

ABSTRACT

Patients with type 2 diabetes mellitus (DM2) are recognised to have a higher risk of fragility fractures. With the increasing prevalence of DM2 in Singapore and an ageing population, the impact of DM2 on fragility fracture is expected to rise. The aim of this article is to review updated information on bone fragility and fracture risk in DM2 patients, to discuss the impact of diabetes treatment on bone metabolism, as well as the efficacy of anti-osteoporosis treatments for this population. An algorithm is proposed for the identification and management of DM2 patients at increased fracture risk.

Keywords: Osteoporosis, type 2 diabetes mellitus, glycaemic control, anti-resorptive treatment

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INTRODUCTION

Epidemiology - DM2 and fragility fractures

Diabetes and fragility fractures are both major global health challenges. The global prevalence of diabetes among adults over 18 years has risen from 4.7 percent in 1980 to 8.5 percent in 2014.¹ Worldwide, one in three women, as well as one in five men over the age of 50 years old, will experience osteoporotic fractures.² Asians, especially South Asians, are predisposed toward DM2 to a greater extent than Caucasians.³ Singapore has a prevalence of DM2 at 10.5 percent which is higher than the world average of 8.8 percent, with estimates of prevalence rising to 15 percent in 2050.⁴ It is also projected that more than 50 percent of all fragility fractures will occur in Asia by the year 2050.⁵ Studies have shown that patients with DM2 have a higher risk of fragility fracture, including a 40 percent to 70 percent increased fracture risk at the hip.⁶⁻⁷ Taken together, this implies a burgeoning epidemic of diabetes and fragility fractures, especially in Asian countries such as Singapore.

DM2 and Bone Metabolism

Patients with DM2 typically have lower bone turnover, and the accumulation of advanced glycation end-products (AGEs) in

collagen is thought to contribute to lower bone formation. Together with low bone turnover, reduction in unmineralized matrix, and increased collagen glycation may contribute to increased fragility of diabetic bone.⁸ Recent studies have also shown that AGEs accumulation with altered mineral maturity affects the quality of bone independent of bone volume fraction, which may explain the epidemiological evidence that in DM2 patients who despite paradoxically having higher quantity of bone have higher risk of fragility fracture.⁹ In histomorphometric and biochemical studies of diabetes patients, bone turnover is low with a reduction in both bone formation and, to a lesser degree bone resorption.¹⁰ Bone turnover may also be affected by late stages of DM2 complications such as renal failure associated adynamic bone disease.

1. Diabetes-related risk factors for fragility fractures

The mechanism for increased fragility fractures in DM2 is complex, but it is likely multifactorial and can be divided into factors related to glycaemic control, anti-diabetic medications and disease complications.

1.1 DM2 Glycaemic control and complications

Chronic hyperglycaemia exposes excess glucose to the free amino acids in circulation or tissue proteins. This non-enzymatic process initially forms reversible early glycation products and later, irreversible advanced glycation end products (AGEs). The accumulation of AGEs in bone matrix as a result of hyperglycaemia alters collagen structure, impacts osteoblasts and osteoclasts function, increases bone marrow adiposity, release inflammatory cytokines, and alters osteocyte number and function, all of which contribute to reducing bone quality.¹¹⁻¹² AGEs also contribute to the development of microvascular complications.

Microvascular complications may affect the bone microvasculature with shifts in production to adipocytes and away from osteoblasts, resulting in an increase in bone marrow adiposity. Some studies have demonstrated an association of bone marrow adiposity with fractures and glycated haemoglobin (A1C) level or fractures.¹³ DM2 patients with microvascular complications have been shown in studies to have cortical bone deficits.¹⁴

In addition, microvascular complications such as sensory neuropathy and retinopathy with visual impairment increase the risk of falling. Older diabetic women have also been reported to have an increased risk of falling.¹⁵

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1.2 Impact of DM2 medications on fracture risk¹⁶

Although lifestyle intervention is the cornerstone of management for patients with DM2, most patients eventually require pharmacological therapy. Many agents are available with differential effects on bone metabolism. Metformin, sulfonylurea, thiazolidinediones (TZDs), dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP-1RA), sodium-glucose co-transporter 2 (SGLT2) inhibitor and insulin are the most commonly used medications. Table 1 depicts a summary of the effects of these DM2 medications on BMD and fracture risks. Furthermore, bariatric surgery is now included in the therapeutic armamentarium for DM2.

Metformin

Metformin primarily decreases hepatic glucose production by inhibiting key enzymes for gluconeogenesis and enhances peripheral insulin sensitivity. Experimental studies have indicated beneficial effects on bone formation, whereas large clinical studies resulted in neutral or positive effects on BMD and fracture risk in different and various large patient cohorts.¹⁷ There is no current evidence from randomised controlled trials. However, these observational data strongly suggest a protective role of metformin on bone health.¹⁸⁻²⁰

Sulfonylureas (SU)

SU are SU receptor-1 agonists, which initiate inhibition of the adenosine triphosphate sensitive K⁺ channel and results in the depolarization of cell membrane, leading to increased endogenous insulin secretion. With the exception of the Osteoporotic Fractures in Men (MrOS) study¹⁷, which suggests that SU increase fracture risk in old men with DM2, the rest of the studies are indicative of a beneficial or at least neutral effect on fracture risk.²¹⁻²³ Furthermore, the effect of SU on bone metabolism and BMD seem to be neutral as well. However, the high risk of hypoglycaemia may increase the number of falls and fractures, and this should be taken into account when selecting therapy for these patients.

Thiazolidinediones (TZDs)

TZDs are peroxisome proliferator-activated receptor γ agonists that modulate gene expression, resulting in improved glucose uptake, beta-cell function and insulin sensitivity. Studies have shown that TZDs may potentially reduce bone density and increase fractures risks compared with other antidiabetic medications.²¹ This effect has now been confirmed in randomised studies and meta analyses.²⁴⁻²⁶ This risk was similar with pioglitazone and rosiglitazone, did not vary with age and was associated with reductions in BMD.²⁸ The risk was also reported to be higher in women and those above 65 years old²⁸ with a reduction in risk following discontinuation of the TZD.²⁹ A key part of the TZD action is the activation of adipogenesis, for which peroxisome proliferator-activated receptor γ is required. Adipocytes and osteoblasts are both derived from mesenchymal, and activation of adipogenesis is

known to be associated with suppression of regulators of bone differentiation.³⁰ Thus, the effects of TZDs on bone are closely linked to their metabolic effects, and it should be avoided in women who are at increased fracture risk.

Dipeptidyl peptidase -4 inhibitor (DPP-4i)

DPP-4i are oral antidiabetic medications that inhibit the enzyme DPP-4, and its inhibition would potentially affect glucose regulation through multiple effects. The SAVOR-TIMI trial found no effect of saxagliptin on fracture risk³¹ and a meta-analysis of various medications in this category found a protective effect on fracture prevention.³² However, a recent post hoc analysis of 20 randomised clinical trials (RCTs) found a slightly higher incidence of fractures with saxagliptin as compared to the control group.³³ The TECOS trial with sitagliptin found a neutral effect on fractures.³⁴ Thus, taken together, there are more data supportive of a more neutral effect of this class of drugs on fractures. Further studies are needed to confirm any possible beneficial effect on bone protection.

Glucagon-like peptide-1 receptor agonist (GLP1 RA)

GLP1 RA potentiates glucose induced insulin secretion and inhibits glucagon release. They also delay gastric emptying, reduce appetite and induces significant weight loss. A meta-analysis of clinical trials found no effect of treatment on fractures as serious adverse events³⁶, although a meta-analysis found a protective effect of liraglutide and a negative effect of exenatide.³⁷ However, none of the studies included was powered for bone outcomes. Thus, these results should be interpreted with caution.

Sodium-Glucose Transport Protein 2-Inhibitors (SGLT2-i)

SGLT2i inhibits the sodium-glucose cotransporters, resulting in loss of glucose through urine and reduction in glucose concentrations. Several agents are available in this class, of which canagliflozin has been demonstrated to potentially exert negative effects on bone density, bone resorption and fracture risk at the hip.³⁷⁻³⁸ This increased fracture risk was seen more commonly in those who were older, with a past history of cardiovascular diseases, lower baseline glomerular filtration rate and higher baseline diuretic use and may be mediated by increased falls. This has now resulted in the revision of the labelling of this drug and addition of new warning by the U.S. Food and Drug Administration in September 2015. Empagliflozin and dapagliflozin have not been shown to exert significant changes in BMD, bone markers, or fracture risk and are thought to have a neutral effect on bone.³⁹⁻⁴⁰ Further studies are needed to elucidate the long-term safety and mechanism of bone loss in this new class of drug.

Insulin

There are no specific RCT designed to investigate the effects of insulin on bone health. However, it has been consistently shown that patients who are treated with insulin in general

present with an increased prevalence of fracture. Higher fracture risks are also associated with longer duration of diabetes, presence of more DM complications, increased risk of falls, and increased incidence of hypoglycaemia.

Bariatric surgery

Bariatric surgery is now a well-established therapeutic option in DM2 patients with BMI > 35 (Asian 32.5) kg/m². This has been recognised as the most effective way to sustain weight loss and improve glycaemic control requiring fewer medications. However, studies have shown that fracture risk seems to be increased between one to two years after surgery and is more associated with biliopancreatic diversions and Roux-en-Y gastric bypass. It is unclear whether sleeve gastrectomy is safe for skeletal health as it is a new procedure, and its skeletal effects have not been well defined.⁴¹

2. Fracture risk assessment in DM2 patients

2.1 Dual-energy X-ray absorptiometry (DXA) scans limitations and pitfalls

DM2 patients, despite their higher fracture risks, are known to have a five to ten percent higher areal BMD compared to non-DM2 subjects.⁴²⁻⁴³ The increase in BMD was more pronounced in younger men, presence of higher BMI and higher HbA1C. However, these meta-analyses had substantial heterogeneity in the study designs and definitions of DM2.⁴³

This relatively higher BMD in those with DM2 implies that an even lower proportion of subjects with a fracture will have a BMD T score < -2.5 (i.e. in the osteoporotic range) than among the non-DM2 population.⁴⁴ Studies have shown that for a given BMD T score, the fracture risk was higher in DM2 patients compared to those without DM2. Moreover, a T-score in a woman with DM2 is associated with hip fracture risk is equivalent to a woman without DM2 with a T score of approximately 0.5 units lower. Nevertheless, data have clearly confirmed that while BMD systemically underestimates fracture risk, it still stratified fracture risk in elderly patients with DM2.⁴⁵

Some studies suggest that DM2 may be associated with a more rapid bone loss which may result in increased fracture risks.⁴⁶⁻⁴⁷ Trabecular Bone Score (TBS) is a grey-level textural metric that is obtained from lumbar spine dual-energy X-ray absorptiometry (DXA) images. Decreased TBS has been found to be associated with an elevated risk for osteoporotic fractures independent of BMD in cohort studies. These results were confirmed by a recent meta-analysis of prospective cohort data⁴⁸ and adopted as evidence in position papers.⁴⁹⁻⁵⁰ However, studies in different ethnic groups have shown variable results, particularly with respect to each gender.⁵¹⁻⁵² Recent analyses indicate that TBS evaluated on DXA scans is inversely related to BMI and abdominal fat⁵³, whether TBS represents alterations of bone structure in diabetes, therefore, remains unknown.

2.2 Other measures of bone quality

Since reduced BMD alone does not fully explain increased in fracture risk and bone fragility in DM2 patients, there are ongoing studies looking into other techniques in measuring bone quality. These include HR-pQCT (Xtreme CT) at the distal radius and/or tibia, and studies in postmenopausal women with DM2 showed a trend toward greater cortical porosity compared to controls.⁵⁴ Trabecular bone volume is more heterogeneous and is preserved in patients with DM2. Further studies have also shown that DM2 patients with microvascular disease demonstrated cortical deficits on HR-pQCT. Higher cortical porosity in mid cortical and periosteal layers in DM2 patients with prior fracture compared to DM2 patients without history of fractures suggests that these cortical sub-compartments may be sensitive to DM2 induced toxicity and may reflect microvascular disease.^{14, 55}

Other measurements of bone strength, such as microfinite element analysis and microindentation of the tibia outer cortex have shown lower results compared to control.⁵⁶⁻⁵⁷ However, these methods of measurement of bone strength are yet to be made accessible outside the research context.

3. Anti-Osteoporosis treatments in DM2 patients

No randomised clinical trials have directly evaluated the anti-fracture efficacy of osteoporosis treatment in diabetic patients. The clinical evidence regarding the efficacy of anti-osteoporosis treatments in diabetic patients is provided by post hoc analyses in subgroups from randomised clinical trials enrolling osteoporosis patients and from a few observational studies.

In the Fracture Intervention Trial (FIT), postmenopausal women including DM2 patients with femoral T score < -1.6 were randomly treated with alendronate or placebo for three years. In a post hoc analysis, it was reported that DM2 status did not alter the effect of alendronate on BMD gain versus placebo.⁵⁸ Data extracted from the Danish national prescription registry reported that DM2 with or without complications did not influence fracture risk in patients who adhered to alendronate.⁵⁹ In osteoporotic Japanese women with DM2, risedronate treatment showed similar responses in BMD of LS Spine and bone markers between DM2 and non-DM2 patients.⁶⁰

Data are not available currently specifically evaluations DM2 patients in their response to IV bisphosphonates and denosumab. Anti-fracture efficacy of raloxifene was similar between patients with and without DM2 in the RUTH (Raloxifene Use for The Heart) trial⁶¹ and in a Danish cohort. Teriparatide treatment had a similar effect in DM2 versus non-DM2 patients on vertebral and hip BMD.⁶² However, its effects specifically on bone strength and fracture risk remain to be specifically evaluated.

New and future osteoporosis medications

Abaloparatide may have potential in the treatment of bone fragility in DM2 as it can stimulate bone formation with a lesser increase in bone resorption. Romosozumab, an anti-sclerostin antibody, is currently under investigation as a new anabolic treatment and has been shown to enhance bone mass and strength in animal diabetic models.⁶³ Whether this would translate to better bone health in DM2 patient remains to be seen. Recent signals of increased cardiovascular risk are of potential concerns, especially in DM2 patients.⁶⁴ Further prospective studies are needed to understand this better.

4. Management of bone fragility in DM2 patients

Figure 1 shows a suggested algorithm for diagnosing osteoporosis and initiation of treatment in DM2 patients. The criteria are based on the presence of fragility fracture and/or a low BMD.⁶⁵

BMD intervention threshold of $T < -2.0$ have been adopted in this algorithm to allow for the paradoxically elevated BMD results in DM2 patients. However, this suggested adjustment and cut-off have not been validated in the Asian and middle eastern population.

FRAX computation in DM2 patient has also been suggested to be adjusted to take into account DM2 as a risk factor for fractures. Conventional clinical risk factors can be employed to identify DM2 patients at increased fracture risk. However, it is worth noting that FRAX does not fully capture the risk of osteoporotic fractures in DM2 patients and systematically underestimates fracture risk. Hence for a given FRAX score, fracture risk of a DM2 patient is in fact higher compared to a non-DM2 patient. FRAX adjustments have been proposed as follows, and either of these options may be adopted:^{44, 66}

- Substitute Rheumatoid Arthritis as type 2 DM in FRAX
- Reducing the T score by 0.5 deviations
- Adding ten years into the age

4.1 General measures

Lifestyle intervention

Lifestyle intervention is always recommended in patients with DM2 and is the basis of any clinical guidelines. However, weight loss is associated with both muscle and bone loss that may increase the risk of bone fragility and sarcopenia.⁶⁷ Thus, adequate protein intake and weight-bearing exercises are important to prevent sarcopenia and sarcopenic-obesity⁶⁸. Physical activity helps to prevent bone loss during weight loss program and is associated with decreased sclerostin and improvement in quality of life.⁶⁹ Other lifestyle measures such as avoidance of smoking and limiting alcohol intake (less than three units per day) are also essential.

Lower levels of 25-hydroxy-vitamin D levels have also been associated with DM2 as well, mostly in the obese and

insulin-resistant states. Although the benefits of vitamin D supplementation on bone have not been demonstrated in diabetics, by analogy with the non-DM2 patient, a daily vitamin D intake of 800 IU/d may be recommended. Progressive higher doses of vitamin D may be required to achieve optimal serum levels of vitamin D. An adequate calcium intake (preferably from diet, 100 mg/day) is recommended as well.

Glycaemic control

Good glycaemic control and prevention of chronic hyperglycaemia are important in reducing advanced glycation end products (AGEs), glycation of collagen and microvascular complications which are important in the maintenance of skeletal health. Glycaemic targets should be individualised, balancing the demonstrated benefits of prevention of microvascular complications and risk of hypoglycaemia. Antidiabetic treatments such as thiazolidinediones should be avoided in DM2 patients with osteoporosis and risk of fragility fractures. Canagliflozin, although not necessarily all SGLT2i, should be avoided in these patients as well.

4.2 Pharmacologic therapy

In addition to lifestyle measures, patients at high risk of fractures should receive pharmacological therapy. At the current time and in the absence of strong evidence against, bisphosphonates remain the first choice for osteoporosis treatment in DM2 patients. Although there are no specific data on DM2 patients on the efficacy of denosumab, this may be a preferred treatment option, especially in patients who have renal impairment or are unable to tolerate bisphosphonates. However, the use and potential benefit of anti-resorptive drugs in patients with DM2 who are characterised by near normal BMD and/or low bone turnover markers whose bone fragility may mostly result from poor bone material properties remains unproven and needs further studies. In this context, anabolic agents such as teriparatide, abaloparatide or romosozumab present a potential interest. Table 2 depicts a summary of the effect of anti-osteoporosis medications on BMD and fracture risks in DM2 patients.

CONCLUSION

The pathophysiology of fragility fractures in DM2 patients is complex and multifactorial. Longitudinal studies have established the limitation of current tools such as BMD and FRAX in estimating fracture risks. The optimal management of fragility fractures in DM2 patients has yet to be established in long term prospective studies. The current consensus is based on expert opinions and working group, which may change as the data evolves in this area. Good glycaemic control, lifestyle intervention and exercise remain important cornerstone of osteoporosis treatment in DM2 patients. Anti-osteoporosis treatments should be started in DM2 patients with a history of fragility fracture or at risk of fragility fractures. Future studies and new trials will further evaluate and prospectively investigate the efficacy and safety of osteoporosis treatment in DM2 patients.

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LEARNING POINTS

- **Patients with type 2 diabetes have an increased risk of fracture despite paradoxically higher BMD values.**
- **Individualised glycaemic control with the use of medications that have been shown to have lower risk in worsening BMD and increasing risk of fragility fracture is important in managing DM2 patients with risk of fragility fractures.**
- **Current anti-osteoporosis treatments are recommended for DM2 patients with fragility fractures and at risk of fragility fractures.**
- **FRAX underestimates the risk of fracture, and several adjustments can be made to reflect this which includes lowering the T score by 0.5 SD, substitute Rheumatoid Arthritis as type 2 DM in FRAX, and adding ten years into the age.**

Table 1: Effects of Diabetes Medications on Bone Mineral Density (BMD) and the risk of fracture in DM2 patients

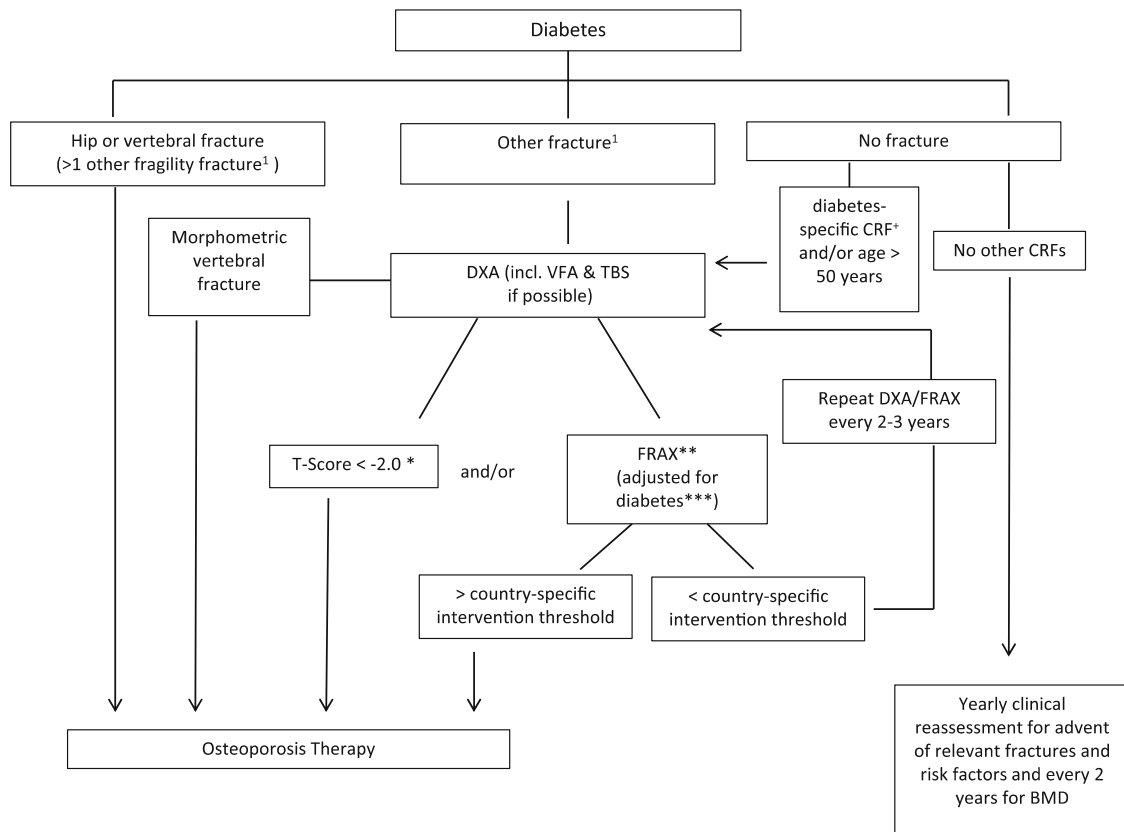
Medications	BMD	Fracture risk
Metformin	= / ↑	↓ / =
Sulphonylureas	NA	↓ / = / ↑
Thiazolidinediones	↓ ↓ / =	↑ ↑ / =
<u>Incretins</u>		
GLP1 analogue	↑ / =	=
DPP4 inhibitor	--	↓ / =
SGLT2 inhibitors	=	= / ↑
Insulin	=	↑

*↑ increase, ↓ decrease, = unchanged, NA not available, GLP glucagon like peptide, DPP4 dipeptidyl peptidase inhibitor 4, SGLT2 sodium/glucose cotransporter 2

Table 2: Effects of Osteoporosis Medications on Bone Mineral Density (BMD) and Fracture Risk in DM2 Patients

Medications	BMD	Risk of fracture
Alendronate	↑	NA / =
Risedronate	NA	=
Raloxifene	↑	↓ / =
Denosumab	NA	NA
Teriparatide	↑	=

*↑ increase, ↓ decrease, = unchanged, NA not available

Figure 1: Fracture risk evaluation in patients with DM2**Table 3: Risk factors for fractures in Diabetes****Common risk factors**

- FRAX Clinical Risk Factors * (Age, sex, weight, height, previous fracture, family history of hip fracture, current smoking, glucocorticoid, rheumatoid arthritis, alcohol, BMD)
- Low BMD
- Recurrent falls

Disease-specific risk factors

- Diabetes duration > five years
- Diabetes medication: insulin, TZDs, possibly SGLT2i (canagliflozin)
- HbA1c > 7 percent
- Microvascular complications: peripheral and autonomic neuropathy, retinopathy, nephropathy