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REVIEW ARTICLE

Bone Metabolism and Fracture Risk in Diabetes Mellitus

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Abstract

Individuals with Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are at increased risk for fragility fractures. Bone mineral density (BMD) is decreased in T1DM but often normal or even elevated in T2DM when compared with age-matched non-DM populations. However, bone turnover is decreased in both T1DM and T2DM. The pathophysiologic mechanisms leading to bone fragility is multifactorial, and potentially leads to reduced bone formation, altered bone microstructure and decreased bone strength. Interestingly, different antidiabetic treatments may influence fracture risk due to effects on glycemic control, triggering of hypoglycemic events or osteoblastogenesis.

Key words: bone metabolism, diabetes mellitus, bone remodeling, biomarkers

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic non-communicable disease with increasing global prevalence. By 2015, there were over 415 million adults living with DM, and this number is expected to increase to 642 million by 2040.[1] Apart from the major DM-related complications such as cardiovascular diseases, osteoporotic fracture is increasingly recognized as an important complication of type 1 DM (T1DM) and type 2 DM (T2DM) in both men and women.[2] Worldwide, over 9 million osteoporotic fractures occur annually, and the effect of reduced bone mineral density (BMD), including osteoporosis, is predicted to result in over 5 million disability adjusted life years (DALY) and 188,000 deaths each year. The incidence of hip fractures in individuals with T1DM was 383 per 100,000, six-fold higher than the overall incidence of hip fracture in the age-matched, non-diabetic population.[3] The odds ratio of vertebral fracture in T2DM was 1,86 and 4,73 in women and men,[4] respectively, with a relative risk of 1,83 (95% CI: 1,25-1,53).[5] These studies were largely done using the cross-sectional design and showed only associations rather than causality of DM and the incidence of fracture. However, taken together, these data indeed show the increased fracture risk in individuals with DM. The presence of microvascular complications in DM have also been associated with reduction of BMD in T1DM[5] and with bone micro-architectural abnormalities in T2DM.[6-9]

Increasing evidence shows the interaction between plasma glucose levels and bone metabolism, revealing mechanisms through which bone fragility may develop in DM. Whether this interaction translates into increased risk for fragility fractures and decreased BMD in all DM populations remains unclear. Studies reported conflicting findings of changes in BMD. Whereas BMD is decreased in T1DM,[10-15] it is either increased or unchanged in T2DM.[16-21] Intriguingly, a meta-analysis found that both DM types are associated with increased risk of hip fracture.[2] In this review, we discuss bone metabolism and remodeling, the pathophysiologic mechanisms by which bone fragility may occur in DM, and the effects of glucose-lowering drugs on bone health.

Bone Metabolism and Remodeling

The structural components of bone consist of a largely mineralized extracellular matrix, collagen, and cells. Bone is a living organ that is continuously being remodeled, in a process that involves a balance in the tearing down of bone structure (bone resorption) and its rebuilding (bone formation). This resorption and formation allows for the repair of micro-fractures and the modification of structure in response to stress.[22] Bone resorption is initiated by osteoclasts, which attach to bone surface and secrete acid and hydrolytic enzymes that resorb bone, releasing minerals and collagen fragments.[23] After osteoclastic

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resorption is completed, a reversal phase takes place in which mononuclear cells prepare the bone surface for new osteoblasts to begin bone formation by laying down a layer of glycoprotein-rich material to which the osteoblasts can adhere.[24] Bone formation is subsequently initiated by osteoblasts, which produced type I collagen and other proteins, such as osteocalcin, which then form osteoid, a substrate for which mineralization can occur. The newly formed osteoid then begins to accumulate matrix molecules and mineralize.[22] In healthy adults, bone resorption and formation is a tightly balanced process. Both high or low rates of remodeling with an imbalanced bone resorption and formation can be associated with decreased or increased bone mass.

The synthesis of type I collagen during the bone formation phase involves the intertwining of one alpha-2 and two alpha-1 polypeptide chains to form a helical structure known as procollagen, followed by cleavage of their amino-terminal and carboxy-terminal peptides to form tropocollagen. The N-telopeptide (NTX) is the pyridinoline crosslink in the N-telopeptide region that joins alpha-1 chains to alpha-2 chains,[25] whereas the C-telopeptide (CTX) is a fragment of the alpha-1 peptide with an isomerized bond between the aspartate and the glycine from the carboxytelopeptide region.[26] NTX and CTX, together with the bone-specific alkaline phosphatase and amino terminal propeptide of type 1 procollagen (P1NP) are the most clinically useful markers of bone turnover.[27,28] Osteoblasts produce osteocalcin, which is also used as a marker of bone formation.[29] Furthermore, bone resorption results in the release of bone mineral and the collagen-rich osteoid, whereas osteoid formation involves the production of the byproducts of collagen and other proteins. These substances may be released in the circulation, and can be measured in serum and urine to provide information on the rate of bone resorption and formation, and are collectively termed in the clinic as "bone turnover markers" (BTM)[23] (Table 1).

Fracture Risk and Diabetes Mellitus

Fracture risk is significantly higher in both T1DM and T2DM populations when compared to the general population.[2] The incidence of hip fracture in individuals with T1DM were reported to be six times higher than in the population (mean age 65 years) and 2,5-fold higher than in the T2DM population.[3]

T1DM

A meta-analysis of 5 studies reported that T1DM is associated with an overall relative risk (RR) of 8,9 (95% CI 7,1–11,2) for hip fractures when compared with an age-matched nondiabetic population.[2] Most studies in young and older, male and female individuals with T1DM reported a decrease in BMD at the radius and femur.[30-38] This decrease ranges from 22 to 37%.[5] Individuals with T1DM showed decreased trabecular and/or cortical volumetric BMD at the distal radius or tibia compared with non-diabetic controls,[30,39-43] and some studies reported the associations of these alterations with poor glycemic control.[40, 41]

T2DM

The risk of hip fracture is particularly increased in individuals with T2DM.[21,44,45] The risk is even higher in those treated with insulin[3,46] and poor glycemic control,[47] as reflected by high HbA_{1c} levels, which may indicate the more advanced disease state. Studies have also reported increased fracture risk in individuals with more hypoglycemic episodes.[48] A meta-analysis of four cohorts showed that the RR of hip fractures reached 2,7 (95% CI, 1,7-4,4).[2] The risks for other fractures appear to also increase in T2DM compared to healthy individuals, such as fractures of the wrist [49] and foot,[21,50] as well as of the vertebrae.[4]

Although earlier studies reported lower or unchanged BMD, recent large studies found that in T2DM, in contrast with T1DM, BMD is increased when compared to controls.[20,49, 51-60] Furthermore, this increase in BMD remained after adjustment for body weight and composition,[55, 60] and ranges between 5 to 10% above age-matched, non-diabetic controls.[50] Bone fragility depends not only on the reduction in bone mineral mass, as reflected by BMD, but also from changes to the bone microstructure and the components of the bone material. This is likely to account for the increased risk of fracture despite the increased BMD seen in individuals with T2DM. Indeed, MRI studies revealed greater cortical porosity in individuals with T2DM compared with non-diabetic controls,[61,62] a finding repeated by a study using quantitative CT (Xtreme-CT), especially in those with fractures and/or microvascular complications.[6-9] Recent diagnostic advances enable the measurement of *in vivo* bone material strength (BMS) by the minimally invasive, bone microindentation testing.[7,63] Postmenopausal women with T2DM demonstrated lower BMS and greater radial cortical porosity. Poor BMS was correlated with poor long-term glycemic control over the past 10 years.[7] A study in a similar population with fragility fractures suggests that severe deficits in cortical bone quality, as depicted by an increase in porosity, is a likely cause of fragility fractures.[8] Regardless of the difference in BMD alterations between T1DM and T2DM, DM alone has been shown to be predictive of increased post-fracture mortality risk during hospitalization[64] and up to one year after discharge[65,66] in individuals with hip fracture.

Mechanisms of DM-induced Bone Fragility

The mechanisms of DM-induced bone fragility in T1DM and T2DM are complex and only partially overlap.[67] Individuals with T1DM are mainly experiencing β-cell failure and low levels of IGF1which disrupt the function of osteoblasts during growth. As a result, low peak bone

mass can occur at a young age.[68] In contrast, individuals with T2DM developed bone fragility at a later stage of the disease, and consequently, at a later age due to the lack of insulin, glucose toxicity, advanced glycation end products (AGEs), cytokines and adipokines that are affecting osteocyte, bone turnover and collagen.[69]

Table 1. Bone turnover markers

Markers	Full name	Origin	Comment	Source of Variability		
				Renal	Liver	Circadian rhythm
Resorption						
u-CTX	Urinary carboxy-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen, generated by cathepsin K	Requires adjustment to levels of urinary creatinine Specificity: collagen type I, with highest contribution probably from bone Changes in levels of u-CTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of u-CTX[110]			X
s-CTX	Serum carboxy-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen, generated by cathepsin K	Source of variability: food consumed (so must be collected after an overnight fast) Changes in levels of s-CTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of s-CTX[110]	X	X	X
u-NTX	Urinary amino-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen type I	Requires adjustment to levels of urinary creatinine Specificity: collagen type I, with highest contribution probably from bone Changes in levels of u-NTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of u-NTX[110]			X
s-NTX	Serum amino-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen type I, generated by cathepsin K	Specificity: collagen type I, with highest contribution probably from bone Changes in levels of u-NTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of s-NTX[110]	X		X
s-ICTP or CTX-MMP	Carboxy-terminal crosslinking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen generated by matrix metalloproteinases	Specificity: collagen type I, with highest contribution probably from bone Marker is not responsive to usual treatments for osteoporosis Lower s-PICP to s-ICTP ratio were reported in T2DM[12] Troglitazone use in T2DM individuals is associated with a decrease in s-ICTP[111]	X	X	X
u-DPD	Urinary deoxypyridinoline	Proteolytic hydrolysis of collagen, found in bone	Requires adjustment to levels of urinary creatinine Specificity: highest contribution from bone Sources of variability: UV radiation Changes in levels of u-DPD were reported in both T1DM and T2DM[112] Troglitazone use in T2DM individuals is associated with a decrease in u-DPD[111]			X
u-PYD	Urinary pyridinoline	Found in bone, cartilage, tendon, blood vessels	Requires adjustment to urinary creatinine Specificity: highest contribution from bone and cartilage Sources of variability: active arthritis and UV radiation		X	X
s-TRAP	Serum tartrate-resistant acid phosphatase	Includes two isoforms: type 5a (platelets, erythrocytes and other sources) and type 5b (osteoclasts)	Sources of variability: influenced by haemolysis and blood clotting Changes in levels of s-OC were reported in both T1DM and T2DM[112] Levels of s-TRAP is affected by long-term use of insulin in T1DM[36]			X
Formation						
s-OC	Serum osteocalcin	Hydroxyapatite-binding protein exclusively synthesised by osteoblasts and odontoblasts	Specificity: specific marker of osteoblast function Rapid degradation in serum may lead to heterogeneity of OC fragments measured Sources of variability: large inter-laboratory variation Changes in levels of s-OC were reported in both T1DM and T2DM	X		X
u-OC	Urinary osteocalcin	Hydroxyapatite-binding protein exclusively synthesised by osteoblasts and odontoblasts	Adjusted to levels of urinary creatinine (/Cr) Specificity: specific marker of osteoblast function Changes in levels of u-OC were reported in non-insulin dependent DM[112]	X		X
s-ALP	Serum alkaline phosphatase (total)	Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of various tissues: liver, bone, intestine, spleen, kidney and placenta	Specificity: non-specific for bone (about 50% is liver isoform in healthy individuals) Changes in levels of s-ALP were reported in both T1DM and T2DM Troglitazone use in T2DM individuals is associated with a decrease in s-ALP[111]			X
s-BALP	Serum bone-specific alkaline phosphatase	Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of osteoblasts	Specificity: specific for bone, but with some cross-reactivity with liver isoform (up to 20%) Changes in levels of s-BALP were reported in T2DM[112] Troglitazone use in T2DM individuals is associated with a decrease in s-BALP[111]			X
s-PICP	Procollagen type I C propeptide	Precursor molecules of collagen type I synthesised by osteoblasts	Specificity: mostly derived from bone collagen type I (around 90%). Short serum half-life. Regulated by hormones (thyroid, IGF-1) Lower s-PICP to s-ICTP ratio were reported in T2DM[12]			X
s-PINP	Procollagen type I N propeptide	Precursor molecules of collagen type I synthesised by osteoblasts	Specificity: mostly derived from bone collagen type I A ssay: may recognise trimer alone (intact) or trimer and monomer (total PINP) Changes in levels of s-P1NP were reported in both T1DM and T2DM			X

Adapted from Vasikaran et al.[109]

Table 2. Studies reporting on bone turnover in individuals with DM

Study author	Participants	BTM measured	Comments
Reyes-Garcia et al.; 2013[110]	78 T2D (43 men, 35 women), 55 controls	OC (ns)- RIA) (DiaSorin, Stillwater, Minnesota USA; normal range 1.8–6.6 ng/ml, CTX ↓ EIA (Elecsys ß CrossLaps, Roche Diagnostics SL, Barcelona, Spain; normal range 0.01–6 ng/ml)	Vertebral fractures in 27.7% of T2D and 21.7% of controls Cross-sectional
Yamamoto et al.; 2012[111]	255 T2D (postmenopausal women and men), 240 controls	OC↓, CTX↓ (electrochemiluminescence immunoassay on an automated analyzer; Roche Diagnostics GmbH, Mannheim, Germany), PTH↓	Excluded if serum creatinine was higher than normal range
Manavalan et al.; 2012[112]	18 T2D PM, 27 controls PM	OC↓, ELISA (IDS), CTX ↓ ELISA	At least 1 year use of antiglycemic medication eGFR b 60 ml/min excluded
Bhattoa et al.; 2013[113]	68 male T2D, 68 male controls	OC↓, CTX↓ electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).	Renal disease excluded Case-control
Ardawi et al.; 2013[114]	482 T2D PM women, 482 controls PM	LIASON autoanalyzer (DiaSorin Inc., Stillwater, MN, USA)	VF in 24.5% of T2D and none in controls
Hamilton et al.; 2012[115]	26 T1D, 27 T2D	CTX ↑, OC (ns), PTH (ns)	
Akin et al.; 2003[116]	57 T2D PM, 20 controls PM	OC↓, NTX↓	BMI significantly lower in controls, fasting, chronic disease excluded
Reyes-Garcia et al.; 2013[110]	78 T2D, 55 controls	CTX↓, PTH↓, enzyme immunoassay (EIA) and ELISA	Vertebral fractures in 27.7% of T2D and 21.7% of controls
Jiajue et al.; 2014[117]	236 T2D PM, 1055 controls PM	CTX↓, P1NP↓	Renal disease excluded
Farr et al.; 2014[7]	30 T2D PM, 30 controls PM	CTX↓, P1NP↓	Stage 4 and 5 chronic kidney diseases excluded MI significantly lower in controls. Performs microindentation
Manavalan et al.; 2012[112]	18 T2D PM, 27 controls PM	Circulating OC(+) cells ↓	At least 1 year use of antiglycemic medication eGFR b 60 ml/min excluded
Bhattoa et al.; 2013[118]	68 male T2D, 68 male controls	OC↓, CTX↓	Renal disease excluded
Gaudio et al.; 2012[119]	40 T2D PM, 40 controls PM	CTX↓	Renal bone disease excluded
Ardawi et al.; 2013[114]	482 T2D PM, 482 controls PM	IGF-1↓, sclerostin ↑, OC↓, CTX↓, P1NP↓, NTX↓	VF in 24.5% of T2D and none in controls
Hernandez et al.; 2013[120]	2431 subjects of these 45 T2D	CTX and P1NP↓ in T2DM individuals who use statins	PM females and older men , Coexisting medical disorder that might affect bone metabolism was excluded.
Sarkar and Choudhury; 2013[121]	108 T2D, 50 controls	OC↓	T2D was newly diagnosed.
Movahed et. al.; 2012[122]	382 PM of these 102 T2D	OC↓, CTX↓	The diabetes group is a subgroup of the total population.
Sosa et al.; 1996[123]	47 female NIDDM, 252 female controls	OC (ns), ALP (ns)	No renal disorders
Chen et al.; 2013[124]	55 T2D, 27 controls	Plasma ALP↑, OC↓	No history of metabolic bone disease

Alkaline phosphatase (ALP), C-terminal cross-link of collagen (CTX), estimated glomerular filtration rate (eGFR), insulin-like growth factor-1 (IGF-1), myocardial infarction (MI), Non-insulin dependent diabetes mellitus (NIDDM), not significant (ns), tosteocalcin (OC), procollagen type 1 N-terminal propeptide (P1NP), postmenopausal (PM), parathyroid hormone (PTH), type 1 diabetes (T1D), type 2 diabetes (T2D), vertebral fracture (VF),

Low Bone Turnover

Most published studies in individuals with DM have reported low bone turnover (Table 2). Osteocalcin level, a marker of bone formation, is decreased in both T1DM and T2DM,[70-72] and is negatively correlated with HBA_{1c} level.[70] The negative correlation with HBA_{1c} was also reported for CTX, a marker of bone resorption.[70] When looking separately at T1DM and T2DM, osteocalcin levels have been reported to be decreased in T1DM and only borderline significantly decreased in T2DM.[73] Similarly, P1NP and NTX also tended to be lower in individuals with DM.[5] Consistently, histological study of DM found decreased number of osteoblasts and osteoid.[74] In general, the processes involved in the decreased bone formation in T2DM include a decrease in bone quality, alterations of the mesenchymal cell differentiation and bone microcirculation, as well as changes in osteoblasts and osteoclasts (Figure 1).

Adipokines

Adiponectin, a protein hormone secreted by adipose tissue, was found to be decreased in T2DM.[75] Adiponectin was reported to have an anabolic effect on osteoblasts and inhibits osteoclastic activity *in vitro*.[76] However, clinical studies reported conflicting findings on whether there were negative correlations between adiponectin levels and BMD in individuals with T2DM. Leptin, another adipokine which is secreted by white adipose, bone marrow adipocytes and osteoblastic cells, was found to be lower in individuals with DM compared with controls. A negative correlation between leptin and NTX was found in individuals with T2DM, whereas a positive correlation was found with leptin and Z-scores at the distal radius, but not at the femoral neck or lumbar spine.[77] Interestingly, in vitro and animal studies showed that high glucose level increases the expression of adipogenic markers such as the peroxisome proliferator-activated receptor (PPAR)-γ, adipocyte fatty acid binding protein (aP2), resistin and adipsin, whereas it suppresses cell growth, mineralization, and expression of osteogenic markers including Runx2, collagen I, osteocalcin, osteonectin.[78,79] Further studies are needed to precisely explain the role of adiponectins in affecting bone fragility.

Advanced Glycation End Products (AGEs)

Individuals with DM have increased levels of AGEs due to hyperglycemia and increased levels of oxidative stress.[80] The main mechanisms by which AGEs contribute to damaging the bone tissue are: 1) by forming cross-links with target protein, permanently altering cellular structure, and 2) by interacting with specific receptors to increase oxidative stress and inflammation.[81] The receptor

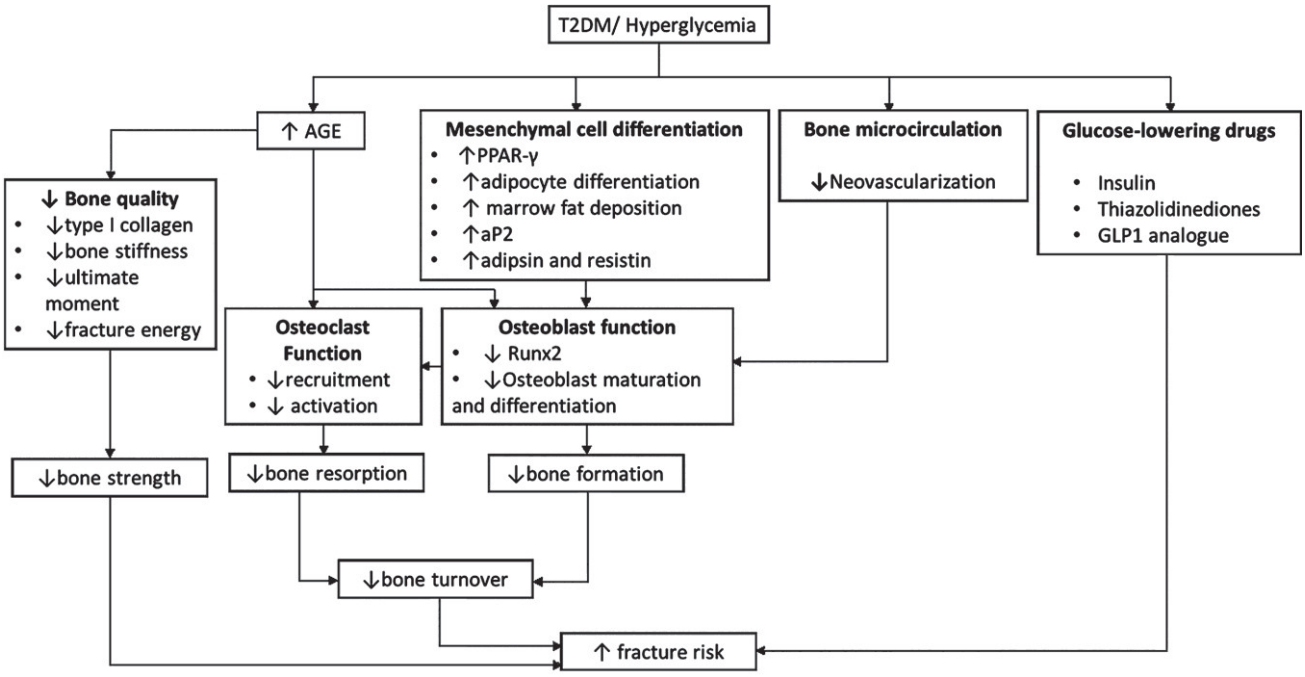

Figure 1. Process involved in the decrease of bone turnover and increase of fracture risk.

for AGEs (RAGE) initiates the intracellular signaling through the binding of AGEs.[82] The soluble isoform of RAGE (known as soluble RAGE, sRAGE) is thought to be produced by proteolytic cleavage of disintegrin and metalloproteinase domain-containing proteins (ADAMs). Activation of the RAGE signaling pathway leads to a positive feedback loop by enhancing the NF-kB expression. Subsequently, important inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and C-reactive protein (CRP) are upregulated through both AGE- and NF-kB-mediated pathways.[82] Increased AGE concentration is negatively associated with bone density and mineralization,[83] and the cross-linking of AGE with collagen alters the mechanical properties of bone, disrupting its remodeling, increasing its stiffness and fragility.[84-86] Pentosidine, a well-known AGE, was also shown to disrupt osteoblast differentiation.[87] Studies found that poor glycemic control was associated with increased risk of fractures in individuals with DM, and suggest that HbA_{1c} level of <8% could reduce fracture risk in individuals with DM.

Insulin and IGF1

Insulin exerts an anabolic effect on bones by promoting osteoblast proliferation and differentiation.[88] Animal studies have shown that diabetic rodents have impaired bone formation following bone injury whereas insulin injection normalized it.[89] Insulin deficiency, as in T1DM, is characterized by low levels or activity of insulin-like growth factor 1 (IGF1). The stimulating activity of IGF1 on osteoblasts is inhibited by high concentration of AGEs or glucose.[90,91] In contrast with T1DM, T2DM is a disease that mainly shows insulin resistance. It remains unclear how in T2DM insulin resistance and insulin deficiency at its later stage may affect bone metabolism and fragility.

Pro-inflammatory cytokines

Pro-inflammatory cytokines have been implicated in both T1DM and T2DM and in the development of complications of both diseases. Elevated pro-inflammatory cytokine levels, such as TNF and IL-6, can activate osteoclastogenesis and inhibit osteoblast differentiation.[92,93] Indirectly, the reactive oxygen species generated due to the exposure of tissue to IL-1, IL-6 and TNF can affect the differentiation and survival of osteoclasts, osteoblasts, and osteocytes.

Glucose-lowering Drugs and Bone Metabolism

Antidiabetic treatment is aimed at achieving good glucose control to reduce the risk of complications. Data showed that 1% reduction in HBA_{1c} levels led to 37% reduction in microvascular complication endpoints.[94] As HBA_{1c}, microvascular complications and bone fragility have been shown to be interrelated, it is reasonable to consider that optimal glucose control may reduce fracture risk. Individuals with poor glycemic control have increased risk for fractures.[47,95,96] In individuals with T2DM, HBA_{1c} levels ≥7,5% were reported to have 62% higher risk for fractures compared to those with HBA_{1c} levels <7,5%. The ACCORD trial reported that there was no substantial benefit for fracture prevention or BMD changes in lowering HBA_{1c} below 7,5%.

Insulin was shown to increase the risk of falls in insulin-treated individuals if their HBA_{1c} levels were ≤6%. It appeared that more aggressive glycemic control in elderly individuals with long term disease might increase hypoglycemic events and thus the risk for falls and fractures.[97] Metformin, the first line drug for DM, was found from most clinical studies to have positive or

neutral effect on BMD and fracture risk in large cohorts.[46,98,99] Sulfonylureas show neutral effect on BTM levels, and studies on its clinical effect has not been established.[46] However, sulfonylureas should be avoided in individuals at risk for bone fragility due to its risk for inducing hypoglycemic events.[67,100] Thiazolidinediones, which includes rosiglitazone and pioglitazone, activate peroxisome proliferator-activated receptors (PPARs), particularly PPAR-γ. *In vitro* and *in vivo* studies show increased adipogenesis and impaired osteoblastogenesis. Meta-analyses confirmed an increased risk for fractures (OR 2.23, 95% CI 1.65–3.01[101] and OR=1.94; 95%CI: 1.60-2.35[102]) in women treated with pioglitazone or rosiglitazone, but not in men. The evidence on the incretin-based treatments, GLP1 analogues and DPP4 inhibitors, are less conclusive.[67] A meta-analysis found that two different GLP1 analogues, liraglutide and exenatide, had protective and negative effects, respectively, on fracture risk. However, these studies were not designed for bone outcomes and differ in their design and power.[103] Studies on DPP4 inhibitors also did not find consistent effects on fracture outcomes.[104,105] Sodium/glucose co-transporter 2 (SGLT2) inhibitors are new generation antidiabetics which exert effects by inhibiting glucose reabsorption in the proximal tubule of the kidney.[106] Data has also not been consistent in this group of drugs. While dapagliflozin and empagliflozin seem to have a neutral effect on bone turnover and BMD parameters, canagliflozin was reported to cause bone loss at the hips[107,108] and increase the risk for hip fractures.

CONCLUSIONS

Fracture risk is known to be increased in both T1DM and T2DM. Levels of BTM were also lower in individuals with DM compared to non-DM controls. Despite increasing data on the association between BMD, BTM and fracture in individuals with DM, there are still challenges in identifying those with high fracture risk. Oxidative stress, inflammation and the production of AGEs increase the risk of complications. Additionally, disturbances in bone collagen metabolism and bone mineralization also reduce bone strength, while altered fat metabolism also affects bone health. A population of individuals are treated with insulin, but its use has been associated with increased fracture risk.[46] It remains unclear whether insulin use is merely a marker for the severity or duration of disease, or induces more hypoglycemic events that lead to falls. Furthermore, it is unknown whether in DM, changes in bone metabolism occurs earlier in the disease course. It is therefore important to consider the treatment approach and education of fall prevention in these individuals who are already at increased risk for fractures. Medications with favorable effect on bone metabolism such as metformin or incretin-based treatments may be the preferred treatment while thiazolidinediones should be used with careful evaluation and patient education. Evaluation by use of BTM may be of benefit, but needs further studies in particular populations of individuals with DM such as premenopausal women or the Indonesian population.

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