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Lower bone mineral density and higher bone resorption marker levels in premenopausal women with type 1 diabetes in Japan

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Keywords
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ABSTRACT

Aims/Introduction: Type 1 diabetes is associated with poorer bone quality. Quantitative ultrasound provides an estimate of bone mineral density (BMD) and can also be used to evaluate bone quality, which is associated with an increased fracture risk in people with type 1 diabetes. The aim of this study was to evaluate the association between menopausal status and a bone turnover marker with heel BMD using quantitative ultrasound in women with type 1 diabetes and age- and body mass index-matched controls.

Materials and Methods: A total of 124 individuals recruited in Kyoto and Osaka, Japan – 62 women with type 1 diabetes (mean age 47.2 ± 17.3 years) and 62 age-, menopausal status-, sex- and body mass index-matched non-diabetic control individuals (mean age 47.3 ± 16.3 years) – were enrolled in this study. Heel BMD in the calcaneus was evaluated using ultrasonography (AOS-100NW, Hitachi-Aloka Medical, Ltd., Tokyo, Japan). A bone turnover marker was also measured.

Results: The heel BMD Z-score was significantly lower in premenopausal women with type 1 diabetes than in the premenopausal control group, but not in postmenopausal women with type 1 diabetes. Levels of tartrate-resistant acid phosphatase-5b, a bone resorption marker, were significantly higher in premenopausal women with type 1 diabetes than in the premenopausal control group, but not in postmenopausal women with type 1 diabetes. The whole parathyroid hormone level was significantly lower in both pre- and postmenopausal women with type 1 diabetes.

Conclusions: Lower heel BMD, higher tartrate-resistant acid phosphatase-5b level and lower parathyroid hormone were observed in premenopausal women with type 1 diabetes. Premenopausal women with type 1 diabetes require osteoporosis precautions for postmenopause.

INTRODUCTION

Type 1 diabetes is an autoimmune disease involving a chronic hyperglycemic state, and its incidence has been rising globally over the past few decades. Besides the well-known diabetic complications, such as retinopathy, nephropathy and neuropathy, type 1 diabetes is also characterized by poor bone health[1,2]. Although type 1 diabetes and type 2 diabetes are associated with an increased risk of fracture, bone mineral density (BMD) has been reported to be higher in type 2 diabetes patients than in type 1 diabetes patients in the hip, femur and spine[3,4].

Women with type 1 diabetes had a fourfold higher risk of fracture at any site than people without diabetes[5]. Although bone mass is reduced, bone quality is also markedly altered in patients with type 1 diabetes[6]. A meta-analysis (16 studies) showed that in adults with type 1 diabetes, BMD was lower in

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the femoral neck than in healthy controls, but there was no difference between the two groups in terms of BMD of the lumbar spine[7]. However, there has been no meta-analysis on heel BMD in women with type 1 diabetes. Individuals with type 1 diabetes show a decreased BMD, yet the natural history and pathogenesis of osteopenia remain unclear[8].

Dual-energy X-ray absorptiometry (DXA) is the gold standard technique used for the analysis of bone mineral content. Quantitative ultrasound (QUS) is a validated, low-cost and readily accessible alternative to DXA measurements of BMD for the assessment of fracture risk[9]. QUS, which is carried out mainly at the heel, provides an estimate of BMD, thus reflecting the bone mass[10]. Assessment of BMD using QUS confirmed the increase in BMD detected using DXA in patients with type 2 diabetes[11]. Furthermore, QUS can also be used to evaluate bone quality, decreased levels of which are associated with an increased fracture risk in older women with diabetes.

Bone turnover comprises two processes: the removal of old bone (resorption) and the laying down of new bone (formation). Markers of bone resorption and formation have been reported to be lower in patients with diabetes. Bone metabolic marker levels are normal or decreased in diabetes patients, which suggests that the matrix becomes hypermineralized[12].

Tartrate-resistant acid phosphatase-5b (TRACP-5b) is a bone resorption marker not affected by renal dysfunction[13]. TRACP-5b is secreted directly by osteoclasts, whereas other markers are products of bone metabolism. High TRACP-5b level was associated with an increased risk of any fracture in elderly women over a mean of 9 years[14]. The menopausal transition is a critical period for bone health, with rapid losses in bone mass and strength[15].

Therefore, the aim of the present study was to evaluate the association of menopausal status and bone turnover marker levels with the heel BMD in women with type 1 diabetes and age – and body mass index (BMI)-matched controls.

MATERIALS AND METHODS

Study design and participants

In the present cross-sectional study, for the 62 women with type 1 diabetes from the National Hospital Organization Kyoto Medical Center who met the registration criteria of the study on osteoporosis prevention of type 1 diabetes, 62 non-diabetic controls in Osaka, Japan, agreed to participate. The control participants were selected from employees and non-diabetic patients of Kawachi General Hospital and Yoshioka Medical Clinic, and local residents.

A total of 124 women, comprising 34 premenopausal women with type 1 diabetes (mean age 33.3 ± 7.9 years), 28 postmenopausal women with type 1 diabetes (mean age 64.0 ± 8.2 years), and age- and BMI-matched non-diabetic controls including 34 premenopausal women (mean age 34.0 ± 7.0 years) and 28 postmenopausal women (mean age 63.5 ± 6.6 years) were enrolled in this study. Eligible participants were women aged >20 years. Exclusion criteria included a history of breast cancer, early menopause, menstrual disorder, dialysis, chronic hepatitis, chronic rheumatoid arthritis, use of anti-osteoporosis drugs, oral steroids, calcium or vitamin D supplements.

The study protocol adhered to the ethical guidelines of the 2013 Declaration of Helsinki, as reflected in prior approval by the ethics committee of Kyoto Medical Center (approval number: 09-036). All participants received a full explanation of the study and provided informed consent.

We evaluated the following variables: height, bodyweight and BMI were measured. Serum Ca, serum phosphorus, glycated hemoglobin (Arkray, Inc., Shiga, Japan) and creatinine (Cr; Shino-Test Corporation, Kanagawa, Japan) were measured using an automatic biochemical analyzer (AU580; Beckman Coulter, Inc., Tokyo, Japan). The estimated glomerular filtration rate was calculated using the following equation: estimated glomerular filtration rate = $194 \times Cr^{-1,094} \times age^{-0.28716}$. Plasma 25-hydroxyvitamin D_2 ($25[OH]D_2$) and $25(OH)D_3$ concentrations were measured using liquid chromatography tandem mass spectrometry. The 25(OH)D level is the sum of the levels of $25(OH)D_2$ and $25(OH)D_3$. In controls, 25(OH)D levels were measured in May in most cases, and in participants with type 1 diabetes, 25(OH)D levels were measured throughout the year.

The serum whole parathyroid hormone (wPTH) level was measured using an immunoradiometric assay (Whole PTHTM [1–84] Specific; Scantibodies Laboratory, Inc., Santee, CA, USA). The serum TRACP-5b activity was measured using a novel fragment-absorbed immunocapture enzymatic assay (Osteo Links TRAP-5b; DS Pharma Biomedical Co., Ltd., Osaka, Japan). Serum bone alkaline phosphatase (BAP) was measured using an enzyme immunoassay (MicroVueTM BAP; DS Pharma Biomedical Co., Ltd., Osaka, Japan). Serum osteocalcin (OC) was measured using an electrochemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA).

The heel BMD was evaluated using the osteo sono-assessment index after ultrasonographic (AOS-100NW; Hitachi-Aloka Medical, Ltd., Tokyo, Japan) examination of the calcaneus [17,18]. The Z-score describes the standard deviation by which the heel BMD in an individual differs from the mean value expected for that individual's age and sex, and the T-score describes the standard deviation of an individual's BMD compared with the mean value of a young healthy reference population, with the difference expressed in standard deviations[19].

A dietary analysis program (Excel Eiyou-kun version 6.0, Kenpausha, Tokyo, Japan) was used to calculate energy intake and macronutrient content. We calculated the daily intake of the five following vitamins and minerals: calcium, magnesium, phosphorus, and vitamins D and K[20]. Calcium deficiency was defined as <650 mg/day according to the recommended dietary allowance[21]. 25(OH)D deficiency was defined as <20 ng/mL[22]. Self-reported physical activity was obtained through the Japanese version of the IPAQ (the usual 7 days, short, self-administered version). We assessed specific types of exercise: walking and moderate- and vigorous-intensity activities[23]

Statistical analysis

Data are expressed as the mean ± standard deviation. Women with type 1 diabetes were initially compared with their age- and BMI-matched non-diabetic controls. The unpaired *t*-test was used to compare the two groups. Categorical variables were compared using the χ^2-test. Significance was determined to be present if *P*-values were <0.05. All statistical analyses were carried out using IBM SPSS Statistics for Windows software version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Glycated hemoglobin levels were significantly higher in premenopausal and postmenopausal women with type 1 diabetes than in their respective controls, although there were no significant differences in BMI between the individual groups (Table 1). The heel BMD Z-score was significantly lower in premenopausal women with type 1 diabetes than in the premenopausal control group, but not in postmenopausal women with type 1 diabetes.

TRACP-5b levels were significantly higher in premenopausal women with type 1 diabetes than in premenopausal controls, but not in postmenopausal women with type 1 diabetes.

wPTH levels in both pre- and postmenopausal women with type 1 diabetes were significantly lower than those in their respective control groups. There was no difference in BAP or OC levels between women with type 1 diabetes and their respective control groups. Poor glycemic control (glycated hemoglobin level >8%) was not associated with BMD in either premenopausal or postmenopausal women with type 1 diabetes.

The correlation coefficient between TRACP-5b and BAP was significant ($P < 0.01$) in premenopausal women with type 1 diabetes (0.708), postmenopausal women with type 1 diabetes (0.638), premenopausal control women (0.631) and postmenopausal control women (0.628). However, there was no correlation between wPTH and these bone metabolic markers.

We measured $25(OH)D_2$ levels, but the values were below the assay sensitivity (<4.0 ng/mL). The prevalence of 25(OH)D deficiency in premenopausal women with type 1 diabetes and in the control group was 94% and 88%, respectively, which was not significantly different. The prevalence of 25(OH)D deficiency in postmenopausal women with type 1 diabetes and in

Table 1 | Comparison of clinical variables between women with type 1 diabetes and controls

Variables	All		Premenopause		Postmenopause	
	T1D (*n* = 62)	Control(*n* = 62)	T1D (*n* = 34)	Control (*n* = 34)	T1D (*n* = 28)	Control (*n* = 28)
Age (years)	47.2 ± 17.3	47.3 ± 16.3	33.3 ± 7.9	34.0 ± 7.0	64.0 ± 8.2†	63.5 ± 6.6†
BMI (kg/m^2)	21.9 ± 2.7	21.7 ± 2.6	21.8 ± 2.7	21.4 ± 2.8	22.1 ± 2.6	22.1 ± 2.5
Diabetes duration (years)	12.0 ± 10.5	–	11.2 ± 9.0	–	12.9 ± 12.3	–
Diabetic neuropathy (%)	35	–	26	–	46	–
Diabetic retinopathy (%)	21	–	12	–	32	–
Diabetic nephropathy (%)	11	–	0	–	25	–
Heel BMD						
Z-score	–0.03 ± 0.88*	0.32 ± 1.0	–0.08 ± 0.85*	0.53 ± 1.19	0.03 ± 0.94	0.07 ± 0.65
T-score	–0.62 ± 1.00	0.30 ± 1.2	–0.07 ± 0.85*	0.45 ± 1.05	–1.27 ± 0.86	–1.22 ± 0.54
HbA1c (%)	8.0 ± 1.5*	5.6 ± 0.3	8.0 ± 1.7*	5.4 ± 0.3	8.1 ± 1.2*	5.8 ± 0.3†
eGFR (mL/min/1.73 m^2)	89.1 ± 21.9	83.1 ± 16.8	100.9 ± 19.6*	91.3 ± 7.7	74.7 ± 14.9†	67.3 ± 12.8†
Serum Ca (mg/dL)	9.5 ± 0.3*	9.3 ± 0.4	9.5 ± 0.3*	9.3 ± 0.3	9.6 ± 0.3	9.4 ± 0.5
Serum P (mg/dL)	3.7 ± 0.5*	3.5 ± 0.5	3.6 ± 0.5*	3.5 ± 0.5	3.8 ± 0.4	3.5 ± 0.4
Serum whole PTH (pg/mL)	21.7 ± 8.0*	31.6 ± 13.2	22.6 ± 9.6*	32.3 ± 15.9	20.7 ± 5.6*	30.7 ± 9.0
Bone formation markers						
BAP (U/L)	28.4 ± 11.4	26.4 ± 9.7	25.6 ± 11.5	21.1 ± 6.3	31.7 ± 10.6†	32.9 ± 9.4†
OC (ng/mL)	15.2 ± 6.5	16.1 ± 6.2	13.6 ± 5.7	12.7 ± 3.7	17.1 ± 7.1†	20.2 ± 6.3†
Bone resorption marker						
TRACP-5b (mU/dL)	338.6 ± 147.0	311.4 ± 171.2	273.2 ± 136.6*	215.2 ± 89.0	404.6 ± 146.1†	428.2 ± 175.2†
25(OH)D (ng/mL)	13.8 ± 4.4	15.4 ± 5.2	12.5 ± 3.9	14.0 ± 5.2	15.4 ± 4.4†	17.0 ± 4.7
Sufficient, >30 (%)	0	0	0	0	0	0
Insufficient, 20–30 (%)	11	18	6	12	18	25
Deficient, <20 (%)	89	82	94	88	82	75

Data are reported as the mean ± standard deviation. *$P < 0.05$ versus control, † $P < 0.05$ versus premenopausal status. The Z-score is the number of standard deviations by which the osteo sono-assessment index (OSI) in an individual differs from the mean value expected for age and sex. The T-score is the number of standard deviations by which the OSI in an individual differs from the mean value expected in young healthy women. 25(OH)D, 25-hydroxyvitamin D; BAP, bone-specific alkaline; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; P, phosphatase; T1d, type 1 diabetes; TRACP5b, tartrate-resistant acid phosphatase 5b; wPTH, whole parathyroid hormone.

the control group was 82% and 75%, respectively, which was not significantly different. There were no cases of 25(OH)D sufficiency. The 25(OH)D concentration in postmenopausal women with type 1 diabetes was significantly higher than that in premenopausal women with type 1 diabetes.

In all women with type 1 diabetes, wPTH did not show a correlation with 25(OH)D level, but in the whole control group, wPTH showed a correlation with 25(OH)D level trending towards significance (–0.245, $P = 0.059$).

There were no differences in energy intake, macronutrients and micronutrients, except vitamin K, between the type 1 diabetes and control groups. Calcium, phosphorus, zinc, vitamin K and magnesium intake in postmenopausal women with type 1 diabetes were higher than those in postmenopausal women with control, but similar to that in premenopausal women with type 1 diabetes and in premenopausal women with control (Table 2).

There were no differences in terms of vigorous and moderate-intensity physical activity between the type 1 diabetes and control groups individually. Walking time in the type 1 diabetes group was significantly lower than that in the control group individually, but sedentary time in postmenopausal women with type 1 diabetes was significantly greater than that in postmenopausal control group (Table 2).

DISCUSSION

The heel BMD evaluated using ultrasound was lower in premenopausal women with type 1 diabetes than in premenopausal controls.

Findings of lower heel BMD in premenopausal women with type 1 diabetes were consistent with the Wisconsin Diabetes Registry Study by Kujath *et al.*[24] and the study by Danielson KK *et al.*[25] using DXA, and the study by Strotmeyer *et al.*[26] using ultrasound. The reason for the lower BMD in type 1 diabetes patients in the premenopausal period remains unknown. There was no difference in the heel BMD between postmenopausal women with type 1 diabetes and controls in the present study. No QUS BMD reports for postmenopausal type 1 diabetes were found.

In a previous cross-sectional study, 52 women with type 1 diabetes and age-matched controls had similar BMD and Z-scores at the hip, femoral neck, and spine[27]. BMD of the total hip, femoral neck, lumbar spine (L1 to L4) and distal forearm in women with type 1 diabetes remained within acceptable ranges for their age and BMI for postmenopausal women in a longitudinal observational study[28].

Steps/day showed a significant positive correlation with calcaneal ultrasound variables in 113 postmenopausal women aged 60–85 years[29]. Furthermore, 10 weeks of aerobic endurance training in rats suggests that it does not have protective effects on bone in the short term or that type 1 diabetes rats have compromised bone health[30]. Further research including exercise intervention is required to investigate these issues.

Healthy diet and physical exercise are important for the prevention of fractures in type 2 diabetes[31]. In Japan, the addition of vitamin D to foods (such as vitamin D in milk) is not common. In the present study, those who used vitamin D supplements were excluded. There were no cases of 25(OH)D sufficiency. In our study, both type 1 diabetes and control premenopausal groups had a lower 25(OH)D concentration than

Table 2 | Comparison of lifestyle factors between women with type 1 diabetes and controls

Variables	All		Premenopause		Postmenopause	
	T1D	Control	T1D	Control	T1D	Control
Smoking (%)	3.2	9.7	5.9	11.8	0	7.1
Dietary intake						
Total energy (kcal)	1774 ± 432	1725 ± 417	1699 ± 386	1814 ± 358	1864 ± 472	1616 ± 463
Protein (E%)	14.4 ± 2.1	13.8 ± 2.1	13.9 ± 2.2	13.4 ± 2.3	15 ± 2†	14.2 ± 2
Fat (E%)	31.2 ± 4.1	32.4 ± 5	32.5 ± 3.7	33.3 ± 4.9	29.7 ± 4†	31.2 ± 4.9
Carbohydrate (E%)	54.4 ± 4.8	53.9 ± 6.2	53.6 ± 4.5	53.3 ± 6.4	55.3 ± 5.0	54.6 ± 5.9
Calcium (mg)	559 ± 229	494 ± 183	495 ± 191	488 ± 168	637 ± 251 *†	501 ± 203
P (mg)	968 ± 331	874 ± 235	874 ± 254	884 ± 211	1081 ± 380 *†	861 ± 264
Zn (mg)	7.6 ± 2.2	6.9 ± 1.7	7 ± 1.8	7.1 ± 1.6	8.3 ± 2.4 *†	6.6 ± 1.8
Vitamin D (μg)	7.0 ± 4.7	6.3 ± 3.3	5.5 ± 3.1	5.5 ± 2.9	8.8 ± 5. 6†	7.2 ± 3.6
Vitamin K (mg)	214 ± 95*	172 ± 72	189 ± 94	160 ± 60	245 ± 88 *†	187 ± 83
Magnesium (mg)	222 ± 78	205 ± 56	198 ± 61	203 ± 45	251 + 87 *†	208 + 68
Exercise (min/day)						
Vigorous PA	5 ± 14	4 ± 13	4 ± 12	2 ± 6	6 ± 16	7 ± 18
Moderate PA	18 ± 44	19 ± 50	14 ± 30	11 ± 24	23 ± 58	30 ± 68
Walking time	53 ±87*	120 ± 121	65 ±113*	122 ± 110	40 ± 33*	117 ± 135
Sedentary time	425 ± 279*	310 ± 217	384 ± 267	367 ± 212	475 ± 290*	240 ± 204†

Data are reported as the mean ± standard deviation. *$P < 0.05$ versus control, † $P < 0.05$ versus premenopause status. E; energy, P; phosphorus, PA; physical activity; T1D, type 1 diabetes; Zn; zinc.

those in the postmenopausal groups. In particular, the 25(OH)D concentration in the premenopausal type 1 diabetes group was significantly lower than that in the postmenopausal type 1 diabetes group.

The research on osteoarthritis/osteoporosis against disability (ROAD) study of the general population showed that the prevalence of vitamin D insufficiency and deficiency was 89.4% and 2.5% in premenopausal women, and 85.8% and 1.5% in postmenopausal women, respectively[32]. In the ROAD study, vitamin D intake was associated with increased serum vitamin D levels. The difference between the present study and that of the previous study might be explained by vitamin D intake (5.5–8.8 μg in the present study vs 11.6–22.9 in the ROAD study). In the present study, walking time in pre- and postmenopausal type 1 diabetes groups was significantly lower than that in the individual control group.

Although there were no differences in calcium and vitamin D intake between the premenopausal two groups, calcium and magnesium intake of postmenopausal women with type 1 diabetes was significantly higher than that in postmenopausal control. A meta-analysis showed that there was no clear association between calcium intake, vitamin D intake, physical activity and bone density in any study, although the prevalence of calcium deficiency was high and encompassed >50% of participants in a majority of studies. Despite this finding, there was no clear association between calcium intake and bone density in any study[33,34].

Magnesium deficiency contributes to osteoporosis directly by crystal formation and acting on bone cells[35]. The Mediterranean diet was associated with a lower risk of hip fracture[36]. Not only nutrients (calcium and magnesium), but also a healthy dietary pattern might be associated with a reduced risk of bone fracture in postmenopausal women with type 1 diabetes.

The wPTH levels were significantly decreased in both pre- and postmenopausal women with type 1 diabetes in the present study. The wPTH level is not affected by renal dysfunction, unlike intact PTH levels. In addition, it shows PTH activity[37,38]. A more accurate evaluation of PTH can be carried out when simultaneously evaluating pre- and postmenopausal cases. PTH is a hormone that maintains calcium homeostasis. In general, PTH levels are increased when 25(OH)D concentration is decreased[39]. It has also been reported that PTH levels are suppressed and decreased by hyperglycemia[40]. Diabetic bone disease is characterized by low bone turnover resulting from impaired PTH secretion[41]. Therefore, in type 1 diabetes patients, PTH levels vary depending on the blood glucose level and 25(OH)D concentration. In the present study, 25(OH)D levels were comparable between women with type 1 diabetes and controls in pre- and postmenopausal groups. Therefore, 25(OH)D has an equivalent effect on wPTH; the wPTH level in pre- and postmenopausal women with type 1 diabetes appears to be significantly lower than in control groups individually due to high blood glucose levels.

Premenopausal women with type 2 diabetes indeed have lower bone turnover compared with non-diabetic controls[42]. In premenopausal women with type 1 diabetes, the wPTH level was decreased, but the level of TRACP-5b, a bone resorption marker, was increased; therefore, levels of BAP and OC, bone formation markers, did not appear to be increased relative to that in control groups. However, a significantly higher bone resorption marker level would be disadvantageous for BMD.

In contrast, unlike premenopausal women with type 1 diabetes, despite a significant decrease in wPTH levels, TRACP-5b, a bone resorption marker level, and bone formation marker levels were comparable between postmenopausal women with type 1 diabetes and postmenopausal controls. There was no imbalance between bone resorption markers and bone formation markers in postmenopausal women with type 1 diabetes.

TRACP-5b is relatively new in development, so there are few reports of its use in type 1 diabetes patients[43]; however, the results in two reports are comparable[24,43]. Serum TRACP-5b, BAP and OC are widely used in primary care settings in Japan[44]. The mechanism underlying elevated TRACP-5b levels in premenopausal women with type 1 diabetes is unknown. The serum TRACP-5b level is considered an informative diagnostic and prognostic marker of oxidative stress in patients with osteoporosis[45,46]. Oxidative stress levels might explain the higher TRACP-5b levels in premenopausal women with type 1 diabetes. In the present study, the duration of disease was similar in both premenopausal and postmenopausal women with type 1 diabetes.

To investigate bone turnover and PTH in women with type 1 diabetes, we excluded not only patients on dialysis and those with gastric palsy, which had a major effect on bone turnover, but also women with secondary osteoporosis, except type 1 diabetes patients, as identified using the FRAX fracture risk assessment scale[47]. Thus, the current status of women with type 1 diabetes in Japan with many mild complications can be ascertained. Defects in osteoblast differentiation and activity are the main culprits underlying bone fragility in a rodent model of type 1 diabetes[48]. Initial clues pointing to these mechanisms were identified as a decrease in the bone formation marker, carboxyterminal propeptide of type 1 collagen, in pediatric studies[49]. Other contributing factors include an accumulation of advanced glycation end-products and the development of diabetes complications (such as neuropathy and hypoglycemia), which cause further decline in BMD, worsening geometric properties within bone and increased fall risk[48,50].

The results of human studies evaluating the effects of diabetes on markers of bone resorption have been mixed, with both an increase and a decrease reported in different studies among individuals with type 1 diabetes[48]. Many factors, such as hyperglycemia, renal function and sedentary behavior, affect bone marker levels and BMD in patients with type 1 diabetes. In the present study, hyperglycemia, larger estimated glomerular filtration rate, lower PTH, higher TRACP-5b level and shorter walking time in the premenopausal type 1 diabetes group were observed compared with the control group.

Estrogen deficiency leads to bone loss in postmenopausal osteoporosis, because bone formation, albeit enhanced, fails to

keep pace with the stimulated osteoclastic bone resorption. The mechanism driving this uncoupling is central to the pathogenesis of postmenopausal osteoporosis[51]. However, this mechanism is not understood in premenopausal status. Further examination including propeptide of type 1 collagen, advanced glycation end-products and other factors is required to investigate the mechanism of premenopausal status in the future. Follow-up studies are currently in progress. We will analyze the data to compare bone formation and resorption markers in the future.

The present cross-sectional studies had some limitations. Low premenopausal BMD in women with type 1 diabetes increases the risk of fracture, especially when coupled with a reduction in BMD due to menopause later in life. The present study showed only fragmentary results and could not point to a simple causal relationship. The mechanism underlying the lack of differences in BMD between the postmenopausal women with and those without type 1 diabetes is unknown.

In the present study, the calcium and magnesium intakes of the postmenopausal women with type 1 diabetes were higher than those of the control group, but were similar between the premenopausal women with and those without type 1 diabetes. Nutrients, such as calcium and magnesium, are proven beneficial for bone health[52]. Owing to high calcium and magnesium intakes, the protective effects for BMD might be observed in postmenopausal women with type 1 diabetes.

Increases in PTH level are age related and are a causal factor of bone loss[53]. PTH levels are negatively correlated with the BMDs of the femoral neck and total hip in postmenopausal Chinese women[54]. In the present study, the PTH levels of the postmenopausal women with type 1 diabetes were lower than those of the controls. Declining estrogen levels result in decreased BMD, and lower PTH levels might inhibit bone resorption in postmenopausal women with type 1 diabetes. Therefore, lower PTH levels might inhibit a decrease in the heel BMD Z-score. Longitudinal studies that include the premenopausal women with type 1 diabetes and the controls in the present study are required to confirm these issues.

This is one of the largest type 1 diabetes case–control studies of heel BMD in pre- and postmenopausal women. However, because we excluded patients at high risk of fracture to examine the relationship between bone turnover, PTH and BMD, women with type 1 diabetes were relatively young.

There are seasonal differences in vitamin D status in adults[55]. Vitamin D levels differ in time when they vary from season to season. In the summer, vitamin D production is high, because ultraviolet light levels are high, whereas it is low in the winter[56]. In the present study, we did not determine the measurement timing; therefore, vitamin D levels might be affected by seasonal differences. Because of this, seasonal differences in vitamin D status should be considered. Careful attention should be paid to interpreting the present results, because seasonal differences were not considered in this study. Furthermore, vitamin D intake and environmental factors, such as sunscreen use, affect vitamin D levels[57,58]. Further examination is required to confirm these issues during the same seasons.

In osteoporosis, inheritance is also a major factor[59]. It is necessary to consider the prevention of osteoporosis, including severe complications, cases involving men and addressing any genetic factors.

DXA BMD is more accurate and precise than heel BMD using QUS in the diagnosis of postmenopausal osteoporosis. In the present study, we adopted the heel BMD using QUS because of its low cost and non-radiative nature. Individuals with low BMD might be advised to undergo a DXA scan to confirm the diagnosis. Further examinations including DXA are required to confirm these issues.

The findings of the present study showed that low peak bone mass in premenopausal women with type 1 diabetes evaluated by a heel ultrasound might be a risk factor for postmenopausal osteoporosis. Elevated levels of TRACP-5b, a well-defined biomarker of bone resorption and osteoclast activity, and a lowered level of wPTH, which maintains calcium homeostasis, might explain the mechanism underlying lower heel BMD in premenopausal women with type 1 diabetes.

Unlike postmenopausal women with type 1 diabetes, premenopausal women with type 1 diabetes with the same duration of diabetes had significantly lower heel BMD and more risk factors for BMD reduction than non-diabetic controls. Bone turnover appears to be a disadvantage in premenopausal women with type 1 diabetes, in contrast to postmenopausal type 1 diabetes. Premenopausal women with type 1 diabetes need to take precautions for osteoporosis for postmenopause.

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DISCLOSURE

The authors declare no conflict of interest.

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