 were measured with dual-energy X-ray absorptiometry (QDR-4500, Hologic Co., Waltham, MA), as we previously reported [5–7]. It showed a marked decrease (0.686 g/cm^2: T 65%, Z 72%) in November 1996. $1\alpha(OH)D_3$ (0.5 μg/day, *po*) was administered, but BMD was still low at 0.675 g/cm^2 in March 1997. Endocrinological examinations revealed low serum testosterone 0.6 ng/ml (normal 2.7–10.7 ng/ml) and high LH (10.2 mIU/ml) and FSH (30.5 mIU/ml), indicating primary hypogonadism. Other hormone levels were normal, as shown in Table 1. LHRH (100 μg, *iv*) test showed almost normal responses of both LH and FSH. hCG loading (5000 U/day, *im*, 3 days) test resulted in a low response of testosterone up to 1.8 ng/ml. These findings prompted us to investigate a possibility of Klinefelter syndrome, as a major cause of male hypogonadism presenting with osteoporosis. Chromosomal analysis on peripheral blood leukocytes revealed a mosaicism of Klinefelter syndrome (XXY/XY/XX: cell count %; 91%, 5%, 4%, respectively). Testosterone replacement therapy (testosterone enanthate 125 mg, *im*) was started on March 3, 1997 and repeated every two weeks for five times until May 5, when BMD was measured again. BMD showed a great increase up to 0.712 g/cm^2, compared to that before testosterone replacement therapy (Fig. 1). Both LH and FSH levels were decreased to normal range (0.5 and 6.4 mIU/ml, respectively) after testosterone replacement.

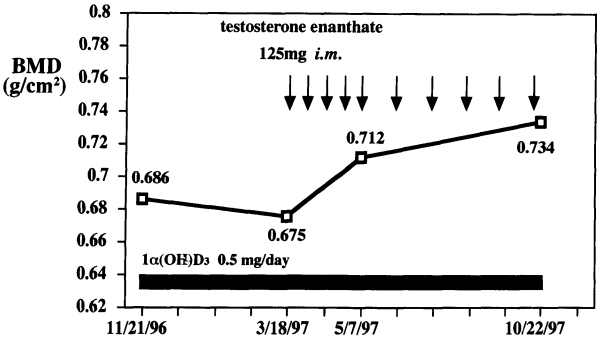

Fig. 1. Clinical course of the patient showing an increase in bone mineral density (BMD) after testosterone replacement therapy.

Discussion

The present case was diagnosed as having Klinefelter syndrome at his age of 54 years. Although he had been indicated to be infertile, he had been undiagnosed since he lacked some of the typical clinical features to Klinefelter syndrome,

such as tall stature, gynecomastia or low intelligence. Diabetes mellitus is frequently associated with Klinefelter syndrome. We have recently reported that BMD is correlated with endogenous or exogenous insulin in NIDDM [7]. However, the markedly reduced BMD value of the present case was greatly deviated from that predicted by the correlation between BMD with urinary C-peptide level or that with insulin dosage [7]. Furthermore, $1\alpha(OH)D_3$ (0.5 μg/day) treatment, which we previously reported to be effective in increasing BMD [6], failed to increase BMD. These findings prompted us to investigate other etiologies of secondary osteoporosis, and the diagnosis of Klinefelter syndrome was obtained.

Hypogonadism has been recognized as a major cause of osteoporosis in man [1–4]. It was reported that about half of the man referred for evaluation of osteoporosis had hypogonadism, almost invariably long-standing and undiagnosed [8]. In particular, Klinefelter syndrome, a relatively common chromosomal disorder, has been known to be associated with osteoporosis since earlier [1, 3, 4]. A study with single photon absorptiometry indicated that bone density is decreased in about 25% of patients with Klinefelter syndrome [8].

The mechanisms by which testosterone deficiency causes a bone deficit is poorly understood [9]. Androgen receptor has been identified in mouse and human osteoblast cell lines [10, 11]. Both the activities of 5α-reductase and aromatase, which convert testosterone into dihydrotestosterone and into estradiol respectively, were low in osteoblastic cells [10]. These findings suggest that testosterone itself may act directly on osteoblasts without conversion to dihydrotestosterone or estradiol [10]. Testosterone is also reported to modulate the responsiveness of human osteoblast-like cells for PTH [12]. However, the male cases with loss-of-function mutation of estrogen receptor [13] and with aromatase deficiency [14] have been identified, both of which were associated with osteoporosis, suggesting an important role of estrogen in bone maturation and mineralization in men. Therefore, estrogen might have acted to increase BMD in the present case. Furthermore, the effects of other androgens, such as dehydroepiandrosterone (DHEA), on bone cells, or the effect of other factors than testosterone deficiency, *eg* chromosomal defect itself, on bone metabolism cannot be excluded in Klinefelter syndrome [2], since BMD value did not correlate with serum testosterone level [15].

Testosterone replacement therapy is expected to increase BMD in hypogonadal man. However, study about the effects of testosterone replacement on BMD is relatively limited [9], whereas the positive effect of testosterone on fat-free mass and muscle size has been well recognized [16]. It remains to be elucidated whether BMD may be completely normalized [9]. Finkelstein *et al.* have reported with photon absorptiometry and quantitative computed tomography that patients with hypogonadotropic hypogonadism and initially open epiphysis showed a significant increase in BMD after testosterone treatment up to 2 years, but those with initially closed epiphysis showed minimal improvement [15]. Guo *et al.* have reported that total body BMD was increased after treatment with hCG in six men with isolated hypogonadotropic hypogonadism, who showed increased serum testosterone concomitantly with an increase in serum bone Gla-protein and a decrease in serum bone alkaline phosphatase or urinary N-terminal telopeptide of type I collagen [17]. This suggests that testosterone therapy may increase bone formation and decrease bone resorption. In a very recent report about long-term testosterone treatment in 72 hypogonadal men including 21 cases with Klinefelter syndrome [18], BMD, measured with quantitative computed tomography, was mostly increased during the first year of testosterone treatment in previously untreated patients with low initial BMD. In the present case, BMD was clearly increased shortly after testosterone replacement, suggesting that testosterone replacement could be rapidly effective to increase BMD in osteoporosis associated with Klinefelter syndrome.

In summary, we present a case of mosaicism Klinefelter syndrome, whose BMD was rapidly increased after testosterone treatment. It is suggested that testosterone replacement therapy has beneficial effect on BMD in established osteoporosis associated with Klinefelter syndrome. Although the present case was diagnosed as having mosaicism Klinefelter syndrome by investigating etiologies for osteoporosis, it may be stressed that male hypogonadism, in general, should be adequately suspected in the presence of infertility and from the findings of physical examination.

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