

Chronic Parathyroiditis Manifesting Hypocalcemia to Hypercalcemia

the parathyroid gland but no evidence of commonly observed parathyroid adenoma, hyperplasia or carcinoma. Spontaneous remission due to sudden hemorrhage or infarction of parathyroid adenomas was reported in several cases of primary hyperparathyroidism (2, 3). This can be confirmed by findings of degenerative or necrotic tissues with hemosiderin deposits. Such rare cases are considered to be different from our case since there was neither hemorrhagic nor infarctive trace in the present study.

The pathological findings observed seem to simply lead us to the conclusion that the complicated clinical course could be explained by a mechanism associated with chronic parathyroiditis similar to that of Hashimoto's disease. Hashimoto reported patients with diffuse goiter and clarified the four histological characteristics: diffuse lymphocytic infiltration, formation of lymphoid follicles, destruction of epithelial cells, and proliferation of fibrous tissue (4). The term "Hashimoto's disease" or "Hashimoto thyroiditis" is used to refer not only to goitrous thyroiditis but also chronic thyroiditis or autoimmune thyroiditis including atrophic and nongoitrous thyroiditis. Thyroid function of this disease is variable, from hypothyroidism or euthyroidism to hyperthyroidism. There are some case reports in which the clinical manifestations change as a result of transition between chronic thyroiditis and Graves' disease (5-16). Graves' disease is also classified among autoimmune organ-specific diseases characterized by lymphocytic infiltration of the thyroid and circulating antibodies directed to thyroid-stimulating hormone (TSH) receptors including thyroid-stimulating antibodies. Some patients with primary hypothyroidism subsequently develop hyperthyroidism (5-13). Several factors are considered to explain the changes of thyroid function: disappearance or decrease in titer of a blocking type of TSH receptor antibodies (7-9, 11-13) and emergence or increase in titer of a stimulating-type of TSH receptor antibodies (6-10, 12, 13). Although antibodies against the parathyroid gland were not studied in this case, there was the possibility that such parathyroid-stimulating and/or -blocking antibodies might be involved. Immunohistochemical staining for PTH was weakly positive in lymphoid follicles in the parathyroid gland of this case. However the results of immunohistochemical staining for PTH do not reveal the state of function of the parathyroid glands, whether they are hypofunctional or hyperfunctional. Negative or weak staining is caused by hormone deficiency or by hypersecretion. For example, the vasopressin content in the posterior lobe can be evaluated using magnetic resonance (MR) imaging. On MR T1-weighted images, the posterior lobe is demonstrated as a characteristic hyperintense signal under normal conditions (17), and the signal intensity of the posterior lobe is thought to reflect the content of neurosecretory granules containing vasopressin. The hyperintense signal of the posterior lobe of the pituitary gland is absent in diabetes insipidus on MR T1-weighted imaging, in which vasopressin-deficient hyposecretion occurs. In contrast, the vasopressin content in the posterior lobe is also decreased in patients with uncontrolled

diabetes mellitus, which was thought to be caused by persistent vasopressin hypersecretion (18).

Chronic parathyroiditis is rarely studied. In two extensive studies of parathyroid glands from 800 autopsies, only a single case of chronic parathyroiditis was found (19, 20). Hyperplastic parathyroiditis was also reported in a necropsy case, the function of which was unknown (21). Chronic parathyroiditis was also observed in a few cases of hypoparathyroidism (22, 23).

Thus far five cases of isolated hyperplastic parathyroiditis presenting with hyperparathyroidism have been reported. Two cases of chronic parathyroiditis associated with parathyroid hyperplasia and hyperparathyroidism are described by Bondeson et al (1). One case was a 62-year-old male whose serum calcium continually increased to 11.2 mg/dl (normal range 8.8-10.4 mg/dl). The patient became normocalcemic the day after parathyroidectomy, and serum calcium remained normal at follow-up after 4 years. The removed parathyroid glands contained lymphoid follicles with germinal centers. At the operation four enlarged parathyroid glands were identified. The three larger parathyroid glands were removed while the smallest one was left intact. The other case was a 53-year-old male whose serum calcium was increased to 10.8 mg/dl. Three enlarged parathyroid glands were removed while the smallest one, considered to be normal-sized, was left intact. This patient also became normocalcemic the day after the operation, and serum calcium remained normal at follow-up after 3 years. A third case of hyperparathyroidism associated with parathyroiditis coexisting with brachial-cleft cysts was reported (24). A 57-year-old man, whose calcium levels ranged from 13.52 to 13.60 mg/dl (normal range, 8.4-9.6 mg/dl) and whose PTH was 79.0 pg/ml (normal range, 0-55 pg/ml), had both enlarged inferior parathyroid glands removed. Both glands had similar features, including lymphoid tissue organized into follicles (some of which were replete with germinal centers), and numerous plasma cells (24). The fourth case of hyperparathyroidism associated with chronic parathyroiditis occurred in a multiple endocrine neoplasia type 1 (MEN-1) patient (25), and the fifth case remained hypercalcemic after removal of one parathyroid gland with lymphoid infiltration with germinal centers and one gland normal in microscopic appearance; the other glands were not investigated. In this case PTH was elevated to 164 pg/ml (normal range 10 to 55). Six months postoperatively serum calcium was 11.76 mg/dl and PTH was 90 pg/ml (26). All five cases presented clinically as primary hyperparathyroidism. The clinical course of our case is considered to have initially started as hypofunction, as in Hashimoto's disease, then to gradually have changed to hyperfunction as in Graves' disease, similar to autoimmune abnormalities often observed in the thyroid gland (5-13). Further similar case reports are required to analyze the details of the pathogenic mechanism of the parathyroid dysfunction associated chronic parathyroiditis.

In conclusion, we reported a case of hyperparathyroidism which initially presented with hypocalcemia associated with

lymphoid follicles with germinal centers in one parathyroid gland and later one atrophic and one normal parathyroid gland pathologically.

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Original Article

Decreased bone mineral density at the distal radius, but not at the lumbar spine or the femoral neck, in Japanese type 2 diabetic patients

T. Majima¹, Y. Komatsu²✉, T. Yamada¹, Y. Koike¹, M. Shigemoto¹, C. Takagi¹,
I. Hatanaka¹ and K. Nakao²

(1) Department of Endocrinology and Metabolism, Rakuwakai Otowa Hospital, Kyoto, Japan

(2) Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho Sakyo-ku, 606-8507 Kyoto, Japan

✉ Y. Komatsu

Email: komatsuy@barium.rirc.kyoto-u.ac.jp

Phone: +81-75-7513168

Fax: +81-75-7719452

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Abstract The purpose of this study is to assess the association between type 2 diabetes and bone mineral density. This study included 145 Japanese patients (64 men and 81 women) with type 2 diabetes and 95 non-diabetic control subjects (41 men and 54 women) of similar age. We measured bone mineral density (BMD) at the sites with different cortical/cancellous bone ratio (lumbar spine, femoral neck, and distal radius) using dual-energy X-ray absorptiometry. BMD and Z score at the distal radius were significantly lower in type 2 diabetic patients than those in control subjects, and in type 2 diabetic patients, the Z score at the distal radius was lower than that at their own lumbar spine and femoral neck. In type 2 diabetic patients, negative correlation between BMD and the mean HbA1c during the previous 2 years was found significantly at the distal radius in both genders and at the femoral neck in women. These results indicate the selective cortical bone loss in type 2 diabetes and suggest the importance of also determining BMD at the radius and keeping good metabolic control to prevent bone loss in type 2 diabetic patients.

Keywords Bone mineral density - Distal radius - Insulin levels - Type 2 diabetes mellitus

Introduction

Decreased bone mineral density (BMD) is an established complication of type 1 diabetes [1, 2]. However, contradictory results have been reported in BMD of type 2 diabetic patients thus far:

several studies have shown that BMDs at the lumbar spine and the femoral neck were either unaltered [2, 3, 4, 5, 6, 7, 8, 9, 10] or increased [3, 6, 7, 8, 10, 11, 12, 13], rarely decreased [4, 10, 14] and that BMD at the distal radius was decreased [1, 15], not different [3, 6], or increased [3]. These complicated results suggest that examining BMDs at different sites may reveal different results, especially in type 2 diabetic patients. Therefore, it seems insufficient to measure the BMD of type 2 diabetic patients at a single site. Thus, in this study, we measured the BMD of Japanese type 2 diabetic men and women at the sites with different cortical/cancellous bone ratio: lumbar spine, femoral neck, and distal radius, using dual-energy X-ray absorptiometry (DXA).

Some papers reported that BMD was decreased more severely in the poorly controlled type 2 diabetic patients [1, 14]. On the other hand, some papers reported that insulin was an important factor in maintaining BMD [16, 17, 18, 19]. Japanese type 2 diabetic patients have the racial feature that they are mildly obese, with decreased capacity of insulin secretion, from a relatively early stage of the disease [20, 21]. It is, therefore, of interest to assess the relationship of BMD with BMI, the metabolic control and the capacity of insulin secretion in Japanese type 2 diabetic patients.

Subjects and methods

Subjects

One hundred and forty-five Japanese patients with type 2 diabetes (64 men and 81 women) were included in this study (Table 1). They were randomly selected from patients attending the diabetes clinic of Rakuwakai Otowa Hospital during the period between December 2002 and April 2003. Type 2 diabetes was diagnosed on the basis of an abnormal glucose tolerance test result, classic symptoms, and laboratory findings. The inclusion criteria for this study were type 2 diabetes diagnosed at the age of over 30 years and duration of diabetes for more than 2 years. Among 64 type 2 diabetic men, 20 were treated by diet only, 25 with oral medication, and 19 with insulin, and among 81 type 2 diabetic women, 25 were treated by diet only, 22 with oral medication and 34 with insulin. No patient had a history of ketosis and no patient had diabetic retinopathy, nephropathy or peripheral neuropathy.

Table 1 Means \pm SD of the variables assessed in examined subjects (N.D. not done)

Variable	Men		Women	
	Diabetic patients	Control subjects	Diabetic patients	Control subjects
	(n=64)	(n=41)	(n=81)	(n=54)
Age (years)	62.8 \pm 12.0 ^{NS}	62.9 \pm 11.3	66.6 \pm 11.4 ^{NS}	66.1 \pm 11.8
BMI (kg/m ²)	23.6 \pm 3.6 ^{NS}	23.1 \pm 2.5	23.6 \pm 4.6 ^{NS}	23.2 \pm 3.1
Creatinine (mg/dl)	0.75 \pm 0.2 ^{NS}	0.72 \pm 0.2	0.63 \pm 0.2 ^{NS}	0.63 \pm 0.2
Calcium (mg/dl)	9.2 \pm 0.3 ^{NS}	9.3 \pm 0.3	9.2 \pm 0.4 ^{NS}	9.3 \pm 0.5
Phosphate (mg/dl)	3.3 \pm 0.7 ^{NS}	3.4 \pm 0.6	3.5 \pm 0.7 ^{NS}	3.4 \pm 0.6
Urinary NTx/Cre	38.8 \pm 11.7	N.D.	44.9 \pm 18.6 ^{NS}	50.6 \pm 19.3

(nmol BCE/mmol Cre)				
ALP (IU/l)	229.0±57.7	N.D.	245.8±66.5 ^{NS}	234.4±66.5
IRI (μU/ml)	7.0±3.6	N.D.	6.4±3.6	N.D.
Urinary CPR (μg/day)	62.8±42.3	N.D.	45.2±32.6	N.D.
FPG (mg/dl)	153.7±46.6 [†]	90.8±5.3	155.5±62.4 [†]	91.2±5.5
Mean HbA1c (%)	7.8±1.6	N.D.	7.6±1.6	N.D.

P values for comparisons between patients with type 2 diabetes mellitus and control subjects: ^{NS}*P*>0.05,

[†]*P*<0.01

The non-diabetic healthy control subjects were 41 Japanese men and 54 women (Table 1) and were selected from patients attending the clinic of Rakuwakai Otowa Hospital for their annual medical checkups during the same period. The diabetic patients and the control subjects were similar with regard to physical activity.

All subjects were interviewed by the doctor or nurse and underwent laboratory blood tests. We excluded the subjects who had a history of any fractures and other diseases (liver disease, renal dysfunction, malignancy, hyperthyroidism, hyperparathyroidism, hypercorticism, or hypogonadism) and those who had a history of taking medications (active vitamin D3, bisphosphonates, calcitonin injection, estrogens, steroids, thyroid hormone, diuretics, heparin or anticonvulsants) that could influence bone metabolism. All the subjects were subjected to plain X-ray (anteroposterior and lateral views) for the lumbar spine, and patients with scoliosis, compression fractures or ectopic calcifications that could interfere with the bone mineral results were excluded. No subjects were smokers or alcoholics. All subjects gave informed consent.

BMD measurements

BMD was measured at the lumbar spine (L2–L4), the femoral neck, and the distal radius, by DXA (Hologic QDR 4500c, Hologic, Waltham, Mass., USA). To eliminate technical variation, the same operator measured all the subjects. Values of BMD at the lumbar spine were presented as the mean of those at L2–L4. T scores and Z scores were calculated on the basis of the normal reference values of the age- and gender-matched Japanese group provided by the DXA system manufacturer.

Biochemical measurements

Serum calcium, phosphate, creatinine and fasting plasma glucose (FPG) were measured by routine methods. In the type 2 diabetic patients, plasma HbA1c was measured by the latex agglutination method (Fuji Rebio, Tokyo, Japan) and was presented as the mean of several values during the last 2 years before BMD measurement. In diabetic patients treated by diet only or with oral medications (i.e., 45 diabetic men and 47 diabetic women), serum immunoreactive insulin (IRI) was measured by immunoradiometric assay (BML, Kawagoe, Japan) after overnight fasting, and urinary connecting peptide immunoreactivity (CPR) was measured by radioimmunoassay (BML) of the 24-h urine samples collected and stored at –20°C. As markers of bone formation and resorption, serum alkaline phosphatase (ALP) and urinary N-terminal telopeptide of type I collagen normalized by creatinine (NTx/Cr) were measured in diabetic patients and control women. ALP was measured by the routine method (*P*-nitrophenyl-phosphate substrate method).

Urinary NTx in the second urine samples in the morning was measured by enzyme-linked immunosorbent assay (BML).

Statistical analysis

Data were analyzed by *t*-test between two group differences, by one-way factorial ANOVA and Fisher's protected least significant difference (PLSD) method among three group differences, and by Pearson's correlation test for examining correlation. Statistics were calculated with Statview version 4.0 (Abacus Concepts, Berkeley, Calif., USA). A *P* value <0.05 was considered as statistically significant.

Results

Table 1 shows a comparison between type 2 diabetic patients and control subjects. There was no significant difference between the two groups in age, BMI and the biochemical parameters except FPG. Among the three diabetic subgroups treated in different ways: diet only, oral medication, and insulin, there was also no significant difference in age, BMI and the mean HbA1c as well as the number of each subgroup (data not shown).

Table 2 and Fig. 1A show a comparison of BMD, T score and Z score between type 2 diabetic patients and control subjects. BMD, T score and Z score at the distal radius were significantly lower in type 2 diabetic patients than in control subjects but were not different at the lumbar spine and the femoral neck, although the Z score at the lumbar spine was significantly higher in type 2 diabetic women. Among the three diabetic subgroups with different treatments, there was no significant difference in BMD, T score and Z score at the three sites (data not shown).

Table 2 BMD, T score and Z score at the lumbar spine, the femoral neck and the distal radius in type 2 diabetic patients and control subjects. Values are means \pm SD

Parameter	Men		Women	
	Diabetic patients	Control subjects	Diabetic patients	Control subjects
Lumbar spine				
BMD (g/cm ²)	0.972 \pm 0.176 ^{NS}	0.975 \pm 0.108	0.861 \pm 0.193 ^{NS}	0.831 \pm 0.162
T score (SD)	-0.640 \pm 1.481 ^{NS}	-0.614 \pm 0.905	-1.259 \pm 1.618 ^{NS}	-1.509 \pm 1.360
Z score (SD)	0.120 \pm 1.005 ^{NS}	0.096 \pm 0.595	0.533 \pm 1.175 [†]	0.025 \pm 0.979
Femoral neck				
BMD (g/cm ²)	0.759 \pm 0.137 ^{NS}	0.767 \pm 0.108	0.620 \pm 0.153 ^{NS}	0.660 \pm 0.118
T score (SD)	0.820 \pm 1.083 ^{NS}	0.755 \pm 0.723	-1.533 \pm 1.408 ^{NS}	-1.167 \pm 1.079
Z score (SD)	0.118 \pm 1.049 ^{NS}	0.087 \pm 0.787	0.087 \pm 1.320 ^{NS}	0.152 \pm 1.075
Distal radius				
BMD (g/cm ²)	0.665 \pm 0.092*	0.721 \pm 0.080	0.493 \pm 0.109 [†]	0.547 \pm 0.095
T score (SD)	-1.287 \pm 1.311*	-0.492 \pm 1.144	-3.321 \pm 2.131 [†]	-2.257 \pm 1.858

Z score (SD)	-0.610±1.101 [†]	0.044±1.014	-0.397±1.583*	0.175±1.224
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P-values for comparisons between type 2 diabetic patients and control subjects: ^{NS}P>0.05, *P<0.05, [†]P<0.01

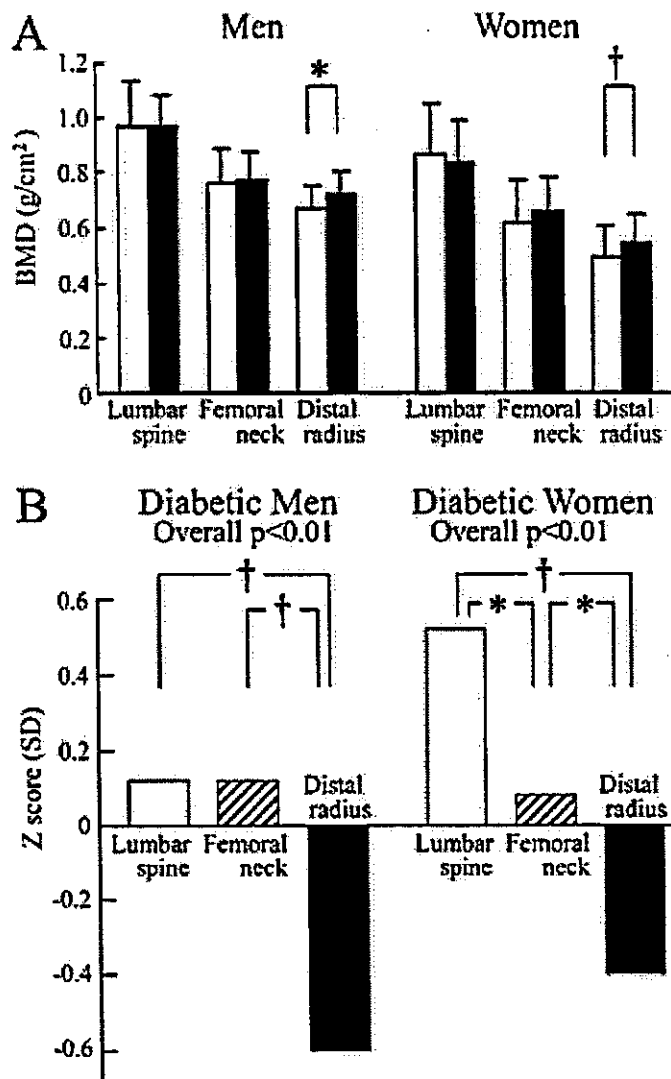


Fig. 1 A Comparison of BMDs at the lumbar spine, the femoral neck and the distal radius between patients with type 2 diabetes mellitus (*open columns*) and control subjects (*closed columns*). Each column represents the mean \pm SD. *P<0.05, [†]P<0.01. **B** Comparison of Z scores at the lumbar spine (*open columns*), the femoral neck (*shaded columns*) and the distal radius (*closed columns*) in patients with type 2 diabetes mellitus. Each column represents the mean value. *P<0.05, [†]P<0.01.

Figure 1B shows a comparison of Z scores at different sites in type 2 diabetic patients, analyzed by one-way factorial ANOVA and Fisher's PLSD test. Z score at the distal radius was significantly lower than those at the lumbar spine and the femoral neck in both men and women, and at the lumbar spine it was significantly higher than that at the femoral neck in women, but not in men.

Table 3 shows correlations of BMD with age, BMI and the biochemical parameters in type 2

diabetic patients. However, correlations of BMD with IRI and urinary CPR were calculated only in type 2 diabetic patients treated by diet only or with oral medications (i.e., 45 diabetic men and 47 diabetic women) because those two parameters were not measured in our insulin-treated patients, as mentioned above. BMDs at the three sites in both genders were associated negatively with age and positively with BMI, except BMD at the distal radius in men with BMI ($P=0.0754$). Urinary NTx/Cr was negatively correlated with BMD at the lumbar spine in both genders, at the femoral neck in men, and at the distal radius in women. ALP was not correlated with BMD, except at the femoral neck in men. IRI was positively correlated with BMD at the lumbar spine in women, at the femoral neck in both genders, and at the distal radius in men. Urinary CPR was positively correlated with BMD at the femoral neck and the distal radius in both genders. FPG was not correlated with BMD at any site. The mean HbA1c was negatively correlated with BMD at the femoral neck in women and at the distal radius in both genders (Fig. 2D, E, F), and there was a tendency of negative correlation of the mean HbA1c with BMD at the lumbar spine and at the femoral neck in men (Fig. 2A, C).

Table 3 Correlations of BMD with age, BMI and the biochemical parameters in type 2 diabetic patients. Values are correlation coefficients. IRI immunoreactive insulin, CPR connecting peptide immunoreactivity, FPG fasting plasma glucose

Parameter	BMD					
	Men			Women		
	Lumbar spine	Femoral neck	Distal radius	Lumbar spine	Femoral neck	Distal radius
Age	-0.310*	-0.519 [†]	-0.409 [†]	-0.409 [†]	-0.575 [†]	-0.692 [†]
BMI	0.375 [†]	0.435 [†]	0.224 ^{NS}	0.365 [†]	0.493 [†]	0.438 [†]
Creatinine	0.156 ^{NS}	-0.019 ^{NS}	-0.034 ^{NS}	0.130 ^{NS}	0.049 ^{NS}	0.042 ^{NS}
Calcium	0.047 ^{NS}	0.051 ^{NS}	0.200 ^{NS}	0.107 ^{NS}	0.005 ^{NS}	0.267 ^{NS}
Phosphate	0.051 ^{NS}	-0.065 ^{NS}	0.079 ^{NS}	-0.158 ^{NS}	-0.136 ^{NS}	-0.166 ^{NS}
Urinary NTx/Cre	-0.346 [†]	-0.247*	-0.127 ^{NS}	-0.303*	-0.215 ^{NS}	-0.258*
ALP	-0.140 ^{NS}	-0.325 [†]	-0.073 ^{NS}	-0.050 ^{NS}	-0.137 ^{NS}	-0.091 ^{NS}
IRI	0.085 ^{NS}	0.305*	0.304*	0.394 [†]	0.382 [†]	0.218 ^{NS}
Urinary CPR	0.108 ^{NS}	0.296*	0.314*	0.287 ^{NS}	0.534 [†]	0.488 [†]
FPG	-0.069 ^{NS}	-0.019 ^{NS}	0.035 ^{NS}	0.056 ^{NS}	-0.137 ^{NS}	-0.049 ^{NS}
Mean HbA1c	-0.182 ^{NS}	-0.240 ^{NS}	-0.289*	-0.032 ^{NS}	-0.314 [†]	-0.219*

P values for correlations of BMD with age, BMI and the biochemical parameters in type 2 diabetic patients:
^{NS} $P>0.05$, * $P<0.05$, [†] $P<0.01$

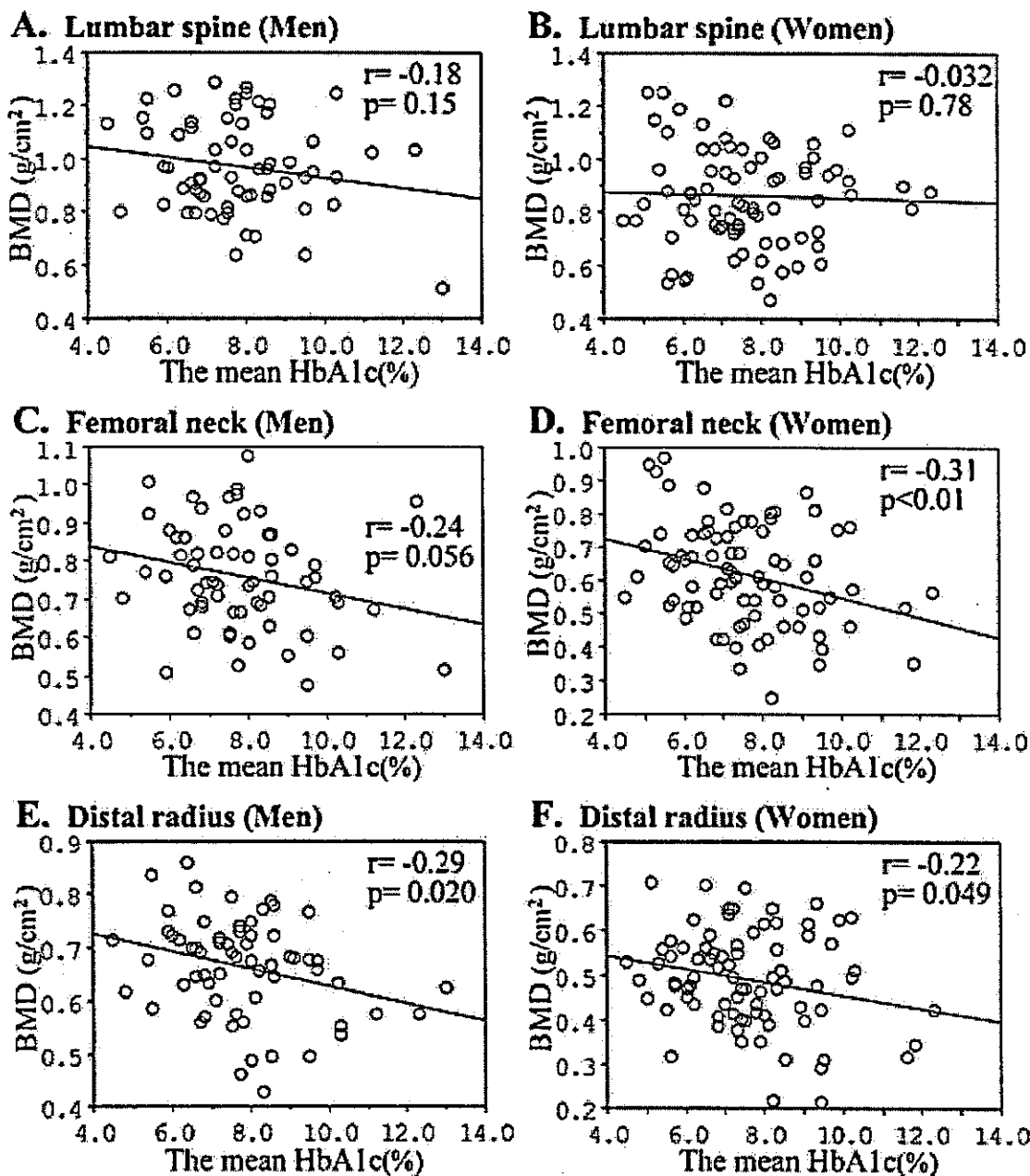


Fig. 2A-F Correlation between the mean HbA1c and BMD at the three sites: lumbar spine (A, B), femoral neck (C, D) and distal radius (E, F) in diabetic men (A, C, E) and diabetic women (B, D, F). For each figure the BMD measurements at each site were plotted against the mean HbA1c levels. The line reflects the regression and r mean correlation coefficients and P values for correlations between the mean HbA1c and BMD at the three sites.

Discussion

Our study revealed that BMD of type 2 diabetic patients was significantly lower at the distal radius, but not different at the lumbar spine and the femoral neck, than that of control subjects. and our new finding was that the Z score was the lowest at the distal radius among the three sites (lumbar spine, femoral neck and distal radius) in type 2 diabetic patients. Our results showed that

the higher the cortical/cancellous bone ratio (distal radius >femoral neck >lumbar spine), the lower the Z-score became (lumbar spine >femoral neck >distal radius) in type 2 diabetic women. These results suggest that the rapid loss of cortical bone rather than cancellous bone may occur in type 2 diabetes.

Christensen and Svendsen also reported the difference in Z scores among the three sites (lumbar spine >femur total >distal radius) shown in the present study [6]. They examined the BMD of type 2 diabetic women by DXA, but they did not show the statistical significance among the three sites. Leite Duarte and da Silva [22] reported reduced cortical thickness of bone biopsy samples in type 2 diabetic patients. Those results are compatible with our results, suggesting a selective cortical bone loss in type 2 diabetes.

There seem to be many reasons why BMD and Z score at the distal radius were lower in Japanese type 2 diabetic patients in our study, although those at the lumbar spine and femoral neck were higher or not different. The results of the previous studies about BMD of type 2 diabetes were controversial [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15]. The different insulin levels in type 2 diabetic patients, high in newly onset cases, low in long-standing cases, might be one of the explanations for the contradictory results of the previous studies [3, 11, 18]. Many previous studies and our present study showed a positive correlation of insulin levels with BMDs [16, 17, 18, 19], because insulin has an anabolic effect on bone [23]. Moreover, Haffner and Bauer [16] and Stolk et al. [18] reported that there was a difference between the association of insulin level with BMD at the lumbar spine and at the femur. Also, our results revealed a difference in the association of insulin level with BMD at the three sites. These results might imply a different effect of insulin on cortical bone from cancellous bone. Therefore, Japanese type 2 diabetic patients with low insulin secretion may have the risk of losing cortical bone and have lower BMDs, especially at the distal radius.

The association between BMDs and insulin levels may be the result of the association between BMD and some other osteogenic factors related to insulin: amylin, estrogen, testosterone, and sex hormone-binding globulin (SHBG). Amylin, which is co-secreted with insulin by the pancreatic β cells in response to glucose load, inhibits bone resorption [24] and increases bone formation [24, 25, 26]. Sex steroids, including estrogen and testosterone, are correlated with insulin levels [7, 18, 27], inhibit bone resorption and increase BMD [28, 29]. Low SHBG levels are correlated with high insulin levels [27, 30] and lead to high sex hormone levels, causing increased BMD [17, 31]. In our study, BMI was strongly correlated with insulin levels, both in men and women with type 2 diabetes ($r=0.454$ $P=0.0018$, $r=0.467$ $P=0.0018$, respectively), as reported in the previous studies [3, 17]. Those insulin-related factors may have influenced bone metabolism and caused the difference in association of insulin levels with BMDs at the three sites in our study.

In the present study, the mean HbA1c was negatively correlated with BMD at the femoral neck in women and the distal radius in both genders, but not at the lumbar spine. Therefore, the association of the mean HbA1c with BMD in the present study seems to be different by the cortical/cancellous bone ratio. This difference may have caused the difference of Z score among the three sites in our study.

Higher BMD associated with poor metabolic control in type 2 diabetic patients [3, 6, 7, 8, 10, 11, 12, 13] could be explained by their hyperinsulinemia, as stated by Stolk et al. in their own study [18]. However, on the other hand, in Japanese type 2 diabetic patients their insulin secretion is not high enough to catch up with increased glucose levels [20, 21]. Therefore, poor metabolic control was not associated with hyperinsulinemia, and so did not lead to higher BMD in our study. Krakauer et al. [1] and Gregorio et al. [14] reported that BMD was decreased in the poorly

controlled type 2 diabetic patients and that it was increased by improving metabolic control. Some *in vitro* studies showed that exposure to high glucose impaired the activity of osteoblasts [32] and stimulated osteoclasts [33]. Those results are in agreement with our results, suggesting that metabolic control of type 2 diabetes is important in preventing bone loss as well as other complications.

Higher parathyroid hormone (PTH) secretion, in part by the negative calcium balance in type 2 diabetic patients, might be one of the reasons for the selective cortical bone loss in type 2 diabetes [14, 34]. Although we did not measure serum PTH, serum calcium was not different between the diabetic patients and the controls.

Whether the bone turnover of type 2 diabetes is higher or lower has not reached consensus yet [1, 5, 6, 7, 8, 12, 14, 22, 34, 35]. Some previous studies reported reduced bone formation in bone biopsy samples of type 2 diabetic patients [1, 22], and reduced osteocalcin in type 2 diabetic patients has been repeatedly reported [6, 7, 34]. Those results are interpreted to represent low bone formation in type 2 diabetes [1, 6, 7, 22, 34]. However, in contrast, ALP and bone type alkaline phosphatase (BAP), other bone formation markers, were reported to be elevated in type 2 diabetes in other previous studies [35, 36], as in our study. This is probably because maturation of osteoblasts is inhibited at the mineralization phase after ALP expression in type 2 diabetes [37]. Therefore, considering that in our study ALP was relatively higher and urinary NTx/Cre was relatively lower in type 2 diabetic women, we consider that type 2 diabetic women in our study had relatively a lower rate of bone turnover than controls. This lower rate of bone turnover may offset rapid bone loss with high bone turnover during perimenopausal period [1, 3, 6], especially at the lumbar spine. Therefore, type 2 diabetic women in the present study might not have lost bone at the lumbar spine, and so their BMD at the lumbar spine might have become higher than that of control women and also than their own BMDs at the other sites.

From these observations, it can be seen that cortical bone and cancellous bone could be differently affected by the conditions of type 2 diabetes, including insulin, glucose, BMI, sex steroids and PTH. However, further studies are needed to clarify these issues.

In conclusion, we found that BMD at the distal radius was significantly decreased in type 2 diabetic patients compared with controls and that Z score at the radius was significantly lower than that at their own lumbar spine and their own femoral neck in type 2 diabetic patients. In addition, we found negative correlation of the mean HbA1c during the previous 2 years with BMD at the femoral neck and the distal radius, but not at the lumbar spine, in type 2 diabetic patients. These results suggest a selective cortical bone loss in type 2 diabetes. Therefore, we conclude that it is important to determine BMD at the radius as well and that good metabolic control leads to prevention of bone loss in type 2 diabetic patients.

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