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Original article

Femoral bone structure in Otsuka Long-Evans Tokushima Fatty rats

Akira Minematsu [a,*], Tomoko Hanaoka [b], Yoshihiro Takada [b,c], Shunji Okuda [d], Hidetaka Imagita [a], Susumu Sakata [e]

[a] Department of Physical Therapy, Faculty of Health Science, Kio University, 4-2-2 Umaminaka, Koryo-cho, Kitakatsuragi-gun, Nara 635-0832, Japan
[b] Division of Health Science, Graduate School of Health Science, Kio University, 4-2-2 Umaminaka, Koryo-cho, Kitakatsuragi-gun, Nara 635-0832, Japan
[c] Department of Human Behavior, Faculty of Human Development, Kobe University, 3-11 Tsurukabuto, Nada-ku, Kobe, Hyogo 657-8501, Japan
[d] Department of Modern Education, Faculty of Education, Kio University, 4-2-2 Umaminaka, Koryo-cho, Kitakatsuragi-gun, Nara 635-0832, Japan
[e] Department of Physiology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8521, Japan

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Abstract

Objectives: Type 2 diabetes mellitus (T2DM) increases fracture risk despite normal to high levels of bone mineral density. Bone quality is known to affect bone fragility in T2DM. The aim of this study was to clarify the trabecular bone microstructure and cortical bone geometry of the femur in T2DM model rats.
Methods: Five-week-old Otsuka Long-Evans Tokushima Fatty (OLETF; n = 5) and Long-Evans Tokushima Otsuka (LETO; n = 5) rats were used. At the age of 18 months, femurs were scanned with micro-computed tomography, and trabecular bone microstructure and cortical bone geometry were analyzed.
Results: Trabecular bone microstructure and cortical bone geometry deteriorated in the femur in OLETF rats. Compared with in LETO rats, in OLETF rats, bone volume fraction, trabecular number and connectivity density decreased, and trabecular space significantly increased. Moreover, in OLETF rats, cortical bone volume and section area decreased, and medullary volume significantly increased.
Conclusions: Long-term T2DM leaded to deterioration in trabecular and cortical bone structure. Therefore, OLETF rats may serve as a useful animal model for investigating the relationship between T2DM and bone quality.
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Keywords: Cortical bone geometry; Micro-CT; Otsuka Long-Evans Tokushima Fatty (OLETF) rats; Trabecular bone microstructure

1. Introduction

Type 2 diabetes mellitus (T2DM) increases the risk of fracture despite normal to high levels of bone mineral density (BMD) [1–3]. Vestergaard reported a 1.4-fold increase in hip fracture risk in patients with T2DM, as compared with in healthy people without T2DM, though BMD Z-score of the spine and hip in T2DM patients was high [4]. Thus, it seems likely that bone fragility in T2DM is affected by bone quality rather than bone mass. Bone quality, that reflects bone strength, encompasses bone architecture, turnover, damage accumulation and mineralization [5]. Low bone turnover in T2DM was evident by decreased bone formation/resorption markers, though both the markers were reported to increase in several studies [1–3,6,7]. Moreover, T2DM was associated with decreased total bone area, decreased trabecular bone score (TBS) [2,6,8], decreased cortical bone area and increased cortical porosity [2,3,6,9]. Accumulation of advanced glycation end products impaired enzymatic cross-links and resulted in excessive formation of non-enzymatic cross-links, leading to a decline in bone properties and detrimental effects on bone cells [1–3,6,10]. Patients with inadequately controlled T2DM showed about 1.5-fold increase in fracture risk despite having a higher BMD, as compared with healthy people without

* Corresponding author.
E-mail address: a.minematsu@kio.ac.jp (A. Minematsu).
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diabetes. When T2DM was adequately controlled, there was no difference in fracture risk between T2DM patients and healthy people [11]. Low trabecular bone score was associated with worse glycemic control in T2DM [8], suggesting that hyperglycemia may affect factors that influence bone metabolism. However, there has been no consensus regarding the effects of T2DM on bone metabolism and properties as yet.

Animal models were widely used to examine not only T2DM pathophysiology but also the effects of T2DM on bone quality factors. Since each DM model strain had unique characteristics, the most appropriate DM model was chosen for the study's purpose [12]. Otsuka Long-Evans Tokushima Fatty (OLETF) rats displayed the clinical and pathological features of human non-insulin-dependent diabetes mellitus (NIDDM), as well as the characteristics of late-onset hyperglycemia, chronic DM, mild obesity, male inheritance, hyperplastic foci of pancreatic islets and renal complications [13]. Omi et al. investigated bone metabolism in OLETF rats, and found that OLETF rats can serve as a useful model for NIDDM with osteopenia [14]. However, they did not investigate trabecular bone microstructure (TBM) or cortical bone geometry (CBG). Only a few studies have reported bone-related parameters in OLETF rats so far, though bone structure has been investigated in other rat strain models [15–22]. Thus, TBM and CBG remained unclear in OLETF rats, of which symptoms were similar to those of human T2DM.

The aims of this study were to clarify TBM and CBG in OLETF rats in order to gain further insight on bones in long-term T2DM patients and also to examine whether OLETF rats can serve as a useful animal model for investigating the relationship between T2DM and bone quality.

2. Methods

2.1. Animals

This study was performed in accordance with the Animal Experimentation Guidelines set forth by the Committee for Research Facilities of Laboratory Animal Science at Kio University. Five-week-old male OLETF (n = 5) rats were used as a model for T2DM, and LETO (n = 5) rats were used as controls (Japan SLC Inc., Hamamatsu, Japan). All rats were housed in cages at 23 ± 2 °C under a 12-h day–night cycle for 17 months. They were fed a standard rat chow (CE-2; CLEA Japan Inc., Tokyo, Japan) and water *ad libitum* throughout the experiment. At the age of 18 months, femurs were harvested from all rats under anesthesia.

At the point of analysis (at the age of 18 months), the onset of T2DM in OLETF rats was demonstrated by increased levels of blood glucose concentration (229.3 ± 104.5 mg/dL) and of HbA1c (8.3 ± 1.3%), as compared with those of LETO rats (blood glucose concentration, 70.8 ± 11.5 mg/dL; HbA1c, 5.0 ± 0.1%).

2.2. Bone structure analysis

Left femurs were dissected out, and soft tissues were removed. Using an X-ray micro-computed tomography (micro-CT; Hitachi Medical Corp., Tokyo, Japan), distal femurs were scanned at 65 kV, 90 μA, and with a voxel size of 21.3 μm, in the high-definition mode for analysis of TBM. The region of interest (ROI) for TBM was a 2 mm-length portion of the metaphysis, and therefore the first slice was scanned 1 mm distal from the physeal-metaphyseal demarcation. Likewise, the central portion of femurs were simultaneously scanned by micro-CT at 65 kV, 90 μA, and with a voxel size of 18.1 μm using the high-definition mode for analysis of CBG. The ROI for CBG was a 2 mm-length portion distal from the center of the femur. Scanned data were transmitted to a personal computer, in which TBM and CBG of the ROI were analyzed using the bone analysis software (TRI BON 3D, RATOC System Engineering Co. Ltd., Tokyo, Japan). Individual TBM and CBG parameters were obtained by analyzing 104 slice data from one ROI per animal.

Parameters of TBM were tissue volume (TV), bone volume (BV), bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular separation (Tb.Sp), connectivity density (Conn.D), trabecular bone pattern factor (TBPf), structure model index (SMI) and degree of anisotropy (DOA). Parameters of CBG were cortical bone volume (CV), all bone volume (AV), medullary volume (MV), cortical bone ratio (CV/AV), cortical bone thickness (Ct) and cortical bone section area (CSa).

2.3. Statistical data analysis

All values are expressed as mean ± standard deviation. Differences between OLETF and LETO rats were examined with the Mann–Whitney U test. All statistical analyses were performed using the Excel Statistics software (Excel 2012 version 1.15 for Windows; Social Survey Research Information Co. Ltd., Tokyo, Japan). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Body weight and femur length

There was no significant difference in final body weight between LETO rats (575.7 ± 18.3 g) and OLETF rats (496.1 ± 87.6 g). However, femur length was significantly shorter in OLETF rats (39.4 ± 1.2 mm) than in LETO rats (41.8 ± 0.3 mm).

3.2. TBM and CBG parameters

OLETF rats at the age of 18 months showed the deterioration in TBM and CBG parameters compared with LETO rats at the same age (Table 1). In TBM parameters, BV, BV/TV, Tb.N and Conn.D were significantly lower, and Tb.Th, Tb.Sp, TBPf and SMI were significantly higher, in OLETF rats than in LETO rats. With respect to CBG parameters, CV, CV/AV and CSa were significantly lower in OLETF rats than in LETO rats. To the contrary, MV was significantly higher in OLETF rats than in LETO rats (Table 1).

Fig. 1 shows cortical and trabecular bone transverse sections of the ROI in OLETF rats and LETO rats. Connectivity of trabecular bone at the femoral metaphysis appears to be well maintained in LETO rats, whereas trabecular bone in OLETF rats is diminished and disconnected. Thus, deterioration of trabecular bones at the distal femoral metaphysis is evident in OLETF rats. On the other hand, the cross sections of cortical bones at the femoral diaphysis shows that the internal cortical bone of the femoral shaft is resorbed and thereby bone marrow area is increased in OLETF rats, as compared with in LETO rats.

4. Discussion

Dhaliwal et al. found that TBS is lower in women with T2DM or in women under worse glycemic control ($HbA_{1c} > 7.5\%$) than in women without T2DM [8]. Moreover, the lumbar spine TBS has been reported to predict osteoporotic fractures in DM [23]. Pritchard et al. showed that women with T2DM have larger holes in the trabecular bone network of the radius compared to women without T2DM [24]. However, some studies showed no significant difference in TBM between women with T2DM and those without T2DM [25–27], though the augmented cortical porosity was often reported in women with T2DM [6,9,27,28].

Animal T2DM models showed deterioration in both trabecular and cortical bone structure [15–22]. Body weight decreased after onset of DM in these models [15–22], and bone length of the lower limbs was shorter [16,17,19,21]. In contrast to humans, BMD in the lower limbs of T2DM rats was within the range from low to normal values, compared with that of control rats [15–22]. Shorter femur was shown in this study as reported in the previous studies using T2DM model rats [16,17,19,21]. Lapmanee et al. fed 5-week-old Goto-Kakizaki (GK) rats with normal diet for 11 weeks, and thereafter found that differentiation and turnover of the growth plate chondrocytes are impaired in these GK rats [17]. They also observed that chondrocyte precursors are arrested and retained in the resting zone, and consequently a decrease in the number of matured chondrocytes in the hypertrophic zone causes deceleration in both endochondral bone growth and bone elongation in the GK rats [17]. Kimura et al. showed that in spontaneously diabetic Torii (SDT) *–fa/fa* rats at the age of 40 weeks, hyperglycemia- and obesity-induced deterioration of bone formation involves severe bone loss, shortening in bone length, deterioration in bone geometrical properties and decrease in bone strength [19]. Thus, hyperglycemia in T2DM affected not only bone properties but also bone growth and consequently weakened bone strength [16,19]. Therefore, it seems likely that in OLETF rats, as well as in the above-mentioned other T2DM rats, bone growth/elongation is suppressed by hyperglycemia.

In trabecular bone of T2DM rats, BV/TV and Tb.Th values were smaller, though Tb.N and Tb.Sp remained unchanged [16,17,19,20]. On the other hand, in the present study, OLETF rats exhibited the increase in Tb.Th and Tb.Sp and the decrease in BV/TV, Tb.N and Conn.D. In addition to such TBM deterioration, the increase in TBPf and SMI showed that trabecular bone of OLETF rats is essentially shaped like rod. BMD was higher in OLETF rats than in control LETO rats until age 40 weeks [14]. The BMD and trabecular bone conditions observed in OLETF rats were similar to those in humans [2,6,8]. In histomorphological studies, osteoblast surface normalized by bone surface, osteoid thickness, mineralizing surface, bone formation rate and mineral apposition rate were reduced in T2DM model rats [16–18]. However, osteoclast surface and eroded surface varied among these studies [16–18]. Such differences may be attributed to difference in animal models or the rat ages, which are closely related to the timing of DM symptom onset. Serum osteocalcin and parathyroid hormone levels have been reported to range between low and normal values in T2DM rats [14,16,18,19,22,29], though bone resorption markers and bone resorption activities varied among the studies [14,16,19,22,29]. Thus, bone formation was evidently decreased in T2DM model rats like OLETF rats. Therefore, deterioration of TBM in our OLETF rats would have been caused by impaired bone formation, that is partially due to reduced mineralization and malfunction of osteoblasts.

BMD of lower limbs were lower in T2DM rats than in control rats [19,21,22]. For instance, in OLETF rats, although femoral BMD was higher at age 33 weeks, BMD of the tibia diaphysis was decreased after age 56 weeks [14]. Several studies showed low to normal values for cross-sectional area or cortical thickness and normal to high values for cortical periosteal perimeters [16,17,19,21,22], though the cortical endosteal perimeter remained unchanged [15,17,21]. In T2DM

Table 1
Trabecular bone microstructure and cortical bone geometry parameters

	LETO rats	OLETF rats
Trabecular bone microstructure parameters		
TV (mm^3)	13.3 ± 0.3	13.3 ± 1.2
BV (mm^3)	1.80 ± 0.13	0.40 ± 0.14*
BV/TV (%)	13.5 ± 1.0	3.0 ± 1.1*
Tb.Th (μm)	93.7 ± 0.6	107.8 ± 13.4*
Tb.N (1/mm)	1.11 ± 0.08	0.24 ± 0.12*
Tb.Sp (μm)	283.8 ± 8.1	721.7 ± 277.6*
Conn.D (1/mm)	14.3 ± 1.8	1.3 ± 0.8*
TBPf	9.6 ± 0.6	13.7 ± 3.0*
SMI	2.2 ± 0.1	3.0 ± 0.3*
DOA	1.7 ± 0.1	1.8 ± 0.1
Cortical bone geometry parameters		
CV (mm^3)	13.5 ± 0.4	11.6 ± 1.4*
MV (mm^3)	7.2 ± 0.5	11.7 ± 1.3*
CV/all bone volume (%)	65.2 ± 1.9	49.8 ± 0.6*
Ct (μm)	370.5 ± 61.0	440.7 ± 33.1
CSa (mm^2)	6.6 ± 0.2	5.7 ± 0.7*

Values are expressed as mean ± SD of 5 animals. *Significantly different from LETO rat values ($p < 0.05$).
BV, bone volume; BV/TV, bone volume fraction; Conn.D, connectivity density; CSa, cortical bone section area; Ct, cortical bone thickness; CV, cortical bone volume; DOA, degree of anisotropy; MV, medullary volume; SMI, structure model index; TBPf, trabecular bone pattern factor; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; TV, tissue volume.

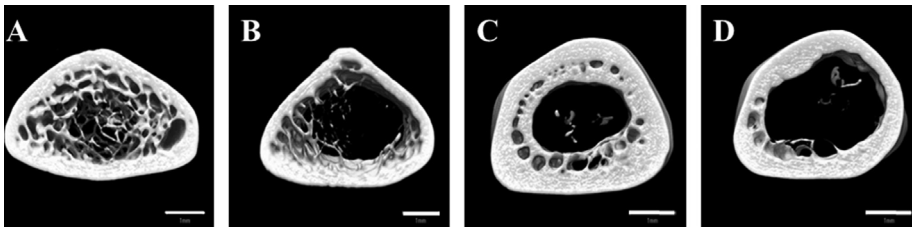

Fig. 1. **Representative cross sections of region of interest in femoral metaphysis trabecular bone and diaphysis cortical bone**. Cross section A and B show metaphysis trabecular bone of LETO rats and of OLETF rats, respectively. Cross section C and D show diaphysis cortical bone of LETO rats and of OLETF rats, respectively. Bar = 1 mm.

rats, bone mechanical strength seems to be primarily dependent on both bone size and bone properties including BMD. Sixteen-week-old GK rats showed lower mineralization surface, lower bone formation rate, lower CSa and shorter tibial length, but normal Ct value, in tibia, as compared with age-matched control rats [17]. Moreover, 6-month-old GK rats showed lower mineralization surface, lower bone formation rate and shorter femoral length, but normal Ct and CSa values, in femur, as compared with control rats [16]. In addition, SDT-fa/fa rats showed lower urine deoxypyridinoline at the age of 8 weeks, and also lower Ct of femur and lower serum osteocalcin at the age of 8, 16 and 40 weeks, compared with control rats [19]. Nine-week-old ZDF-fa/fa rats also showed lower Ct of femur, lower serum osteocalcin and lower serum carboxy-terminal collagen crosslinks, compared with control rats [22]. In the present study, OLETF rats showed increased MV, decreased CV and decreased CSa. In fact, the cortical endosteal area was obviously resorbed (Fig. 1). Thus, the deterioration of CBG was observed in the present OLETF rats as reported in other rat DM models [16,17,19−22]. In view of the above-mentioned facts, such deterioration of CBG, as well as of TBA, would have been caused by impaired bone formation that is partially due to lowered mineralization, impaired differentiation/turnover of growth plate chondrocytes and malfunction of osteoblasts, resulting in small size of bones in our OLETF rats.

Our findings reported herein suggest that long-term DM (age 18 months) leads to the deterioration of both TBM and CBG due to impaired bone formation [29]. T2DM also may affect calcium metabolism. In addition to low serum osteocalcin levels [29], high sclerostin [29] and low vitamin D [14] levels have been reported in OLETF rats. The greater deterioration of TBM and CBG in this study may reflect the chronic DM condition (i.e., DM for long-term period over 1 year). In conclusion, OLETF rats may serve as a useful animal model for investigating the relationship between T2DM and bone quality or bone metabolism. Therefore, OLETF rats may be used to explore a potent rehabilitation modality for preventing or treating bone fragility in chronic DM patients.

Conflicts of interest

The authors declare no conflicts of interest.

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