Acta Medica Okayama

Volume 51, *Issue* 5 1997 *Article* 7

OCTOBER 1997

Osteoporosis due to testicular atrophy in male leprosy patients

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Abstract

A study was conducted to examine the relationship of testicular atrophy to bone metabolism in male leprosy patients. The study consisted of 31 leprosy patients (mean age: 62.0 years) and 31 healthy control men (mean age: 60.0 years). Measurements were made of their serum levels of free testosterone (FT), estradiol (E_2), luteinizing hormone (LH) and 25-hydroxyvitamin D (25 OHD). Bone mineral density (BMD) was measured at radial sites and the lumbar vertebral bodies (L2-L4) by dual-energy X-ray absorptiometry using a Hologic QDR-2000 densitometer. FT and E_2 levels were significantly lower and LH levels higher in leprosy patients than in controls. This represents a primary hypogonadal pattern. A value of 7.20pg/ml of FT (= Mean -1 SD of control) was used as a cut off value, and the subjects were subdivided into a hypogonadal group (HG) and a non hypogonadal group (non-HG). When the subjects were compared for differences in age, age at onset of disease, duration of disease, body mass index and BMD, only the duration of disease and BMD were significantly different between the two groups. Furthermore, BMD of the forearm significantly correlated with FT levels ($r = 0.689$, $P < 0.0001$). Low BMD may be due to orchitis and testicular atrophy.

KEYWORDS: osteoporosis, testicular atrophy, testosterone, leprosy, male

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*PMID: 9359926 [PubMed - indexed for MEDLINE]

ACTA MED OKAYAMA 1997; 51(5): 279-283

Osteoporosis Due to Testicular Atrophy in Male Leprosy Patients

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A study was conducted to examine the relationship of testicular atrophy to bone metabolism in male leprosy patients. The study consisted of 31 leprosy patients (mean age: 62.0 years) and 31 healthy control men (mean age: 60.0 years). Measurements were made of their serum levels of free testosterone (FT), estradiol (E_2), luteinizing hormone (LH) and 25-hydroxyvitamin D (25 OHD). Bone mineral density (BMD) was measured at radial sites and the lumbar vertebral bodies (L2-L4) by dual-energy X-ray absorptiometry using a Hologic QDR-2000 densitometer. FT and E_2 levels were significantly lower and LH levels higher in leprosy patients than in controls. This represents a primary hypogonadal pattern. A value of 7.20 pg/ml of FT (= Mean − 1 SD of control) was used as a cut off value, and the subjects were subdivided into a hypogonadal group (HG) and a non hypogonadal group (non-HG). When the subjects were compared for differences in age, age at onset of disease, duration of disease, body mass index and BMD, only the duration of disease and BMD were significantly different between the two groups. Furthermore, BMD of the forearm significantly correlated with FT levels ($r = 0.689$, $P < 0.0001$). Low BMD may be due to orchitis and testicular atrophy.

Key words: osteoporosis, testicular atrophy, testosterone, leprosy, male

Osteoporosis due to testicular failure in men is less studied than post menopausal osteoporosis in women because of the rarity of this condition (1-3). However, fractures due to osteoporosis are becoming a serious public health problem in elderly men as well as women (4). Some reports suggest that a percentage of undetected hypogonadal men exist in the healthy population, and they have an elevated risk of fracture (4-6). A primary hypogonadal group of men is therefore needed to study the influence of sex hormones on bone metabolism. There are some reports on hypogonadal men (7-12) but these are generally about hypogonadotrophic hypogonadism or a combination of diseases. To the authors' knowledge, there have been no reports on single-disease primary hypogonadism with osteoporosis, except for Klinefelter's syndrome (13-14). We propose that male leprosy patients are most suitable for the study of senile male hypogonadism resulting in osteoporosis.

Leprosy is an acquired disease caused by Mycobacterium leprae afflicting over 5 million people worldwide (15). Many male leprosy patients have atrophic testes and gynecomastia (16-18). The testes are invaded directly or indirectly by the Mycobacterium, and the degree of hypogonadism depends on the severity of the orchitis. A wide range of hypogonadism, from almost normal to total atrophy with replacement by fibrous tissue, has been reported (16). Bone loss and spinal compression fractures in leprosy patients are not uncommon in Japanese leprosariums, but reports of osteoporosis are very few (19). Whether sex hormones are directly related to bone mineral density (BMD) loss in leprosy patients has yet to be determined. We formulated a hypothesis in which the osteoporosis observed in male leprosy patients is due to orchitis. This study was therefore conducted to determine whether free testosterone (FT) or estradiol (E_2) levels actually affect bone mineral density.

Subjects and Methods

Subjects. Thirty-one male leprosy patients aged

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50 to 69 (average: 62.0) were examined. No subject was more than 69 years old in order to exclude the possibility of senile osteoporosis. They had all lived for several decades at the national leprosarium on a small island in Japan, had eaten the same diet and had no problems with the activities of daily living. Cases with liver cirrhosis and diabetes mellitus were excluded due to their possible effects on bone metabolism. None of the patients were receiving androgen replacement therapy. Weight and height were measured, and the body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). The onset time and duration of the leprosy were determined from chart records. The time to a complete cure was judged by negative results on a skin biopsy, which was performed three times. All patients except one were cured of their leprosy. Informed consent was obtained from each patient. In addition, 31 healthy male volunteers (average age: 60.0) without hypogonadism (HG) were used as a control group. Age matching was done between the leprosy group and the controls.

BMD and body constituent determinations. BMD was determined by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR-2000 densitometer (Biologic Inc., Waltham, MA, USA) in 31 specimens. The standard sites were the UD (ultradistal radius), MID (middle distal radius), 1/3 radius (diaphysis of the radius), and the lumbar vertebrae (L2-L4). BMD data were expressed in grams per square centimeter. The average 1/3 radius BMD for healthy Japanese men was $0.723 \pm 0.059\,g/cm^2$ (60-64 years) and 0.756 ± 0.052 (20-39 years; young male adults) (20). We defined osteoporosis as Mean $-$ 1.5 SD of Japanese young male adults ($0.678\,g/cm^2$). Six cases of compression fractures and four cases of osteoarthritis in the lumbar vertebrae were detected on plain X-ray films, and only the normal vertebrae were used.

Hormones and other profiles. Serum levels of FT, E_2 and luteinizing hormone (LH) were measured by radio immunoassay (RIA). 25-hydroxyvitamin D (25 OHD) levels were determined by a competitive protein binding assay (CPBA). All samples were measured using commercial kits (SRL Inc., Tokyo, Japan). A non-fasting blood sample was drawn between 9:00 a.m. and 11:00 a.m., and the plasma was removed and stored at $-80^{\circ}C$ until assay. Intraassay coefficients of variation determined at this laboratory for FT, E_2, LH and 25 OHD were 4.23%, 4.73%, 2.69% and 6.95%, respectively. Interassay coefficients of variation, as specified by the manufacturer, were: FT, 6.63-18.90%; E_2, 2.32-6.10%; LH, 3.29-5.31% and 25OHD, 10.2-12.6%. Many of the subjects had a long history of orchitis, but the damage varied from almost normal to total atrophy. It was impossible to determine the actual degree of atrophy except by testicular biopsy. For the purposes of this study, a value of 7.20pg/ml of FT (= Mean FT $-$ 1 SD of control) was used as a cut off value. The leprosy patients could be divided into a hypogonadal group (HG: FT < 7.20pg/ml, n = 20) and a non hypogonadal group (non-HG: FT ≥ 7.20pg/ml, n = 11).

Statistical analysis. The statistical analyses were performed using the Stat View package, version 4.5 (Abacus Concepts Inc., Berkeley, USA) on an Apple Macintosh computer. All values are expressed as means $\pm$ SEM unless otherwise indicated. Differences between groups were analyzed by an unpaired Student's *t*-test or an analysis of variance (ANOVA) followed by the Scheffe's F-test as required. The relationship between pairs of variables was analyzed by simple linear regression. *P* values less than 0.05 were considered to be statistically significant.

Results

In the present study, the 25OHD levels were essentially normal (14-52ng/ml; mean $\pm$ SE, 29.13 ± 1.53) in all leprosy patients. The age and serum levels of FT, E_2 and LH are summarized in Table 1. FT and E_2 levels were significantly lower and LH levels were higher in the leprosy patients than in the control cases. Furthermore, BMD of the forearm (1/3 radius) correlated significantly with the FT levels ($r = 0.689$, $P < 0.0001$) (Fig. 1) and E_2 levels ($r = 0.566$, $P < 0.001$). Table 2 shows the FT, E_2 and LH levels in the HG, non-HG, and control groups. The subjects were also compared for differences in age, age at onset of leprosy, duration of the disease,

Table 1 Biochemical data of leprosy patients and healthy controls

	Leprosy (n = 31)	Control (n = 31)	*P* value
Age (years)	62.0 $\pm$ 1.0	60.0 $\pm$ 1.2	NS
FT (pg/ml)	5.67 $\pm$ 0.75	11.67 $\pm$ 0.80	$P < 0.0001$
E_2 (pg/ml)	15.33 $\pm$ 1.29	23.53 $\pm$ 1.94	$P < 0.001$
LH (mIU/ml)	18.63 $\pm$ 2.41	5.61 $\pm$ 0.74	$P < 0.0001$

Abbreviations: FT, free testosterone; LH, luteinizing hormone; E_2, estradiol; NS, not significant.

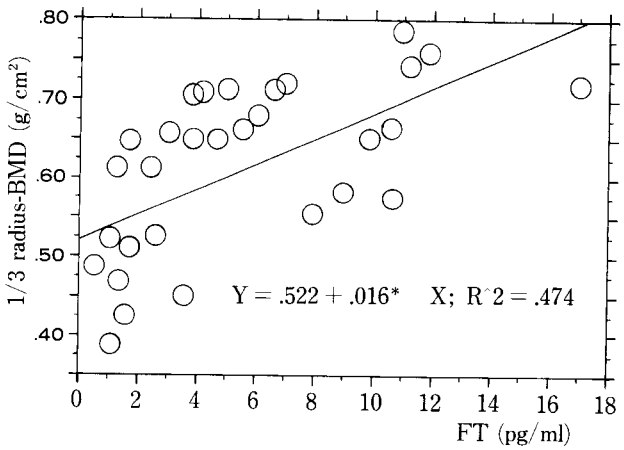

Fig. 1 Correlation between free testosterone (FT) and bone mineral density (BMD). The FT levels are shown to be correlated with the 1/3 radius BMD ($r = 0.689$, $P < 0.0001$).

BMI, BMD (UD, MID, 1/3 radius and L2–L4), and biochemical data in the HG *versus* non-HG groups; the details of this analysis are summarized in Tables 3 and 4. There were no significant differences in age, but there was a significant difference in the duration of the disease between the HG and non-HG groups ($P < 0.05$).

A significant difference in BMD was only seen in the 1/3 radius. The average 1/3 radius BMD of the leprosy patients (n = 31) was $0.613 \pm 0.018\,g/cm^2$ ($0.393 - 0.792\,g/cm^2$). When we defined osteoporosis as Mean $-$ 1.5 SD of Japanese young male adults ($0.678\,g/cm^2$), osteoporosis was present in 17 patients (85.0 %) in the HG group and 4 patients (36.4 %) in the non-HG group. There was no significant difference in BMD of the L2–L4 vertebral bodies. BMI varied from 18.3 to $32.4\,kg/m^2$, and did not correlate with the forearm BMD but rather

Table 2 Biochemical data of HG, non-HG and control patients

	HG (FT < 7.20 pg/ml) (n = 20)	non HG (FT ≥ 7.20 pg/ml) (n = 11)	Control (n = 31)
Age (years)	62.9	60.5	60.0
FT (pg/ml)	3.10 ± 0.46	10.36 ± 0.80**	11.67 ± 0.80**
E_2 (pg/ml)	11.96 ± 0.82	21.46 ± 2.40*	23.53 ± 1.94**
LH (mIU/ml)	21.12 ± 2.74	14.10 ± 4.49	5.61 ± 0.74**

Abbreviations: FT, free testosterone; E_2, estradiol; LH, luteinizing hormone; HG, hypogonadism; non-HG, non hypogonadism.
*, ** Significantly higher than HG groups (* $P < 0.05$, ** $P < 0.0001$).

Table 3 Clinical characteristics of HG and non-HG patients

	HG (FT < 7.20 pg/ml) (n = 20)	non HG (FT ≥ 7.20 pg/ml) (n = 11)	*P* value
BMI	24.5	25.5	NS
Age at onset of disease	14.2	15.4	NS
Duration of disease (years)	42.6	31.9	< 0.05
25 (OH) D (ng/ml)	29.90 ± 1.841	27.73 ± 2.78	NS

Abbreviations: BMI, body mass index; NS, not significant; Others, See Table 2.

Table 4 BMD data of the HG and non-HG patients

	HG (FT < 7.20 pg/ml) (n = 20)	non HG (FT ≥ 7.20 pg/ml) (n = 11)	*P* value
Osteoporosis[a] ($0.678\,g/cm^2$)	17/20 (85.0%)	4/11 (36.4%)	
BMD: UD (g/cm^2)	0.397 ± 0.015	0.424 ± 0.020	NS
BMD: MID (g/cm^2)	0.505 ± 0.016	0.561 ± 0.025	NS
BMD: 1/3 R (g/cm^2)	0.579 ± 0.021	0.676 ± 0.022	< 0.01
BMD: L2-L4 (g/cm^2)	0.818 ± 0.033	0.927 ± 0.047	NS

Abbreviations: BMD, bone mineral density; UD, ultradistal radius; Others, See Table 2.
[a]: A value of $0.678\,g/cm^2$ (Mean $-$ 1.5 SD of Japanese young male adults at radial site) was used as a cut off value for osteoporosis.

correlated with the L2-L4 BMD ($r = 0.367$, $P < 0.05$). There was no significant difference in BMI between the HG and non-HG groups.

Discussion

In the present study, the 25OHD levels were essentially normal in all leprosy patients. The patients were subjected to moderate sun exposure and nutrition was adequate. Low levels of FT and E_2 and high levels of LH are indicative of a primary hypogonadal pattern similar to Klinefelter's syndrome, and suggests a history of orchitis.

A significant difference in BMD was only seen in the 1/3 radius and BMD of the 1/3 radius did not correlated to the BMI. Hence for the study of osteoporosis due to hypogonadism, measuring the radius BMD may be desirable as compared to the lumbar vertebrae.

The age at onset of the leprosy ranged from 9 to 33 years (mean: 14.6), and most patients contracted leprosy before the closure of the epiphysis. The testes might have been damaged before peak bone formation, but there were no significant differences in the age at onset or age when BMD was measured between the HG and non-HG groups. Only the duration of the disease showed a significant difference between the HG and non-HG groups, and correlated negatively with the 1/3 radius BMD ($r = -0.461$, $P < 0.01$). Damage due to orchitis and its effect on BMD may thus depend on the length of the disease, and may be more important than aging. This situation may be roughly analogous to women who have undergone a premenopausal bilateral ovariectomy or hysterectomy.

Based on these findings, both the FT and E_2 would appear to be major determinants of BMD, and a decrease in FT or E_2 levels caused by orchitis may in turn cause secondary osteoporosis in male leprosy patients. However, there is still debate as to which hormone, androgen or estrogen, plays a more important role in affecting BMD in men. Recently, estrogen insensitivity due to a point mutation in the estrogen receptor gene with consequent formation of a premature stop codon was reported in a 28 year old male (21). Serum estradiol and estrone were elevated and serum testosterone concentration was normal. The patients was tall in height and incomplete closure of epiphysis and osteoporotic bones was evident. These findings strongly indicate that loss of E_2 function causes osteoporosis in both males and females. In our case, both FT and E_2 in the HG group were significantly lower than those in the non-HG group and the FT levels correlated with the E_2 levels ($r = 0.665$, $P < 0.0001$). In severely damaged testes, estrogen, which is aromatized from androgen, may not be able to compensate for the loss of testosterone.

In conclusion, very low levels of FT and E_2 may lead to osteoporosis in men with leprosy. If this finding is confirmed by more comprehensive studies, it would point to hormone replacement as an effective means of therapy for such cases (11, 22).

Acknowledgments. The authors express their appreciation to Dr. K. Kawamura, Dr. Y. Kunimune and Y. Terai for collecting the control materials. Thanks are also due to Mr. K. Fukuike, H. Suzuki and K. Tominaga for their help in the preparation of this manuscript.

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Received March 31, 1997; accepted June 10, 1997.