Bone Metabolism and Fracture Risk in Diabetes Mellitus

Melisa Puspitasari,1 Dyah Purnamasari,2 Bambang Setyohadi,3 Harry Isbagio3

1Department of Internal Medicine, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
2Division of Metabolism and Endocrinology, Department of Internal Medicine, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
3Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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 are 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 T1DM6 and with bone micro-architectural abnormalities in T2DM.5-9

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,10-17 it is either increased or unchanged in T2DM.18-21 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

Corresponding author: Dyah Purnamasari, MD
Staff, Division of Metabolism and Endocrinology
Department of Internal Medicine, Faculty of Medicine
University of Indonesia, Cipto Mangunkusumo Hospital
Jl. Salemba 6 Jakarta 10430, Indonesia
Tel. No.: 021-3907703
Fax No: 021-39286589
E-mail address: dyah_p_transeo@yahoo.com
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.24 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 I procollagen (PINP) 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%.3 Individuals with T1DM showed decreased trabecular and/or cortical volumetric BMD at the distal radius or tibia compared with non-diabetic controls,39,39–43 and some studies reported the associations of these alterations with poor glycemic control.44, 41

T2DM

The risk of hip fracture is particularly increased in individuals with T2DM,25,44,45. The risk is even higher in those treated with insulin56 and poor glycemic control,57 as reflected by high HbA1c 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,50,50 as well as 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.63 Recent diagnostic advances enable the measurement of in vivo bone material strength (BMS) by the minimally invasive, bone microindentation testing.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 hospitalization48 and up to one year after discharge45,66 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 IGF1 which disrupt the function of osteoblasts during growth. As a result, low peak bone
mass can occur at a young age.\textsuperscript{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.\textsuperscript{69}

Table 1. Bone turnover markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Full name</th>
<th>Origin</th>
<th>Comment</th>
<th>Source of Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>u-CTX</td>
<td>Urinary carboxy-terminal crosslinking telopeptide of type I collagen</td>
<td>Osteoclastic hydrolysis of collagen, generated by cathepsin K</td>
<td>Requires adjustment to levels of urinary creatinine</td>
<td>X</td>
</tr>
<tr>
<td>s-CTX</td>
<td>Serum carboxy-terminal crosslinking telopeptide of type I collagen</td>
<td>Osteoclastic hydrolysis of collagen, generated by cathepsin K</td>
<td>Pioglitazone is associated with increased levels of u-CTX$^{110}$</td>
<td>X X X</td>
</tr>
<tr>
<td>u-NTX</td>
<td>Urinary amino-terminal crosslinking telopeptide of type I collagen</td>
<td>Osteoclastic hydrolysis of collagen type I</td>
<td>Pioglitazone is associated with increased levels of s-CTX$^{110}$</td>
<td>X</td>
</tr>
<tr>
<td>s-NTX</td>
<td>Serum amino-terminal crosslinking telopeptide of type I collagen</td>
<td>Osteoclastic hydrolysis of collagen type I, generated by cathepsin K</td>
<td>Pioglitazone is associated with increased levels of s-NTX$^{110}$</td>
<td>X X</td>
</tr>
<tr>
<td>s-ICTP or CTX-MMP</td>
<td>Carboxy-terminal crosslinking telopeptide of type I collagen</td>
<td>Osteoclastic hydrolysis of collagen generated by matrix metalloproteinases</td>
<td>Pioglitazone is associated with increased levels of s-ICTP or CTX-MMP$^{110}$</td>
<td>X X X</td>
</tr>
<tr>
<td>u-DPD</td>
<td>Urinary deoxypyridinoline</td>
<td>C-propeptide of type I collagen</td>
<td>Requires adjustment to levels of urinary creatinine</td>
<td>X</td>
</tr>
<tr>
<td>u-PYD</td>
<td>Urinary pyridinium metabolite</td>
<td>Found in bone, cartilage, tendon, blood vessels</td>
<td>Requires adjustment to urinary creatinine</td>
<td>X X</td>
</tr>
<tr>
<td>s-TRAP</td>
<td>Serum tartrate-resistant acid phosphatase</td>
<td>Includes two isoforms: type 5a (platelets, erythrocytes and other sources) and type 5b (osteoblasts)</td>
<td>Pioglitazone use in T2DM individuals is associated with a decrease in s-TRAP$^{110}$</td>
<td>X</td>
</tr>
<tr>
<td>s-OC</td>
<td>Serum osteocalcin</td>
<td>Hydroxypapitate-binding protein exclusively synthesised by osteoblasts and chondroblasts</td>
<td>Specificity: specific marker of osteoblast function</td>
<td>X</td>
</tr>
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<td>u-OC</td>
<td>Urinary osteocalcin</td>
<td>Hydroxypapitate-binding protein exclusively synthesised by osteoblasts and chondroblasts</td>
<td>Specificity: specific marker of osteoblast function</td>
<td>X X</td>
</tr>
<tr>
<td>s-ALP</td>
<td>Serum alkaline phosphatase (total)</td>
<td>Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of various tissues: liver, bone, intestine, spleen, kidney and placenta</td>
<td>Specificity: non-specific for bone (about 50% is liver isomerase in healthy individuals)</td>
<td>X</td>
</tr>
<tr>
<td>s-ALP</td>
<td>Serum bone-specific alkaline phosphatase</td>
<td>Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of osteoblasts</td>
<td>Specificity: specific for bone, but with some cross-reactivity with liver isomerase (up to 20%)</td>
<td>X</td>
</tr>
<tr>
<td>s-BALP</td>
<td>Serum bone-specific alkaline phosphatase</td>
<td>Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of osteoblasts</td>
<td>Specificity: specific for bone, but with some cross-reactivity with liver isomerase (up to 20%)</td>
<td>X</td>
</tr>
<tr>
<td>s-PICP</td>
<td>Procollagen type I C propeptide</td>
<td>Precursor molecules of collagen type I syntheesised by osteoblasts</td>
<td>Specificity: mostly derived from bone collagen type I (around 90%). Short serum half-life, Regulated by hormones (thyroid, IGF-1)</td>
<td>X</td>
</tr>
<tr>
<td>s-PINP</td>
<td>Procollagen type I N propeptide</td>
<td>Precursor molecules of collagen type I syntheesised by osteoblasts</td>
<td>Specificity: mostly derived from bone collagen type I A ssay: may recognise trimmer alone (intact) or trimmer and monomer (total PINP)</td>
<td>X</td>
</tr>
</tbody>
</table>

Adapted from Vasikaran et al.\textsubscript{110}
Long 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,\textsuperscript{58,75} and is negatively correlated with HBA\textsubscript{1c} level.\textsuperscript{76} The negative correlation with HBA\textsubscript{1c} was also reported for CTX, a marker of bone resorption.\textsuperscript{77} When looking separately at T1DM and T2DM, osteocalcin levels have been reported to be decreased in T1DM and only borderline significantly decreased in T2DM.\textsuperscript{78} Similarly, PINP and NTX also tended to be lower in individuals with DM.\textsuperscript{5} Consistently, histological study of DM found decreased number of osteoblasts and osteoclasts.\textsuperscript{79} 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 microradioculation, 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.\textsuperscript{79} Adiponectin was reported to have an anabolic effect on osteoblasts and inhibits osteoclastic activity \textit{in vitro}.\textsuperscript{70} 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.\textsuperscript{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)-\gamma, adipocyte fatty acid binding protein (aP2), resistin and adipin, whereas it suppresses cell growth, mineralization, and expression of osteogenic markers including Runx2, collagen I, osteocalcin, osteonecrtin.\textsuperscript{76,79} Further studies are needed to precisely explain the role of adipokines 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.\textsuperscript{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.\textsuperscript{81} The receptor

<table>
<thead>
<tr>
<th>Study author</th>
<th>Participants</th>
<th>BTM measured</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reyes-Garcia et al.; 2013\textsuperscript{71}</td>
<td>78 T2D (43 men, 35 women), 55 controls</td>
<td>OC (ns), RIA</td>
<td>Vertebral fractures in 27.7% of T2D and 21.7% of controls</td>
</tr>
<tr>
<td>Yamamoto et al.; 2012\textsuperscript{71}</td>
<td>255 T2D (postmenopausal women and men), 240 controls</td>
<td>O:\textsubscript{1}, CTX\textsubscript{1}, (electrochemiluminescence immunoassay on an automated analyzer; Roche Diagnostic GmbH, Mannheim, Germany), PTH↓</td>
<td>Excluded if serum creatinine was higher than normal range</td>
</tr>
<tr>
<td>Manavalan et al.; 2012\textsuperscript{72}</td>
<td>18 T2D PM, 27 controls PM</td>
<td>O:\textsubscript{1}, ELISA (IDS), CTX\textsubscript{1} ↓, ELISA</td>
<td>At least 1 year use of antglycemic medication</td>
</tr>
<tr>
<td>Bhattoa et al.; 2013\textsuperscript{73}</td>
<td>68 male T2D, 68 male controls</td>
<td>O:\textsubscript{1}, CTX\textsubscript{1}, electrochemiluminescence immunoassay (Roche Diagnostic GmbH, Mannheim, Germany).</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Arwai et al.; 2013\textsuperscript{74}</td>
<td>482 T2D PM women, 482 PM controls</td>
<td>LIASON autoanalyzer (DiaSorin Inc., Stillwater, MN, USA)</td>
<td>At least 1 year use of antglycemic medication</td>
</tr>
<tr>
<td>Hamilton et al.; 2012\textsuperscript{75}</td>
<td>26 T1D, 27 T2D</td>
<td>CTX↓, OC (ns), PTH (ns)</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Akin et al.; 2003\textsuperscript{76}</td>
<td>57 T2D PM, 20 controls PM</td>
<td>O:\textsubscript{1}, NTX↓</td>
<td>At least 1 year use of antglycemic medication</td>
</tr>
<tr>
<td>Reyes-Garcia et al.; 2013\textsuperscript{77}</td>
<td>79 T2D, 55 controls</td>
<td>CTX↓, PTH↓, enzyme immunoassay (EIA) and ELISA</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Jiajue et al.; 2014\textsuperscript{78}</td>
<td>236 T2D PM, 1055 controls PM</td>
<td>CTX↓, P1NP↓</td>
<td>Vertebral fractures in 27.7% of T2D and 21.7% of controls</td>
</tr>
<tr>
<td>Farr et al.; 2014\textsuperscript{79}</td>
<td>30 T2D PM, 30 controls PM</td>
<td>CTX↓, P1NP↓</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Manavalan et al.; 2012\textsuperscript{72}</td>
<td>18 T2D PM, 27 controls PM</td>
<td>Circulating O:\textsubscript{1} cells ↓</td>
<td>MI significantly lower in controls. Performs microindentation</td>
</tr>
<tr>
<td>Bhattoa et al.; 2013\textsuperscript{73}</td>
<td>68 male T2D, 68 male controls</td>
<td>O:\textsubscript{1}, CTX↓</td>
<td>eGFR b 60 ml/min excluded</td>
</tr>
<tr>
<td>Gaudio et al.; 2012\textsuperscript{74}</td>
<td>40 T2D PM, 40 controls PM</td>
<td>CTX↓</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Arwai et al.; 2013\textsuperscript{75}</td>
<td>482 T2D PM, 482 controls PM</td>
<td>IGF-1↓, 1.25-OH D↓, PTH↓, O:\textsubscript{1}, CTX↓, P1NP↓</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Hamdan et al.; 2013\textsuperscript{76}</td>
<td>2431 subjects of these 45 T2D</td>
<td>CTX and P1NP↓, in T2DM individuals who use statins</td>
<td>Renal disease excluded</td>
</tr>
<tr>
<td>Sarkar and Choudhury; 2013\textsuperscript{77}</td>
<td>108 T2D, 50 controls</td>
<td>O:\textsubscript{1}↓</td>
<td>The diabetes group is a subgroup of the total population.</td>
</tr>
<tr>
<td>Movahed et al.; 2012\textsuperscript{78}</td>
<td>382 PM of these 102 T2D</td>
<td>O:\textsubscript{1}, CTX↓</td>
<td>No renal disorders</td>
</tr>
<tr>
<td>Scoa et al.; 1996\textsuperscript{79}</td>
<td>47 female NIDDM, 252 female controls</td>
<td>O:\textsubscript{1} (ns), ALP (ns)</td>
<td>No history of metabolic bone disease</td>
</tr>
</tbody>
</table>

**Notes:** Anti-hyperglycemic medication was excluded. The negative correlation with HBA\textsubscript{1c} was also reported for CTX, a marker of bone resorption. When looking separately at T1DM and T2DM, osteocalcin levels have been reported to be decreased in T1DM and only borderline significantly decreased in T2DM. Similarly, PINP and NTX also tended to be lower in individuals with DM. Consistently, histological study of DM found decreased number of osteoblasts and osteoclasts. 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 microradioculation, as well as changes in osteoblasts and osteoclasts (Figure 1).
for AGEs (RAGE) initiates the intracellular signaling through the binding of AGEs. 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.

Increased AGE concentration is negatively associated with bone density and mineralization, and the cross-linking of AGE with collagen alters the mechanical properties of bone, disrupting its remodeling, increasing its stiffness and fragility. Pentosidine, a well-known AGE, was also shown to disrupt osteoblast differentiation. Studies found that poor glycemic control was associated with increased risk of fractures in individuals with DM, and suggest that HbA1c level of <8% could reduce fracture risk in individuals with DM.

Insulin and IGF1
Insulin exerts an anabolic effect on bones by promoting osteblast proliferation and differentiation. Animal studies have shown that diabetic rodents have impaired bone formation following bone injury whereas insulin injection normalized it. 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. 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. Indirectly, the reactive oxygen species generated due to the binding of AGEs can cause bone loss at the hip and increase the risk for fractures. 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. Sulfonylureas show neutral effect on BTM and bone turnover and BMD parameters, canagliflozin was reported to cause bone loss at the hip and increase the risk for fractures. Medications used with careful evaluation and patient education.
neutral effect on BMD and fracture risk in large cohorts.46,98,99 Sulfonylureas show neutral effect on BMD at BTM levels, and studies on its clinical effect has not been established.96 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 1.65-3.01103 and OR=1.94; 95%CI: 1.60-2.35103) 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.100 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 hip107,108 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.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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