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Site-Specific Effect of Testosterone on Bone Mineral Density in Male Hypogonadism

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To assess the correlation between the remaining serum testosterone and bone mineral density(BMD), and to determine the effect of exogenous testosterone on BMD in subjects with male hypogonadism, we evaluated the serum testosterone levels and BMDs of the femur neck, Ward's triangle and the spine(L1-4) in 20 subjects with Klinefelter's syndrome and 7 with hypogonadotropic hypogonadism before and after testosterone replacement. BMDs of the femur neck, Ward's triangle and the spine were below the age-matched normal mean at 77.8 %(21 / 20), 74.1 %(20 / 27) and 88.9 %(24 / 27), respectively. There were significant differences in serum testosterone levels and the spinal BMD between the two groups and the BMD of the spine closely correlated with the serum testosterone level ($R=0.63$, $p<0.001$). Following a mean 11.8±4.9 months of testosterone replacement, the BMD at all sites increased significantly and the pretreatment difference in spinal BMD between the two groups disappeared. We conclude that, although testosterone may increases the bone density, it has a site-specific effect of maintaining and increasing the bone mass especially at the spine in male hypogonadism.

Key Words : *Testosterone, Bone mineral density, Male hypogonadism*

INTRODUCTION

Osteoporosis occurs less commonly in men but considering their physically more active life, male osteoporosis may have more clinical significance in regards to fractures than in women. Hypogonadism is one of the major risk factors of osteoporosis in men (Seeman et al., 1983 ; Swartz and Young, 1988). To prevent osteoporosis, the peak bone mass must be increased and maintained. There is much evidence that testosterone is required to maintain the peak bone mass in males (Krabbe at al., 1984 ; Stepan et al., 1989). In hypogonadism, the peak bone mass is not reached and prior reports showed that testosterone replacement increases the bone mass in male hypogonadism (Baran et al., 1978 ; Isaia et al., 1992). Alhough, one can presume that increasing the testosterone levels has beneficial effects on bone density, some controversys still exists about the effects of the hormone replacement therapy with regard to the proportion of cortical and trabecular bone (Devogelaer et al., 1992) and the status of skeletal maturity (Seeman et al., 1982 ; Finkelstein et al., 1989) in male

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hypogonadism.

Because the levels of testosterone between Klinefelter's syndrome and hypogonadotropic hypogonadism are different, we tried to assess the effect of the remaining testosterone on bone density in patients who developed hypogonadism before the formation of peak bone mass by measuring the BMD (bone mineral density) in 20 patients with Klinefelter's syndrome and 7 patients with hypogonadotropic hypogonadism at several skeletal sites. We also studied the effect of exogenous testosterone on bone density in both groups.

MATERIALS AND METHODS

A total of 27 adult male hypogonadism patients with delayed puberty or infertility, aged from 20 to 45.5 years (mean, 26.7±1.7) were included in this study. None of the patients had been treated prior to the study with gonadotropins, androgens or any other drugs with a documented action on bone metabolism. None of them had any other medical diseases or abnormal diet habits. Twenty patients had Klinefelter's syndrome and the remaining 7 patients had hypogonadotropic hypogonadism (Kallman's syndrome, 2; idiopathic hypogonadotropic hypogonadism, 5)

After a careful history-taking and a physical examination, the radiological bone age was estimated (Meschan, 1985). Biochemical analyses were performed on the blood after an overnight fast. Serum free-testosterone (ICN Biomedicals Inc., CA, USA) and gonadotropin (Du Pont Co., Wilmington, USA) levels were determined by RIA. Klinefelter's syndrome was confirmed by chromosomal analysis. All patients received a testosterone cypionate injection (250mg, i.m.) every 2−4 weeks for a mean period of 11.8± 4.9 months (range, 6−20 months) and 7 of them received supplemental oral androgens.

Bone mineral density (BMD) was determined by dual photon absorptiometry using a Gadolinium-153 source (Lunar Radiation, Wisconsin, USA) at the femur neck, Ward's triangle and lumbar vertebrae (from L1 to L4). The BMD results were expressed as absolute values (g/cm^2) and as standard deviations (Z scores) (Seeman et al., 1982) from the predicted mean for 63 age-matched normal male subjects (Yong et al., 1988).

The pretreatment BMDs in patients with hypogonadism were compared with those for the age-matched normal controls. The difference between Klinefelter's syndrome and hypogonadotropic hypogonadism, the correlation between serum testosterone and BMD, and the effect of testosterone treatment on BMD were assessed by proper statistical methods such as the Mann-Whitney U test, simple regression analysis and the Wilcoxon signed rank test.

RESULTS

There were no differences in age, height or weight between the 20 patients with Klinefelter's syndrome and the 7 with hypogonadotropic hypogonadism. The mean level of serum free-testosterone for those with Klinefelter's syndrome was 1.55±0.33 ng/ml (normal adult male, 3-10 ng/ml) and for those with hypogonadotropic hypogonadism, it was 0.27±0.04 ng/ml and the difference between the two groups was statistically significant ($p<0.001$). The mean radiological bone ages for the Klinefelter's syndrome group and hypogonadotropic hypogonadism group were 18.5±0.35 years and 17.1±0.41 years respectively, and there was a statistically significant difference ($p<0.01$) (Table 1).

Overall, the BMD distribution in hypogonadism was significantly decreased compared to that of the 63 age-matched normal controls; 77.8 %(21/27), 74.1

Table 1. Clinical characteristics before treatment.

	Age (years)	Height (cm)	Weight (kg)	Testosterone (ng/ml)	Bone Age (years)
Klinefelter's syndrome(n=20)	26.5±1.12	173.1±0.83	69.4±1.99	1.55±0.33	18.5±0.35
Hypogonadotropic hypogonadism(n=7)	28.0±3.34	169.0±3.62	63.8±6.00	0.27±0.04	17.1±0.41
Probability*	NS	NS	NS	p<0.001	p<0.01

Values are given as mean±1 standard error.

*Statistics were assessed with Mann-Whitney U test.

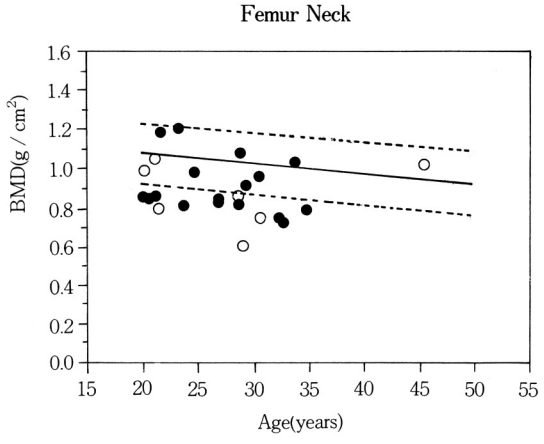


Fig. 1A.

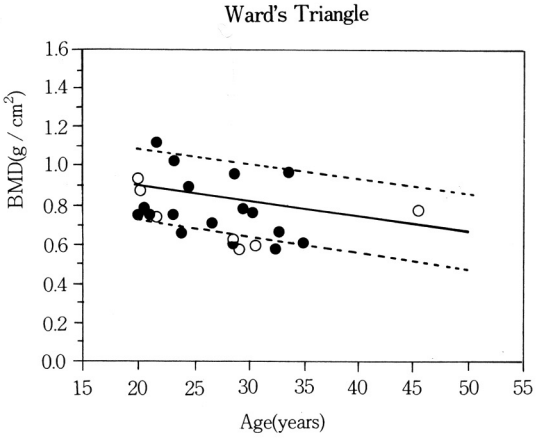


Fig. 1B.

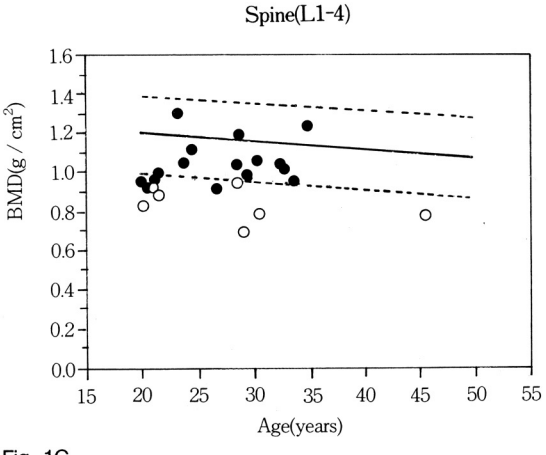


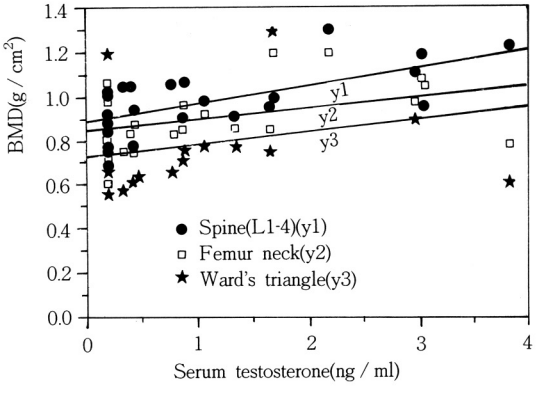
Fig. 1C.

Fig. 1. BMD distribution of 20 Klinefelter's syndrome(●) and 7 hypogonadotropic hypogonadism(○). The solid line indicates the mean BMD of 63 normal adult males, whereas the dotted lines indicate ±1 standard deviation from the mean. A, BMD distribution of femur neck. 77.8%(21/27) of patients are below normal mean. B, BMD distribution of Ward's triangle. 74.1%(20/27) of patients are below the normal mean. C. BMD distribution of lumbar spine. 88.9%(24/27) of patients are below the normal mean.

%(20/27) and 88.9 %(24/27) of the patients had below normal BMDs of the femur neck, Ward's triangle and lumbar spine, respectively (Fig. 1). Especially, all of the patients with hypogonadotropic hypogonadism were below the normal range of BMD for the lumbar spine (Fig. 1C).

Serum testosterone levels had a significant correlation with BMDs at the lumbar spine ($R=0.63$; $p<0.001$) (Fig. 2).

Z-scores for the femur neck and Ward's triangle were similar for the Klinefelter's syndrome group and the hypogonadotropic hypogonadism group, but the spinal Z-scores of the Klinefelter's syndrome group were significantly higher than those of the hypogona-



y1=0.87600+8.2233e-2× R∧2=0.398 p=0.0004
y2=0.84319+4.7967e-2× R∧2=0.131 p=0.0631
y3=0.72267+5.5408e-2× R∧2=0.092 p=0.1247

Fig. 2. Correlation of BMD with serum testosterone level in the 27 patients with hypogonadism. The solid line comes from simple regression analysis with 95% confidence interval and F test.

Table 2. Change of Z-score+ after treatment.

	Before Treatment			After Treatment		
	Femur Neck	Ward's Triangle	Spine (L1-4)	Femur Neck	Ward's Triangle	Spine (L1-4)
Klinefelter's syndrome(n=20)	-0.80±0.19	-0.23±0.22	-0.73±0.13	-0.24±0.18*	0.33±0.24*	-0.78±0.19*
Hypogonadotropic hypogonadism(n=7)	-1.00±0.43	-0.32±0.43	-1.68±0.40	-0.20±0.37*	0.39±0.39*	-0.37±0.30*
Probability**	NS	NS	$p<0.001$	NS	NS	NS

Values are given as mean±1 standard error.
+(patient's BMD-normal BMD)/SD of normal mean.
*Statistically significant($p<0.001$), compared to before treatment. Assessed with Wilcoxon signed rank test.
**Statistics were assessed with Mann-Whitney U test.

dotropic hypogonadism group ($p<0.001$). After testosterone treatment, the BMDs at all skeletal sites in both groups were significantly increased ($p<0.001$), and the pretreatment difference in spinal BMD between the Klinefelter's syndrome group and the hypogonadotropic hypogonadism group disappeared (Table 2).

DISCUSSION

Our results indicate the role of remaining and exogenous testosterone on maintaining and/or increasing the BMD of a specific skeletal site in male hypogonadism.

Peak bone mass is formed early in the 3rd decade and thereafter slowly decreases (Gilsanz et al., 1988). Testosterone plays a major role in maintaining the peak bone mass. Although the direct osteoblastic or calcitonin-mediated effect of testosterone has been observed in previous reports of BMD in hypogonadism (Foresta et al., 1983 ; Colvard et al., 1989), the role of testosterone and its exact mechanism on bone metabolism is not clear yet.

In adult males, castration leads to bone loss (Stepan et al., 1989), and a positive correlation has been demonstrated between low serum testosterone levels and bone density in older men (Foresta et al., 1984). Furthermore, we had a 30-year old patient who had been castrated by a dog bite when he was 4 years old. Alhough his data was not included in this study, his BMD was markedly decreased and was restored to the near normal range after testosterone substitution. So, it is quite clear that testosterone plays a major role in increasing and maintaining bone density in men. Hypogonadism is a major risk factor for osteoporosis in men. Even though they may have other hormonal defects, testosterone substitution increases the bone mass (Bals-Pratsch et al., 1989 ; Greenspan et al., 1989). However, some controversies still exist, in that there is no correlation between serum testosterone levels and bone mass (Devogelaer et al., 1992) and the site specific effects of testosterone with regard to the trabecular or cortical bony proportion are unknown in hypogonadism (Finkelstein et al., 1987 ; Devogelaer et al., 1992). Furthermore, some prior reports pointed out that bone density increases to a greater extent in skeletally immature hypogonadism (Seeman et al., 1982 ; Finkelstein et al., 1989).

In our study, irrespective of the skeletal component proportion (trabecular component proportions at the femur neck, Ward's triangle and the spine were 25 %, 90 % and 50 %, respectively) (Riggs et al., 1982) or skeletal maturity, the overall bone mass increased after treatment. Of interest to us was the pretreatment difference in serum testosterone levels between the Klinefelter's syndrome group and the hypogonadotropic hypogonadism group. Despite the fact that the two groups were similar in chronological age, there were significant differences in skeletal age and lumbar spinal BMD. A statistically significant correlation was found between the serum testosterone levels and the BMD of the spine. After comparing the pretreatment testosterone levels of the two groups, we can speculate that the level of maintained testosterone is very important in determining spinal BMD. After treatment, the testosterone levels were similar for the two groups (data not shown) and the difference in spinal BMDs between the two groups disappeared. These results indicate that in hypogonadism, spinal bone is more sensitive to testosterone than bone at the other sites.

These results are also supported by a prior report that testosterone deficiency is a major risk factor for spinal compression fracture in men (Seeman et al., 1983) and by Diamond et al.(1991) who found similar results in a group of hypogonadal men. The reason for the site specific effect of testosterone on the spine is not clear, but it may be due to the fact that the surface area of trabecular bone is much larger than that of cortical bone in the spine.

In summary, although exogenous testosterone may increase the bone mass in male hypogonadism at every skeletal site, testosterone has a site-specific effect on maintaining and increasing the bone density especially in the spine.

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