World Journal of Diabetes

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DOI: 10.4239/wjd.v6.i5.673

World J Diabetes 2015 June 10; 6(5): 673-678
ISSN 1948-9358 (online)

EDITORIAL

Update on type 2 diabetes-related osteoporosis

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Author contributions: Wongdee K and Charoenphandhu N contributed equally for literature review, data analysis and preparation of the manuscript.

Supported by Grants from the Cluster and Program Management Office (CPMO), National Science and Technology Development Agency (P-11-00639); the Thailand Research Fund (TRF)-Mahidol University through the TRF Senior Research Scholar Grant (RTA5780001 to NC); the Faculty of Allied Health Sciences, Burapha University and Thailand Research Fund through TRF Research Career Development Grant (RSA5780041 to KW); the Research and Development Fund Burapha University (05/2557 to KW); the Faculty of Allied Health Sciences, Burapha University Research Grant of Fiscal Year 2015 (AHS05/2558 to KW).

Conflict-of-interest: Kannikar Wongdee and Narattaphol Charoenphandhu declare no conflicts of interest.

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Received: January 11, 2015
Peer-review started: January 15, 2015
First decision: February 7, 2015
Revised: February 12, 2015
Accepted: March 5, 2015
Article in press: March 9, 2015
Published online: June 10, 2015

Abstract

It was previously understood that body weight gain and obesity observed in type 2 diabetes mellitus (T2DM) could be beneficial since body weight increase elevated bone mineral density and thus helped maintain the skeletal framework. However, a number of recent findings in humans and rodents have revealed that T2DM is not only associated with trabecular defects but also increases cortical porosity, and compromised bone cell function and bone mechanical properties. Hyperglycemia and insulin resistance in T2DM may further induce osteoblast apoptosis and uncoupling bone turnover. Prolonged accumulation of advanced glycation end products and diminished activity of lysyl oxidase, an essential enzyme for collagen cross-link, can lead to structural abnormalities of bone collagen fibrils, brittle matrix, and fragility fractures. Our studies in T2DM rats showed that dyslipidemia, which often occurs in T2DM, could obscure the T2DM-associated changes in bone microstructure and osteopenia. Longitudinal bone growth regulated by the growth plate chondrocytes is also impaired by T2DM since differentiation of growth plate chondrocytes is arrested and retained in the resting state while only a small number of cells undergo hypertrophic differentiation. Such a delayed chondrocyte differentiation may have also resulted from premature apoptosis of the growth plate chondrocytes. Nevertheless, the underlying cellular and molecular mechanisms of insulin resistance in osteoblasts, osteoclasts, osteocytes, and growth plate chondrocytes remain to be investigated.

Key words: Advanced glycation end products; Chondrocyte apoptosis; Collagen; Dyslipidemia; Fracture; Growth plate; Type 2 diabetes mellitus; Osteoporosis

Core tip: Type 2 diabetes mellitus (T2DM) negatively affects bone density and strength by inducing cellular and extracellular matrix failures. Insulin resistance in T2DM deteriorates osteoblast proliferation and activity, but enhances osteoclast activity, leading to uncoupled bone remodeling. Hyperglycemia also aggravates osteoblast dysfunction, thus contributing to cellular failure. Extracellular matrix failure is caused by abnormal collagen synthesis and aberrant collagen structure and alignment, the latter of which results, in part, from advanced glycation end products (AGEs). With hyperglycemia and AGEs, impaired bone strength may occur despite high bone mineral density. It is, therefore, concluded that T2DM can be considered a cause of osteoporosis and/or poor bone mechanical properties.

Wongdee K, Charoenphandhu N. Update on type 2 diabetes-related osteoporosis. *World J Diabetes* 2015; 6(5): 673-678 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i5/673.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i5.673

INTRODUCTION

Although type 1 diabetes mellitus (T1DM) is known to compromise bone microstructure[1,2], how type 2 diabetes mellitus (T2DM) affects bone metabolism has long been debate for decades. It was previously believed that T2DM could be protective against osteoporosis since a number of clinical studies and meta-analyses revealed an increase in bone mineral density (BMD) in T2DM patients[1,2]. However, several recent lines of evidence in both humans and rodents have corroborated that T2DM is indeed detrimental to bone, leading to impaired osteoblast-mediated bone formation, accelerated bone resorption, microstructural defect, and poor bone quality. The previous controversial data stem from the use of low-resolution X-ray-based techniques, including measurement of areal BMD by dual energy X-ray absorptiometry (DXA), rather than evaluation of high-resolution bone microstructure or bone mechanical properties. This article has updated the recent findings of T2DM-related osteopenia and osteoporosis, as summarized in Table 1.

T2DM INCREASES BONE POROSITY AND DECREASES MECHANICAL BONE STRENGTH

Previous investigations in human mostly focus on trabecular bone changes in T2DM, but recent investigations have moved to the study of cortical changes and mechanical properties. By using more advanced techniques, such as high-resolution 3-dimensional computed tomography and microindentation, it was found that T2DM negatively affected bone strength despite the presence of relatively high BMD. Several cross-sectional studies in T2DM patients using high-resolution peripheral quantitative computed tomography (HR-pQCT) and magnetic resonance imaging (MRI) consistently revealed quality defects in both cortical and trabecular networks that would increase fracture risk[3-6]. For instance, Farr *et al*[3] by assessing bone quality with HR-pQCT in 30 postmenopausal T2DM patients at distal radius and distal tibia, found lower cortical thickness in T2DM was lower than normal non-diabetic controls, while bone microindentation testing showed lower bone material strength (BMS) in T2DM patients. Moreover, the radius quality evaluated by MRI, showed trabecular network holes being approximately 10% larger in postmenopausal T2DM patients than normal controls[5]. The cortical part was similarly affected by T2DM[4]. Patsch *et al*[4] investigated changes in bone microarchitecture in postmenopausal T2DM patients with or without fractures at radius and tibia by using DXA and HR-pQCT. Interestingly, they found that T2DM patients with fractures had higher pore-related deficits, *i.e.*, greater cortical pore volume, cortical porosity, and endocortical bone surface, than diabetic patients without fractures[4], consistent with the previous report in the radii of T2DM patients that having greater cortical pore volume (approximately 150%) and cortical porosity (approximately 125%) than normal individuals[6]. These cortical defects were often accompanied by impaired mechanical properties, such as increased failure load and low bone bending strength, that led to reduction in overall bone strength and increase in fracture risk[4,7].

DYSLIPIDEMIA MIGHT OBSCURE T2DM-INDUCED OSTEOPOROSIS

Previously it was believed that greater body weight or obesity associated with T2DM could be beneficial to the skeletal system through increasing BMD and bone mass[7,8]. However, our group recently reported the possible masking effects of dyslipidemia on diabetic bone in rats[9]. In our study, we determined the effects of dyslipidemia on bone microstructure were determined in Goto-Kakizaki (GK) diabetic rats treated with high cholesterol diet compared those fed with normal diet. The GK rats-a non-obese T2DM rat model without obesity-induced bone gain-were found to manifest stable fasting hyperglycemia and insulin resistance, while cholesterol-fed GK rats exhibited hypercholesterolemia, hypertriglyceridemia and hyperglycemia without significant weight gain[10]. Bone histomorphometry revealed that GK rats with T2DM manifested several signs of suppressed osteoblast function, such as decreases in osteoblast surface and bone formation rate, whereas the osteoclast-mediated

Table 1 Recent studies on the type 2 diabetes mellitus-related osteoporosis in humans (2010-2014)

Site of bone	Technique	Subjects	Main findings in T2DM group	Ref.
Distal radius	HR-pQCT	60 postmenopausal women	Low cortical thickness and low trabecular number	[3]
Distal tibia	HR-pQCT		Lower cortical thickness	
Mid-shaft tibia	Microindentation		Poor bone quality (low BMS)	
Distal radius	DXA, HR-pQCT	80 postmenopausal women with or without fractures	Higher cortical porosity in T2DM with fractures	[4]
Ultradistal radius	DXA, HR-pQCT		Higher cortical porosity in T2DM with fractures	
Distal tibia	DXA, HR-pQCT		Lower cortical porosity in T2DM with fractures	
Ultradistal tibia	DXA, HR-pQCT		Lower BMD and cortical porosity in T2DM with fractures	
Distal radius	MRI	60 postmenopausal women	Greater trabecular network holes	[5]
Distal radius	HR-pQCT	38 postmenopausal women	Higher cortical porosity	[6]
Tibia	HR-pQCT		Higher volumetric BMD and trabecular thickness	
Mid-shaft radius	pQCT	1171 men (≥ 65 yr)	Lower bone bending strength	[7]
Mid-shaft tibia	pQCT		Lower bone bending strength	

BMD: Bone mineral density; BMS: Bone material strength; DXA: Dual energy X-ray absorptiometry; HR-pQCT: High resolution-peripheral quantitative computed tomography; MRI: Magnetic resonance imaging; T2DM: Type 2 diabetes mellitus.

bone resorption was markedly enhanced. It was noted that, these microstructural changes disappeared after 16-wk of high cholesterol consumption, suggesting that high cholesterol diet and perhaps the resultant dyslipidemia could obscure the T2DM-associated osteopenia and changes in bone microstructural defect[9]. Thus, the difficulty in detecting bone deterioration in T2DM rats with dyslipidemia could explain, in part, why osteopenia was not observed in some T2DM studies.

T2DM AND LONGITUDINAL BONE GROWTH

Up until now, few studies have investigated relationship between T2DM and longitudinal bone growth. Generally, longitudinal bone growth is controlled by proliferation and differentiation of chondrocytes in the growth plate, which is histologically divided into 3 zones, *i.e.*, resting zone (RZ), proliferative zone (PZ) and hypertrophic zone (HZ). The RZ consists of low mitotic activity stem-like cells that gradually migrate to the PZ where chondrocytes proliferate and align into vertical columns and eventually reach the mature state in HZ. Thereafter, the hypertrophic chondrocytes in HZ undergo apoptosis and are replaced by capillaries and osteoblasts, which later use cartilaginous scaffold as a template for bone formation and bone elongation[11,12]. Since several investigations reported reduced bone length in diabetic rats compared with normal rats[9,13], T2DM may be a cause of aberrant growth plate function. Lapmanee *et al*[9] examined changes in the growth plate of diabetic GK rats and found impairment of chondrocyte differentiation as indicated by increased RZ height and decreased HZ height. It was possible that differentiation of chondrocyte precursors in T2DM rats were arrested and cells remained in the resting state, with only a small number of proliferating cells undergoing differentiation into hypertrophic chondrocytes[9].

Aiemlapa *et al*[14] further demonstrated the underlying mechanism of delayed growth plate chondrocyte differentiation. By using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay for apoptosis, they found premature apoptosis of chondrocytes in the HZ and chondro-osseous junction of GK rats. The massive loss of growth plate chondrocytes was accompanied by an increase in serum IGF-1 level, and overexpression of parathyroid hormone related protein (PTHrP), *runt*-related transcription factor (Runx2) and vascular endothelial growth factor (VEGF) in the growth plate, all of which might have been compensatory responses to mitigate excessive loss of chondrocytes due to premature apoptosis[14]. However, it was possible that the effects of T2DM on the growth plate might be dependent on animal strain and model of DM induction. For instance, Wu *et al*[15] found acceleration of longitudinal bone growth as indicated by bone elongation and increased heights of PZ and HZ in insulin resistant mice induced by high fat diet. In this model, insulin might remain to have a stimulatory effect on bone growth *in vivo* similar to its reported stimulatory effect on metatarsal linear growth *in vitro*[15]. Furthermore, high fat diet-induced dyslipidemia could complicate the matter since 7α-hydroxycholesterol and oxidized low-density lipoprotein (LDL) have been shown to modulate osteoblast and osteoclast functions, which, in turn, could have effects on bone elongation[16,17].

POSSIBLE CELLULAR MECHANISMS OF T2DM-RELATED FRAGILITY FRACTURES

The pathogenesis of T2DM-related fragility fracture can be looked upon from 2 aspects, *i.e.*, cellular failure and extracellular matrix failure. At cellular level, T2DM was associated with diminished activities of osteoblasts, osteoclasts and osteocytes, and increased apoptosis of bone cells[9,18-21]. A decrease in osteocyte density (number of osteocyte-occupied lacunae per unit

area) was conspicuously observed in streptozotocin-induced diabetic rats[21]. Hyperglycemia-induced insulin resistance is another important factor that cause both osteoblast and osteoclast malfunctions[22]. Since insulin is a suppressor of osteoclast-mediated bone resorption[23], T2DM-associated insulin resistance could enhance bone resorption. Moreover, high plasma glucose concentration can induce glucotoxicity in cells including osteoblasts, leading to osteoblast apoptosis[24]. *In vivo* experiment in transgenic liver-specific S503A CEACAM1 mutant (L-SACC1) mice, a model of impaired insulin clearance in the liver causing hyperinsulinemia and insulin resistance, suggested that the abnormally high bone mass in these mice might have resulted from low bone turnover as indicated by decreases in double-labeled surface (as determined by bone histomorphometry) and TRAP-positive osteoclasts, which represent activities of osteoblast-mediated bone formation and osteoclast-mediated bone resorption, respectively[22]. In other words, insulin resistance in this model was associated with a slowdown in bone turnover, which could eventually result in inadequate healing of microcracks, poor bone quality and increased fracture risk[22]. In addition, the experiment in high fat diet-fed Zucker diabetic fatty (ZDF) rats also showed impaired osteoblast function as indicated by downregulation of the expression of osteoblast-specific genes, *e.g.*, bone morphogenetic protein-2 (BMP-2), Runx2, osteocalcin and osteopontin. Suppression of osteoblastogenesis in these ZDF rats possibly compromised bone regeneration capacity. Subcritical bone defect regeneration study further showed that nondiabetic rats filled the defect by 57%, whereas diabetic rats could fill only 21% of bone defect in 12 wk[18].

T2DM not only caused deterioration of bone cell functions (cellular failure), but it also damaged bone extracellular matrix. Most studies suggested that T2DM caused abnormality in the structure of collagen, which is the most abundant protein in organic bone matrix. García-Hernández *et al*[25] reported that high glucose concentration indeed increased biomineralization in human alveolar bone-derived osteoblasts, but the mineral quality was lower than that in low glucose-exposed group. Determination of mineral quality in term of calcium/phosphate (Ca/Pi) ratio in the mineralized extracellular matrix nodules by energy-dispersive X-ray microanalysis (EDX) showed that high concentration of glucose significantly decreased Ca/Pi ratio on day 7 and 14 of treatment. Hammond *et al*[26] further studied nanoscale morphology of type Ⅰ collagen in tibiae of ZDF rats by Raman spectroscopy and reference point indentation (RPI), the latter of which applied a force to determine bone mechanical properties by measuring the relative displacement reference position[26,27]. RPI analysis revealed that bone matrix of ZDF diabetic rats was more resistant to plastic deformation, which might have resulted from abnormal formation of non-enzymatic collagen cross-link, toughening of the matrix, or the presence of advanced glycation end products (AGEs).

AGEs are non-enzymatic carbohydrate modifications of extracellular and intracellular proteins accumulated in long-lived tissues, such as skin and bone, and are often present in the plasma proteins of patients with DM and renal failure[28,29]. A number of investigations have revealed that AGEs are considered a factor that provokes fragility fractures in T2DM by inducing abnormal arrangement of collagen[26,28,30]. By using scanning electron microscope (SEM) and transmission electron microscope (TEM), Aoki *et al*[28] provided evidence that the rats subjected to adenine-induced renal failure exhibited AGEs accumulation and suppression of osteoblast function, similar to that observed in T2DM. SEM showed irregularity in collagen fibril alignment, while TEM revealed a wider diameter of collagen fibril in adenine-treated rats with renal osteodystrophy[28]. Immunohistochemistry also showed greater accumulation of AGEs in peritrabecular osteoblasts of adenine-treated rats than control rats. Further *in vitro* study in AGEs-treated MC3T3-E1 osteoblast-like cells showed a decrease in protein expression of secreted phosphoprotein 1 and lysyl oxidase, a mature osteoblast marker and essential enzyme for collagen cross-link, respectively. It was thus suggested that suppressed osteoblast differentiation and decreased lysyl oxidase production caused structural abnormalities of bone collagen fibrils leading to bone fragility[28].

Collagen is the most abundant protein in bone organic matrix, and it undergoes intra- and extracellular post-translational modifications[31]. To stabilize collagen fibrils, lysyl oxidase catalyzes intra- and intermolecular cross-link between collagen molecules essential for bone strength[31]. It was reported that glycation of collagen caused abnormal arrangement of collagen leading to brittle matrix and fragile bone[26,28,30], but little is known whether a decrease in lysyl oxidase-dependent collagen cross-link contributes to diabetic bone fragility and osteoporosis. The underlying mechanism of AGEs-attenuated lysyl oxidase activity was explored in mouse and rat primary osteoblasts and it was found that the carboxymethylated collagen, a form of AGEs, was not able to promote lysyl oxidase-mediated cross-linking due to failure of binding between abnormal collagen and discoidin domain receptor-2[30].

CONCLUSION

Currently, it can be concluded that T2DM compromises bone microstructure by inducing aberrant bone cell function (cellular failure) and abnormal matrix structure (matrix failure). Regarding the cellular effect, T2DM is associated with increased osteoblast apoptosis, diminished osteoblast differentiation, and enhanced osteoclast-mediated bone resorption, which, in part,

resulted from hyperglycemia and insulin resistance. Prolonged accumulation of AGEs coexisting with a decrease in lysyl oxidase activity causes abnormal structure and alignment of collagen, leading to bone fragility. Several confounding factors in T2DM, particularly body weight gain, obesity, and dyslipidemia, are able to mask the detrimental effects of T2DM, and may delay diagnosis of diabetic osteoporosis. In other words, bone is already damaged in T2DM despite a relatively high BMD. Although deleterious effects of T2DM on bone have been elucidated, the underlying cellular and molecular mechanisms remain unclear. For example, how does insulin resistance occur in osteoblasts and how do phosphorylation of insulin-receptor substrate isoforms (IRSs) and resultant insulin resistance in osteoblasts, osteoclasts and perhaps osteocytes contribute to diabetic bone loss? Indeed, osteocytes residing inside lacunae play an important role in bone remodeling in health and disease since they are responsible for inducing bone loss under certain conditions, such as during lactation[32,33]. Further investigation is required to demonstrate whether osteocytic dysfunction does exist in T2DM.

ACKNOWLEDGMENTS

The authors thank Professor Nateetip Krishnamra for valuable comments on the manuscript.

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P- Reviewer: Grieco A, Hiwatashi A **S- Editor**: Ji FF
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