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Association between basal metabolic function and bone metabolism in postmenopausal women with type 2 diabetes

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ABSTRACT

Objective: Diabetes is a risk factor for osteoporosis, and glycemic control is critical during osteoporosis treatment in patients with type 2 diabetes (T2D). However, diabetic therapies have potentially adverse effects on bone metabolism. Additionally, biomarkers for bone metabolism are directly affected by drug therapies for osteoporosis. This study examined resting energy expenditure (REE) and respiratory quotient (RQ) as indices of bone metabolism in postmenopausal Japanese women with T2D.

Methods: Forty-six postmenopausal Japanese women with T2D were examined. Procollagen type 1 N-terminal propeptide (P1NP, a fasting serum bone formation marker) and carboxy-terminal collagen cross-links-1 (CTX-1, a resorption marker) were evaluated, along with intact parathyroid hormone, 25-hydroxyvitamin D (25[OH]D), urine microalbumin, motor nerve conduction velocity, sensory nerve conduction velocity, R-R interval, body composition, REE, RQ, and bone mineral density at the nondominant distal radius.

Results: The mean T-score was low with high variance (-1.7 ± 1.6), and 18 patients (39%) met the criteria for osteoporosis. REE was positively correlated with body mass index ($\beta = 0.517$; $r^2 = 0.250$), serum calcium ($\beta = 0.624$; $r^2 = 0.200$), glycated hemoglobin A_{1C} for the previous 6 mo ($\beta = 0.395$; $r^2 = 0.137$), and the serum P1NP/CTX-1 ratio ($\beta = 0.380$; $r^2 = 0.144$). RQ was positively correlated with serum 25(OH)D ($\beta = 0.387$; $r^2 = 0.131$).

Conclusion: The basal metabolic rate and diabetic pathophysiology are interrelated with bone turnover.

Introduction

Risk for fracture is particularly high among patients with diabetes [1]. Although the risk for patients with type 1 diabetes is attributed to their lower maximal bone mass (due to insulin deficiency), patients with type 2 diabetes (T2D) typically have a high bone mineral density (BMD) [2,3]. Therefore, the etiology of osteoporosis is thought to differ between patients with insulin deficiency and insulin resistance. Bone metabolism and blood glucose metabolism are considered closely related [4], and low bone mass is thought to be due to unbalanced bone remodeling, which involves both resorption of the bone matrix by osteoclasts and bone formation by osteoblasts [5]. Additionally, the finding that fat regulates bone metabolism has been viewed as an indication that bone metabolism might regulates some aspects of energy metabolism via a feedback loop [6]. Moreover, insulin resistance in patients with metabolic syndrome is associated with the ratio of low resting energy expenditure (REE) to body weight [7], and fracture risk is high in these patients [8,9]. Metabolic effects, with subsequent changes in body mass index (BMI), can be predicted using the respiratory quotient (RQ), which represents inner respiration, and REE in patients with T2D [10]. Furthermore, REE is more closely associated with BMD

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(compared with BMI) in black women [11]. Moreover, osteocalcin, leptin (a hormone that is derived from fat), and serotonin (an anorexigenic neurotransmitter in the brain) are closely related with bone remodeling and energy metabolism [6,12–14]. When taken together, these findings suggest that basal metabolism in patients with T2D may be involved in bone metabolism.

In women who are in late postmenopause, vertebral fracture was well predicted by bone turnover markers, independent of BMD, over a 10-y follow-up period [15]. Thus, serum biochemical markers of bone turnover should predict the risk for vertebral fracture in patients with T2D [16]. Additionally, women with T2D have a particularly high risk for femoral neck fracture, and it recently has been reported that suppression of bone turnover increases the fracture risk in postmenopausal women with T2D [17]. It is also well known that the basal metabolism in postmenopausal women with diabetes is markedly low [18]. Thus, reduced bone metabolism due to a lower basal metabolic ratio is a possible risk factor for fracture in postmenopausal women with T2D. Furthermore, markers for bone turnover can be used to evaluate the efficacy of a drug during osteoporosis treatment, although diabetes also may alter bone metabolism, which then may affect bone turnover markers [19,20].

The aim of this study was to examine the relationship between bone metabolism and basal metabolic function in postmenopausal women with T2D, and to test the hypothesis that basal metabolism is a useful marker for evaluating bone health.

Materials and methods

Patients

We initially recruited 56 postmenopausal Japanese women (>50 y old) with T2D who had attended our clinic for at least 1 y. After a careful examination of their medical histories, 10 patients were excluded from the study based on their intake of dietary supplements in the previous 3 mo (e.g., vitamins), or possible latent adult autoimmune diabetes with the presence of autoimmune antibodies, such as antiglutamic acid decarboxylase antibodies. The remaining 46 patients demonstrated no signs of complications, were not overtly proteinuric, and exhibited no symptoms of major diseases other than hypertension, dyslipidemia, and obesity (BMI $\geq$30 kg/m^2).

Written informed consent was obtained from all patients before participation. The study was approved by the ethics committee of the Tokyo Women's Medical University (IRB number: 2396).

Measurements

To evaluate orthostatic hypotension, blood pressure was measured in the supine and standing positions within a 3-min interval. Blood samples were collected after a 10-h overnight fast, and were used for all the tests that were performed in this study. Serum levels of procollagen type 1 N-terminal propeptide (P1NP) and carboxy-terminal collagen cross-links-1 (CTX-1) were measured at Roche Diagnostics (Tokyo, Japan) in a blinded manner. Serum levels of intact parathyroid hormone (iPTH), 25-hydroxyvitamin D (25[OH]D), calcium, and phosphate were evaluated in our hospital using aliquots of the same serum samples. General serum tests also were performed to measure aspartate aminotransferase, alanine aminotransferase, cholesterol, triacylglycerol, and creatinine levels. Microalbumin content in the patients' first morning urine samples was used to evaluate complications. Motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) were calculated using the Neuropack X1 system (Nihon Kohden, Tokyo, Japan). The R-R interval was calculated as the maximum difference in pulses/min under deep breathing conditions.

Body composition was calculated via the impedance method using a body composition analyzer (Tanita, Tokyo, Japan). REE and RQ were calculated over a 20-min period via respiratory gas analysis in a thermoneutral environment using Vmax Spectra indirect calorimetry (Cardinal Health, Columbus, OH, USA). A diagnosis of retinopathy was recorded within the 6 mo before the patient's participation in this study. BMD was evaluated using dual-energy x-ray absorptiometry (Hologic, Bedford, MA, USA) at the nondominant distal radius. The cortex of the radial bone is thinner than that of the lumbar bone, which causes the radial bone to be fractured more frequently. Furthermore, BMD in the nondominant distal radius has been used to screen for osteoporosis [21–23], and it is common for the first fracture to occur in the distal radius [21,24,25]. Although BMD in the lumbar or femoral neck can increase, BMD in the distal radius is not affected by poor blood glucose control [26]. Therefore, the BMD in the distal radius was considered the most appropriate screening tool for osteoporosis. The T-score described the number of SDs by which an individual's BMD differed from the mean value that is expected in young healthy individuals at the same point.

Statistical analysis

The results were expressed as mean ± SD. All analyses were performed using SPSS software (version 21.0, SPSS, Chicago, IL, USA). Intergroup comparisons were performed using Student's *t* test (with versus without a history of minor fracture, or low versus normal 25[OH]D levels). To evaluate the relationship between basal and bone metabolism, correlational analysis was performed between the various factors. Regression analysis was performed between each pair of variables that exhibited a significant correlation, and all coefficients for determination data were adjusted (r^2). The contributions of blood glucose control, basal metabolism, and aging to bone metabolism were evaluated for each relevant biological parameter that had a significance of $P < 0.1$ in the univariate analysis, and these were assessed in three multiple regression analysis models. Differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

The patients' clinical information is listed in Table 1; the mean age was 65 ± 5.9 y, mean BMI was 24.5 ± 3.6 kg/m^2, and mean duration of diabetes was 15.8 ± 8.7 y. It is notable that none of the patients had been diagnosed with osteoporosis, although 10 had a history of bone fracture. Among these patients, nine had nontraumatic fractures. The patients fractured their arms, lower legs, or toes, and one had fractured her lower leg and finger twice. The MCVs in the ulnar and peroneal nerves were 55 ± 4.5 m/s (normal: 58.2 ± 4.7 m/s [27]) and 46.3 ± 5 m/s (normal: 47.2 ± 3.7 m/s), respectively. The SCVs in the ulnar and sural nerves were 51.5 ± 3.7 m/s (normal: 55 ± 3.8 m/s) and 48.9 ± 7.7 m/s (normal: 50.8 ± 5.1 m/s), respectively. Regarding respiratory load, the mean R-R interval was shorter than the predicted age-related values in five patients, and no significant differences were observed between the blood pressures in the decubitus and standing positions for all patients. There was no significant difference in the neurologic outcomes for patients with or without a history of fracture.

Bone metabolism

The mean BMD and T-score in the tracheal bones were 0.473 ± 0.07 g/cm^2 and −1.76 ± 1.52, respectively. Eighteen patients (39%) had a T-score < −2.5, and were diagnosed with osteoporosis [28]. The serum levels of the bone metabolism markers are listed in Table 1. The mean serum levels of CTX-1 and P1NP were lower in our patients compared with values that have been reported in normal postmenopausal women (CTX-1: 0.36 ± 0.13 ng/mL versus 0.56 ± 0.23 ng/mL, P1NP: 37.6 ng/mL versus 45.05 ng/mL) [20].

CTX-1 levels were significantly and negatively correlated with the patients' initial glycated hemoglobin (Hb)A_{1C} levels ($r = -0.397$, $P = 0.006$) and average HbA_{1C} levels for the previous 6 mo ($r = -0.385$; $P = 0.008$; Fig. 1A); CTX-1 levels were positively correlated with P1NP levels ($r = 0.645$; $P < 0.001$). Additionally, P1NP levels were significantly and negatively correlated with the patients' initial HbA_{1C} levels ($r = -0.41$; $P = 0.005$) and duration of diabetes ($r = -0.36$; $P = 0.01$), and were significantly and positively correlated with their 25(OH)D levels ($r = 0.321$; $P = 0.03$) and CTX-1 levels ($r = 0.645$;