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**REVIEW**

# Bone metabolism and fracture risk in type 2 diabetes mellitus

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**Abstract.** Osteoporosis and type 2 diabetes mellitus (T2DM) are now prevalent in aging and westernized societies, and adversely affect the health of the elderly people by causing fractures and vascular complications, respectively. Recent experimental and clinical studies show that both disorders are etiologically related to each other through the actions of osteocalcin and adiponectin. Meta-analyses of multiple clinical studies show that hip fracture risk of T2DM patients is increased to 1.4 to 1.7-folds, although BMD of the patients is not diminished. Vertebral fracture risk of T2DM patients is also increased, and BMD is not useful for assessing its risk. These findings suggest that bone fragility in T2DM depends on bone quality deterioration rather than bone mass reduction. Thus, surrogate markers are needed to replace the insensitivity of BMD in assessing fracture risks of T2DM patients. Markers related to advanced glycation end products as well as insulin-like growth factor-I may be such candidates, because these substances were experimentally shown to modulate bone quality in DM. In practice, it is important for physicians to assess fracture risk in T2DM patients by evaluating prior VFs and fracture histories using spine X-ray and interview, respectively, until the usefulness of surrogate markers is established.

*Key words*: Type 2 diabetes mellitus, Bone fragility, Fracture risk, Osteocalcin, Adiponectin

**THE NUMBERS** of patients with osteoporosis or type 2 diabetes mellitus (T2DM) are increasing in aging and westernized societies. Both disorders predispose the elderly people to disabled conditions by causing fractures and vascular complications, respectively, which eventually raise their mortality. Although osteoporosis and T2DM are traditionally viewed as separate disease entities, accumulating evidence indicates that there are similar pathophysiological mechanisms underlying them.

## I. Interaction between bone metabolism and glucose/fat metabolism through osteocalcin and Wnt signaling

Osteocalcin (OC), one of the osteoblast-specific secreted proteins, has several hormonal features and is secreted in the general circulation from osteoblasts [1, 2]. Recent animal studies have shown that OC action is related to not only bone metabolism but also glucose metabolism and fat mass [3, 4]. Lee *et al*. showed that OC functions as a hormone that improves glucose metabolism and reduces fat mass, because OC-deficient mouse aggravated these processes [3]. Moreover, Ferron *et al*. showed that recombinant uncarboxylated OC administration to wild-type mice fed by high fat diet regulated gene expression in pancreatic β cells and adipocytes (including adiponectin expression), and prevented the development of metabolic diseases, obesity, and hyperglycemia [4]. Several clinical studies have also confirmed the relationship between OC and glucose/fat metabolism in humans [5-9]. We were the first to show that serum OC level was negatively correlated with plasma glucose level and atherosclerosis parameters in T2DM patients [5]. We also found that undercarboxylated OC was negatively associated with plasma glucose level and fat mass, and positively with adiponectin in the population [6]. In non-DM subjects, it is documented that OC level was inversely related to plasma glucose level and fat mass [7], and was positively associated with insulin sensitivity [8]. Pittas *et al*. have shown that serum OC concentration was inversely associated with fasting plasma glucose (FPG), fasting insulin, homeostasis model assessment for insulin resistance, high-sensitivity C-reactive protein, interleukin-6, body mass index (BMI), and body

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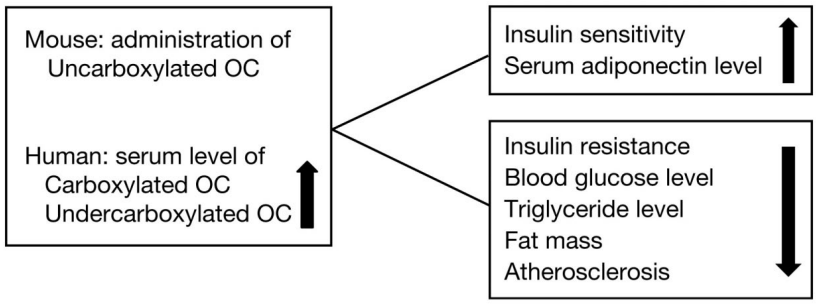


**Fig. 1** Osteocalcin (OC) and metabolic index in animal and clinical studies. When uncarboxylated OC was administered to fat mouse, it increased insulin secretion, while decreased blood glucose level, fat mass, and triglyceride level. In humans, serum carboxylated and undercarboxylated OC levels were positively correlated with insulin sensitivity and adiponectin level, while they were negatively correlated with blood glucose level, fat mass, and atherosclerosis index. Thus, osteoporosis and diabetes are pathophysiologically related to each other through OC action not only in mouse but also in humans.

fat in cross-sectional analyses on the subjects including 5% with T2DM [9]. They also found that OC levels were associated with change in FPG in prospective analyses on the same population [9]. These experimental and clinical findings suggest that bone metabolism and glucose/fat metabolism are etiologically related to each other through the action of OC (Fig. 1).

Wnt signaling is also thought to be a common pathogenesis of osteoporosis and DM. Mani *et al*. showed that a single missense mutation in low-density lipoprotein receptor-related protein 6 (LRP6), the co-receptor for the Wnt-signaling pathway, was genetically linked to osteoporosis as well as DM, hyperlipidemia, and coronary artery disease [10]. In addition, several studies documented that T cell-specific transcription factor (TCF)-4, the partner of β-catenin in the canonical Wnt-signaling pathway, was the strongest T2DM susceptibility gene [11-14]. Manolagas and other researchers suggest that antagonism of Wnt signaling by oxidative stress diverts β-catenin from TCF- to Forkhead box O (FoxO)-mediated transcription, and contributes to the development of osteoporosis as well as insulin resistance and hyperlipidemia [15-18]. Activation of FoxO by reactive oxygen species in early mesenchymal progenitors also leads to decreased osteoblastogenesis by diverting β-catenin away from Wnt signaling [19], which mechanism may be implicated in DM-related bone fragility described in the later section.

## Ⅱ. The involvement of fat tissue in bone metabolism through adiponectin

Body fat and bone mass also seem to be related to each other, because there is a positive correlation between bone mineral density (BMD) and fat mass including visceral adipose tissue [20-22]. Adiponectin is specifically and highly expressed in visceral, subcutaneous and bone marrow fat depots. It is also abundantly present in plasma and has been proposed to play important roles in the regulation of energy homeostasis and insulin sensitivity. We and other researchers have shown that osteoblasts have an adiponectin receptor and that the proliferation, differentiation and mineralization of osteoblastic cells were enhanced by adiponectin [23, 24]. We also clinically found that serum adiponectin was associated with BMD, bone turnover, and the presence of vertebral fractures (VFs) in T2DM patients [25]. Moreover, high glucose was experimentally shown to impair OC expression and secretion from osteoblastic cells [26], and treatments for hyperglycemia in T2DM patients were found to enhance their serum OC level [27]. We found that serum adiponectin level before starting to compensate poorly controlled T2DM could predict the subsequent increase in serum OC level during glycemic control [28]. These findings suggest that adiponectin as well as OC, secreted from fat tissue and osteoblasts, respectively, are involved in the interplay between glucose/fat metabolism and bone metabolism (Fig. 2).

## Ⅲ. Fracture risk in T2DM is not reflected by BMD

Many clinical studies have investigated the association between T2DM and osteoporosis, given that these disorders affect a large proportion of the elderly population. Although BMD is considered as a gold standard for evaluating fracture risk in non-DM osteoporo-

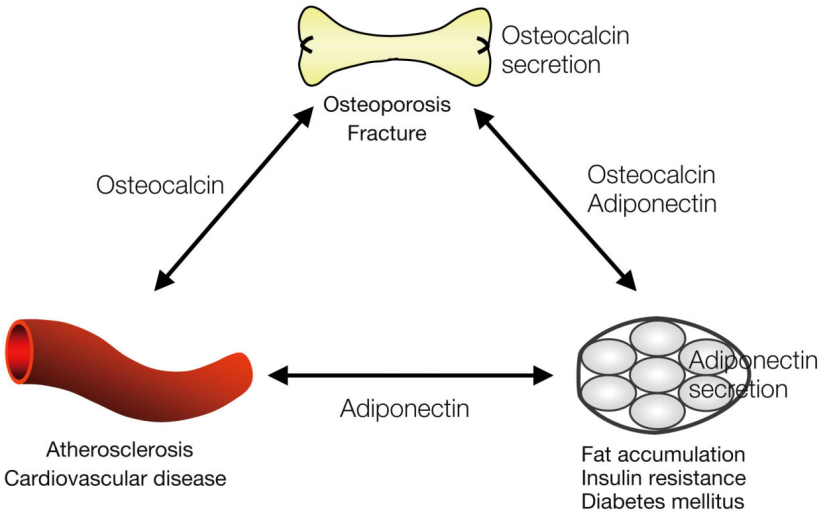


**Fig. 2** Interplay between bone metabolism and glucose/fat metabolism. OC and adiponectin, secreted from osteoblasts and fat cells, respectively, may have beneficial effects on bone, fat tissue, and artery, by protecting against metabolic derangement of these tissues.

sis, accumulative evidence shows that T2DM patients have high fracture rate in spite of the absence of BMD reduction. A recent meta-analysis showed that they had higher hip BMD than non-DM controls (z-score 0.27), despite an increased risk of hip fracture (1.4-fold) [29], suggesting that BMD values may not reflect bone fragility in T2DM. Another meta-analysis also showed that their hip fracture risk was increased to 1.7-fold [30].

In contrast, it is little known about VF risk and its association with BMD. We examined Japanese T2DM patients and non-DM controls about this issue [31, 32]. We found that the presence of T2DM was an independent risk factor for prevalent VFs in women [odds ratio (OR)=1.9] as well as men (OR=4.7) after adjustment for age, BMI, and lumbar BMD by logistic regression analysis. However, another logistic regression analysis showed that BMD at any site was not significantly associated with the presence of VFs in T2DM patients, in contrast to the significant association in non-DM controls. Fig. 3 shows the distribution of lumbar BMD as a function of age in non-DM and T2DM women. In the non-DM subjects, those with VFs (black dots) are clearly grouped in the region with higher age and lower lumbar BMD. In contrast, T2DM subjects with VFs were scattered widely and there are no associations with age or lumbar BMD. In addition, we found that calcaneal quantitative ultrasound (QUS) was also unable to discriminate T2DM patients with prevalent VFs from those without VFs [33], although QUS is thought to be able to evaluate bone quality, especially microarchitecture. Thus, T2DM patients may have an increased risk of VFs independent of BMD or QUS values, suggesting that bone quality, but not bone mass, may define bone fragility causing hip and vertebral fractures in T2DM.

## Ⅳ. Surrogate markers for assessing fracture risk in T2DM

Because BMD is not sensitive enough to assess the risk of osteoporotic fractures in T2DM, the etiology of DM-related bone fragility and its diagnostic markers replacing BMD need to be explored.

### *Pentosidine*

Formation of advanced glycation end products (AGEs) results from sequential nonenzymatic chemical glycoxidation of protein amino groups [34], collectively called the Maillard reaction. AGEs accumulate in various tissues including kidney, brain, and coronary artery atherosclerotic plaques during normal aging, whereas hyperglycemia results in an accelerated rate of AGE formation, suggesting that AGEs have a pivotal role in the development of complications in DM patients [35, 36]. In addition, previous studies have revealed that AGEs accumulate in bone tissue as well [37, 38], and that receptor for AGE (RAGE) is expressed in human bone-derived cells [39], suggesting that AGEs might be associated with DM-related

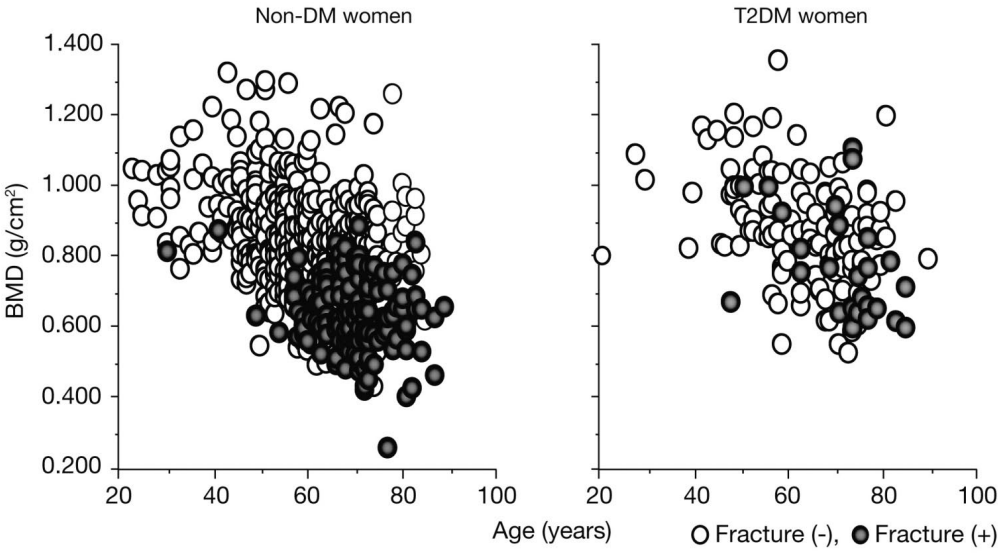


**Fig. 3** The distribution of lumbar bone mineral density (BMD) as a function of age in women with type 2 diabetes mellitus (T2DM). In the control subjects, those with vertebral fractures (VFs) (black dots) are clearly grouped in the region with higher age and lower lumbar BMD. In contrast, T2DM subjects with VFs were scattered widely and there are no associations with age or lumbar BMD, suggesting that BMD is unable to discriminate T2DM subjects with VFs from those without VFs.

bone fragility.

Several experimental studies have shown that AGEs have a negative impact on bone. AGEs inhibit the synthesis of type 1 collagen and OC as well as mature bone nodule formation in osteoblasts [40-42]. We have previously demonstrated that the combination of high glucose and AGEs additionally or synergistically inhibited the mineralization of osteoblastic cells through glucose-induced increase in expression of RAGE *in vitro* [43]. These findings suggest that AGEs accumulation in bone may cause osteoblastic dysfunction. AGEs are also known to increase osteoclast activity. Previous *in vitro* and *in vivo* experiments [44] have indicated that the number of resorption pits was increased when osteoclasts were cultured on AGEs-modified dentin slices, and that AGEs-bone particles were resorbed to a much greater extent than non-AGEs bone particles when implanted subcutaneously in rats. In addition, RAGE knockout mice displayed a decreased number of osteoclasts as well as a significant higher bone mass compared to wild-type mice [45]. Taken together, AGEs accumulation inhibits the differentiation and mineralization of osteoblasts, while it enhances the activity of osteoclasts, possibly leading to uncoupling bone turnover and resultant bone fragility.

AGEs accumulation in bone is also negatively associated with material properties [37, 38, 46]. Collagen cross-links are known to play critical roles in the determination of bone strength [47]. AGEs-type of cross-links, which are formed spontaneously by non-enzymatic glycation and oxidation reaction, are thought to be associated with brittleness of collagen fibers [48, 49], whereas physiological cross-links (enzymatic cross-links) strengthen links of collagen fibers, and lead to the enhancement of bone strength [38, 50]. Spontaneously diabetic WBN/Kob rats have been reported to display a decrease in enzymatic cross-links and an increase in AGE-type of cross links despite the lack of BMD reduction, resulting in the deterioration of bone strength [51].

Among the few AGEs characterized to date, pentosidine is one of the well-known AGEs and is chemically well defined [52-54]. Because the formation of pentosidine requires both glycation and oxidation, serum pentosidine levels are considered to be a useful marker for glycoxidation. Several studies have revealed that pentosidine content in cortical or trabecular bone from vertebra or femur was negatively associated with mechanical properties [37, 38, 46], and that pentosidine content of cortical and trabecular bone derived from patients with femoral neck fracture were higher than those of age-matched controls [55, 56]. However, the assessments of pentosidine content in bone are not easily done in clinical situations, because invasive pro-

cedures like bone biopsy are necessary for preparing specimens. A recent study has revealed that content of pentosidine in plasma shows a significant linear correlation with that in cortical bone [57], suggesting that serum pentosidine level could be used as a surrogate marker for its content in bone and could evaluate bone strength. We have previously shown that serum pentosidine levels were associated with prevalent VFs in postmenopausal T2DM women [OR=2.50 per standard deviation (SD) increase] (Table 1) [58]. This association was independent of BMD, suggesting that it might reflect bone quality rather than bone mass. In addition, an observational cohort study has shown that urine pentosidine levels were associated with increased clinical fracture incidence in those with DM (relative hazard 1.42 per 1 SD increase in log pentosidine) [59]. Urinary pentosidine level at baseline was also reported to predict future VFs in non-DM patients under bisphosphonate treatment [60]. Therefore, serum and urine pentosidine levels might be useful markers for assessing fracture risk in T2DM patients as well as non-DM counterparts.

**Table 1** Odds ratio of surrogate markers for the presence of prevalent VFs.

| | Presence of vertebral fractures | |
|---|---|---|
| | OR (95% CI) | *p* |
| Pentosidine (male) | 0.79 (0.41-1.52) | 0.47 |
| Pentosidine (female) | 2.50 (1.09-5.73) | 0.03 |
| esRAGE (male) | 0.46 (0.25-0.84) | 0.012 |
| esRAGE (female) | 0.32 (0.16-0.67) | 0.002 |
| IGF-I (female) | 0.44 (0.23-0.81) | 0.009 |

Multivariate logistic regression analysis was performed with the presence of VFs as a dependent variable and each of serum levels of biochemical markers adjusted for age, body statue, diabetes status, and renal function as independent variables. Unit of change: per SD increase. esRAGE, endogenous secretary receptor for advanced glycation end products; IGF-I, insulin-like growth factor-I; OR, odds ratio; CI, confidence interval.

***Endogenous secretory RAGE (esRAGE)***

RAGE belongs to immunoglobulin superfamily of cell-surface receptors and is capable of interacting with multiple ligands, including AGEs [61]. When transgenic mice overexpressing human RAGE in vascular cells were crossbred with a transgenic line that develops insulin-dependent DM shortly after birth, more progressive histological change of DM nephropathy was observed compared to controls [62], confirming that RAGE expression stimulates the development of DM complications. Endogenous secretory RAGE (esRAGE), a splice variant of one of the naturally occurring secretory forms of RAGE, is known to carry all of the extracellular domains but lacks the transmembrane and cytoplasmic domains of the receptor [63]. Secreted esRAGE in the extracellular space is thought to act as a decoy receptor that binds and neutralizes AGEs and results in reducing the activity of intercellular signal pathways *via* RAGE [63]. Indeed, administration of a genetically engineered murine soluble RAGE suppressed the development of diabetic atherosclerosis in a dose-dependent manner in streptozotocin-induced apoE-null DM mice [64]. These experimental findings suggest that enhanced RAGE activity may also be clinically linked to reduced bone strength in DM patients. Given the neutralizing nature of esRAGE, it is possible that the ratio of serum esRAGE to AGE levels could be linked to clinical bone problems, such as fractures, more prominently than either parameter alone.

We found that the esRAGE/pentosidine ratio in T2DM patients with VFs was significantly lower than in those without VFs. Multivariate logistic regression analysis adjusted for age, height, weight, $HbA_{1c}$, serum creatinine, DM duration, therapeutic agents, DM complications, osteoporotic risk factors, and lumbar BMD identified the serum esRAGE level and esRAGE/pentosidine ratio as factors associated with the presence of VFs, independent of BMD in men (OR=0.46 and OR=0.34 per SD increases, respectively) and in women (OR=0.32 and OR=0.14 per SD increases, respectively) (Table 1) [65]. These results show that serum esRAGE level and esRAGE/pentosidine ratio are more useful than BMD for assessing the risk of VFs in T2DM patients.

***Insulin-like growth factor-I (IGF-I)***

Bone remodeling is regulated by systemic hormones and locally produced factors, both acting in concert to maintain bone mass [66-68]. Insulin-like growth factors (IGFs) are synthesized in osteoblasts and are among the most important regulators of bone cell function due to their anabolic effects on the skeleton [69]. The key role of the IGF system in the local regulation of bone formation is demonstrated by the finding that approximately 50% of basal bone cell proliferation could be blocked by inhibiting the actions of IGFs endogenously produced by bone cells in serum-free cultures [70]. In osteoblast-specific knockout mice of IGF-I receptor, significant reduction in trabecular bone mass

and deficient mineralization has been observed [71]. On the other hand, circulating IGF-I, mainly produced in the liver *via* regulation by growth hormone and diet, acts in an endocrine manner, which also activates bone remodeling and exerts anabolic effects on bone tissues [72-74]. Liver-specific IGF-I gene-null mice reveals a marked reduction in bone volume, periosteal circumference, and medial lateral width, suggesting that circulating levels of IGF-I also directly regulate bone growth and density [75]. Indeed, our clinical studies showed that serum IGF-I levels were positively associated with BMD and inversely with the risk of VFs in postmenopausal non-DM women [76, 77]. These findings suggest that serum IGF-I levels could be clinically useful for assessing bone mass and the risk of VFs in the non-DM population.

It is also possible that IGFs are linked to the pathogenesis of DM-related complications [78]. Impaired production of IGFs could cause bone complication in DM by diminishing bone cell function [69]. An *in vivo* study has demonstrated that IGF-I levels in serum and cortical bone were significantly reduced in spontaneously diabetic Goto-Kakizaki rats, which displayed a significant decrease in BMD at long bone metaphyses and vertebrae [79]. On the other hand, several *in vitro* studies have shown that the stimulatory actions of IGF-I on osteoblasts were blunted by high glucose concentrations or AGEs. High glucose concentrations significantly impaired the proliferative and functional responses of osteoblastic MG-63 cells to IGF-I [80]. AGEs also significantly decreased IGF-I secretion in osteoblastic MC3T3-E1 cells [81]. Thus, high glucose concentrations or AGEs may cause the resistance of osteoblasts to IGF-I actions in local environment.

In T2DM patients, however, the relationship between serum IGF-I levels and bone metabolism has little been documented. We indicated that serum IGF-I levels were significantly and inversely associated with the presence of VFs in postmenopausal T2DM women (OR=0.44 per SD increase) in a fashion independent of age, body statue, DM status, renal function, insulin secretion, or lumbar BMD (Table 1) [82]. We also found that serum IGF-I level was inversely associated with the number of prevalent VFs independent of lumbar BMD in postmenopausal T2DM women, suggesting that serum IGF-I could be clinically useful for assessing the severity of multiple VFs in the population [83]. Accordingly, circulating IGF-I may have a protective effect on VFs, and this effect might be related to bone quality but not to bone mass in postmenopausal T2DM women.

## V. The effects of antidiabetic drugs on bone metabolism in T2DM

It is well documented that some antidiabetic drugs affect bone metabolism in T2DM. Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone are peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, and are widely used for treatment of T2DM patients. PPAR-γ is also expressed in bone marrow cells, and it acts as a molecular switch that regulates the fate of pluripotent mesenchymal stem cells, which are able to differentiate into adipocytes or osteoblasts. Previous *in vitro* studies have shown that TZDs stimulate the differentiation into adipocytes in preference over osteoblasts [84, 85]. Haploinsufficiency of the PPAR-γ gene in mice induces a high bone density phenotype characterized by increased bone formation [86, 87], whereas treatment of rodents with PPAR-γ agonists induces bone loss characterized by deficient osteoblast function [88-89].

Accumulating evidence also indicates that TZDs negatively impact on bone metabolism in humans. Grey *et al*. have shown that 14-week rosiglitazone treatment decreased bone formation markers, OC, procollagen type I N-terminal propeptide, and femoral neck BMD in healthy postmenopausal women [90]. Schwartz *et al*. have reported that long-term use of TZDs caused reduction of whole body BMD and lumbar BMD in older T2DM women by a 4-year observational cohort study [91]. We also found that serum OC level, femoral neck BMD, and radial BMD were significantly decreased at 6 months in T2DM patients treated with pioglitazone [92]. Recently, a meta-analysis has revealed that lumbar and femoral neck BMD was significantly reduced, and that risk of fractures was significantly increased in women exposed to TZDs (OR=2.23), but not in men [93]. Moreover, a previous clinical trial showed that risk of fractures in the bones of the extremities (foot, hand, and proximal humerus) was significantly increased, while there was no increased risk identified for clinical vertebral or hip fractures [94,95], suggesting a negative impact on cortical bone. In contrast, little is known whether morphometric fracture rate in vertebra, which contains a relatively higher proportion of trabecular bone, is increased or not. We found that treatment with pioglitazone was significantly and posi-

tively associated with the presence of prevalent VFs in postmenopausal women (OR=3.38), but not in men, when VFs were evaluated by X-ray films [96]. This finding suggests that postmenopausal women treated with pioglitazone have high risks of VFs as well as the bones of the extremities.

## VI. Fracture risk assessment of T2DM patients in clinical practice

In face of the ineffectiveness of BMD in assessing fracture risks in T2DM, the major clinical problems are how to assess the risks and when to start therapies for preventing fractures in daily practice for patients. Although the markers related to AGEs as well as IGF-I are potential candidates for fracture risk assessments, it is unclear whether or not they could predict the occurrence of new fractures of T2DM patients in a prospective fashion.

On the other hand, the presence of prevalent VFs could be used for the assessment of bone quality in individual patients, because a large study on the incidence of VFs in postmenopausal osteoporosis showed that patients with previous VFs were more likely to suffer from new VFs [97, 98] and hip fractures [97] independent of BMD than those without VFs during several-year study periods. Patient histories of non-VFs that previously happened are also established risk factors for additional fractures [99]. We found that 38% of T2DM men and 31% of T2DM women had prevalent VFs by X-ray films, and that 16% each of T2DM men and women had histories of previous non-VFs [32]. Thus, if T2DM patients undergo spine X-ray examination or are questioned about their fracture histories, it is likely that about half of them are picked up as those who have bone fragility and need osteoporosis treatment for fracture prevention. These procedures are simple and are recommended for all of physicians engaged in T2DM treatments.

Recently, the fracture risk assessment (FRAX) algorithm has been developed by the WHO, which could assess the fracture risk of an individual even if BMD is not measured [99, 100]. Since this algorithm integrates the influence of several well validated risk factors for fracture that are independent of BMD, it might be useful for the case-finding strategy picking up T2DM patients at high risk for fracture. Only recently, Schwartz *et al*. have indicated that femoral neck BMD T score and FRAX score were associated with hip and nonspine fracture risk among older adults with T2DM; however, in these patients compared with participants without DM, the fracture risk was higher for a given T score and age or for a given FRAX score [101]. These findings suggest that femoral neck BMD and FRAX score may be partially effective for assessing hip and nonspine fracture risk in T2DM patients, although they are not as sensitive as in non-DM counterparts.

## VII. Conclusion

The fact that BMD is not useful for assessing fracture risks in T2DM seems problematic, because T2DM populations are expanding in every country. T2DM patients may drop out from fracture prevention if doctors diagnose osteoporosis based on BMD values alone. Practitioners should be aware of the importance of evaluating prior VFs and fracture histories by spine X-ray and interview, respectively. These procedures would broaden the spectrum of osteoporosis treatments into T2DM population. Simultaneously, further studies are needed to clarify whether or not surrogate biochemical markers such as pentosidine, esRAGE, and IGF-I, as well as the WHO FRAX algorithm, would be useful for predicting the occurrence of new fractures of T2DM patients prospectively, with sensitivity and specificity comparative to those of BMD in non-DM osteoporosis.

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