Diabetes and bone health

Vidhya Jahagirdar, Neil J Gittoes

Article points

1. Diabetes and osteoporosis are increasingly prevalent diseases.

2. Diabetes and its complications influence important determinants of bone strength such as the material properties of bone, bone density and mineral content as well as bone micro-architecture and bone turnover.

3. Diabetes is an important clinical risk factor for osteoporosis and fracture, and as clinicians it is important to remember this association when managing people with diabetes.

Key words

– Bone

– Metabolic disorder

– Osteoporosis

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Diabetes and osteoporosis represent two major public health challenges. Osteoporosis is characterised by decreased bone mineral density and micro-architectural changes of the bone leading to increased risk of low trauma (fragility) fractures. Both diabetes and osteoporosis are associated with significant morbidity, decreased quality of life and reduced life expectancy. This article will explore the current literature on the inter-relationships between diabetes and bone health, the impact on patients and the management strategies that may be considered in primary care to minimise risk of diabetes-related bone disease and improve outcomes.

Diabetes and osteoporosis represent two major public health challenges. Osteoporosis is characterised by decreased bone mineral density (BMD) and micro-architectural changes of the bone leading to increased risk of low trauma or fragility fractures that are sustained as a result of a fall from standing height or less (*Figure 1*). Both diabetes and osteoporosis are associated with significant morbidity, decreased quality of life and reduced life expectancy. The total number of adults with diabetes is projected to rise to 4.6 million (9.5% of the adult population) by 2030 in England (Holman et al, 2011). Osteoporosis is also a condition that increases in prevalence with ageing (*Figure 2*). Age-related bone loss and post-menopausal physiological changes result in an increased prevalence of osteoporosis from 2% at 50 years to 25% at 80 years of age (NICE, 2012). One in two women and one in five men sustain one or more osteoporotic fractures in their lifetime. In the United Kingdom, osteoporosis results in over 200 000 fractures each year and costs the NHS over £1.73 billion per annum (National Osteoporosis Guideline Group [NOGG], 2016).

While age, female gender, glucocorticoid use and family history are well-recognised risk factors for osteoporosis and osteoporotic fractures, the association between diabetes and osteoporosis is tantalising, but poorly understood. Other disease conditions associated with diabetes, such as diabetic nephropathy, retinopathy, neuropathy and obesity, as well as medication used in the management of diabetes, may affect bone health, increase risk of falls and predispose patients to osteoporotic fractures. These factors are confounders in attempting to delineate causal links between diabetes and osteoporosis.

The aim of this article is to explore the current literature on the inter-relationships between diabetes and bone health, the impact on patients and the management strategies that may be considered in primary care to minimise risk of diabetes-related bone disease and improve outcomes.

Epidemiology of fractures in diabetes

The interaction between diabetes and osteoporosis is poorly understood. Both type 1 and type 2 diabetes are associated with increased risk of osteoporosis and fracture, and this risk is greater in type 1 than type 2 (Vestergaard, 2007). Various factors, such as type of diabetes, onset and duration, metabolic control, BMI, BMD, falls risk, diabetic complications and treatment, may influence bone health in diabetes. There are no well-designed randomised controlled trials (RCTs) or carefully evaluated epidemiological studies that have looked into all the above factors as potential attributors to fracture risk in diabetes.

Type 1 diabetes

BMD is lower in children and adolescents with type 1 diabetes than children without diabetes. As type 1 diabetes is usually diagnosed in children, the early and chronic alterations in bone metabolism may result in lower peak bone mass. This may contribute to osteoporosis and an increased risk of
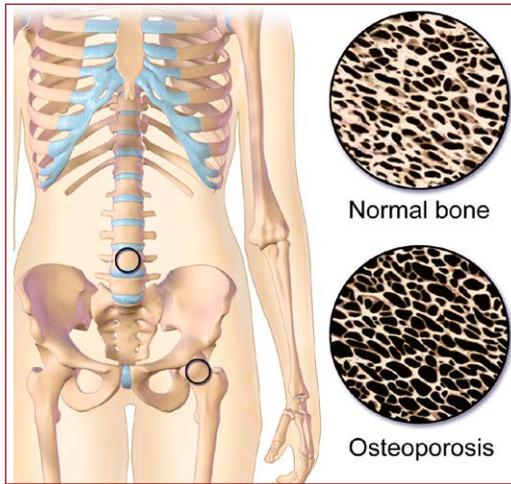
Figure 1. Osteoporosis is characterised by decreased bone mineral density and micro-architectural changes of the bone leading to increased risk of low trauma fractures (Blausen Medical Communications, 2016).

fracture in later life (Bonjour and Chevalley, 2014).

According to a recent meta-analysis, type 1 diabetes is associated with three times increased background risk of any fracture and the risk is elevated in both men and women. In individuals with type 1 diabetes compared to people without the condition, the relative risk (RR) for hip fracture was 3.78 (95% confidence interval [CI], 2.05–6.98; $P<0.001$) and for spine was 2.88 (95% CI, 1.71–4.82; $P<0.001$). The risk of hip fracture in women was five times higher and in men four times higher when compared to people without diabetes (Shah et al, 2015).

Type 2 diabetes

The prevalence of osteoporosis based on BMD is significantly lower in type 2 diabetes as studies have demonstrated normal or increased BMD in type 2 diabetes when compared to age-matched controls (Vestergaard, 2007). In type 2 diabetes, BMD is not a reliable indicator of fracture risk in isolation as the risk of fractures is increased independent of BMD (Vestergaard et al, 2005). Fracture risk has also been reported to be independent of other usually reliable predictors of fracture risk in type 2 diabetes, including age, physical activity and BMI (RR 2.6 [95% CI], 1.5–4.5; Janghorbani et al, 2007).

How does diabetes affect bone?

Diabetes and its complications influence important determinants of bone strength such as the material properties of bone, bone density and mineral content as well as bone micro-architecture and bone turnover (*Figure 3*).

Oxidative stress

Diabetes is reported to affect bone metabolism adversely through several mechanisms. Advanced glycation end-products (AGE) are produced as a result of oxidative stress in diabetes and are important mediators of diabetic complications such as diabetic retinopathy, nephropathy, neuropathy and atherosclerosis (Goh and Cooper, 2008). AGE accumulation in bones is also detrimental and leads to abnormal structure and alignment of collagen, contributing to bone fragility (Katayama et al, 1996).

Insulin deficiency

Insulin has an anabolic effect on bone. Insulin deficiency and reduced insulin-like growth factor-1 (IGF-1) have been linked to inhibition of osteoblast differentiation and osteopaenia in type 1 diabetes (Kanazawa et al, 2011). Treatment with insulin has been reported to stabilise BMD (Hofbauer et al, 2007). Hence, adequate optimisation of glycaemic control with insulin in type 1 diabetes may prevent osteopaenia and osteoporosis later in life.

Page points

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3. Insulin deficiency and reduced insulin-like growth factor-1 have been linked to the inhibition of osteoblast differentiation and osteopaenia in type 1 diabetes.
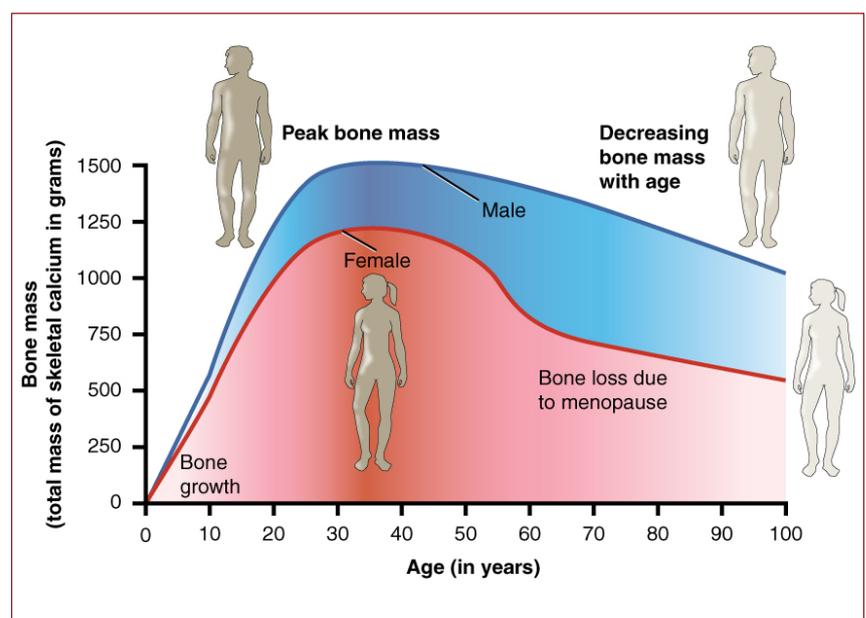

Figure 2. Peak bone mass is reached at 30 years of age. Bone mass then decreases with age, more so in women (Anatomy & Physiology, 2013).
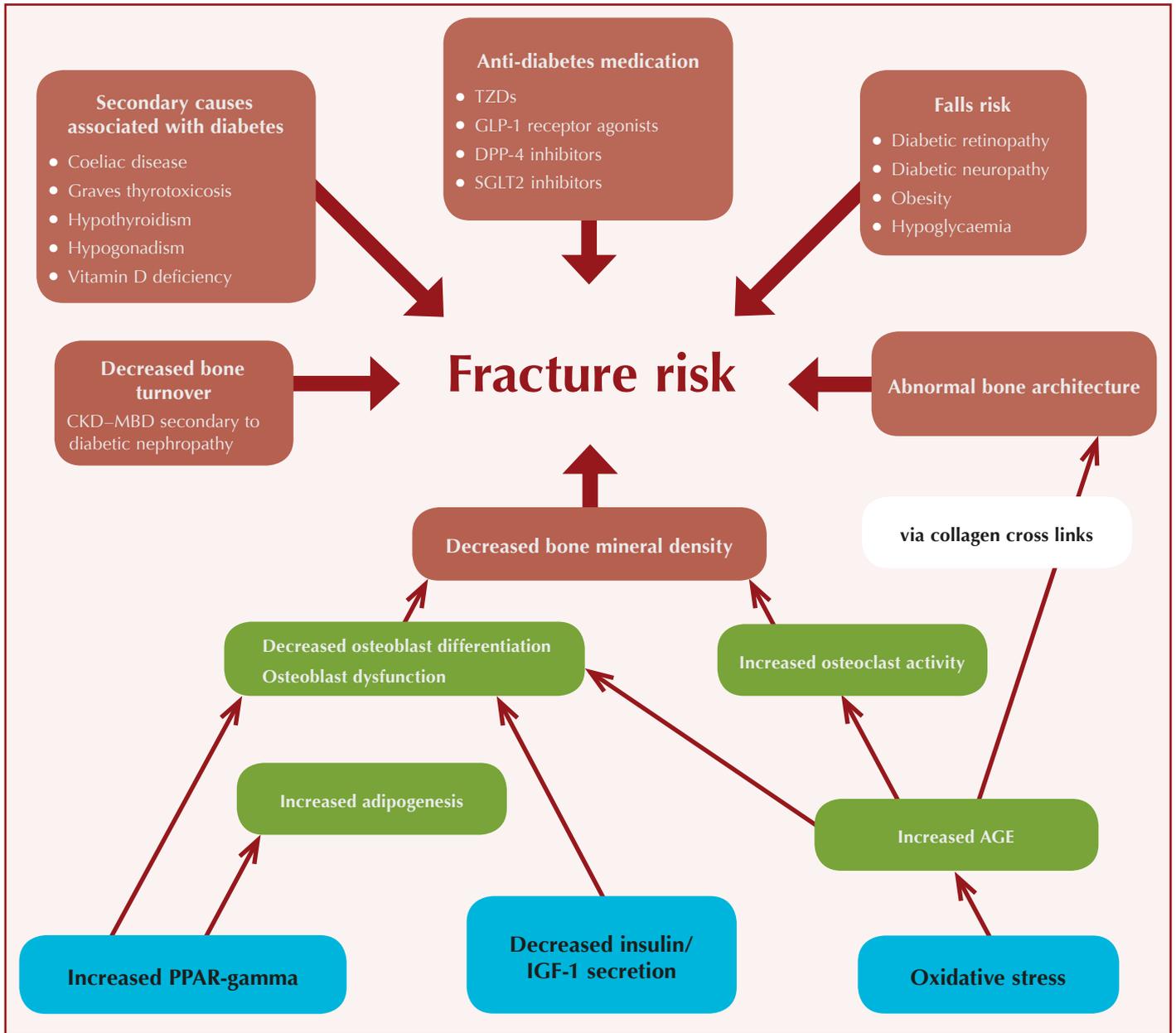
Figure 3. The factors influencing bone health and fracture risk in diabetes. AGE=advanced glycation end-products; CKD–MBD=chronic kidney disease–mineral and bone disorder; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; IGF-1=insulin-like growth factor-1; PPAR-gamma= peroxisome proliferator-activated receptor-gamma; SGLT2=sodium–glucose cotransporter 2; TZD=thiazolidinedione.

Diabetic nephropathy and chronic kidney disease (CKD)

Diabetic nephropathy often leads to CKD, and it is the most common cause of end-stage renal disease requiring renal replacement therapy in the UK (25%; UK Renal Registry, 2014). Disorders of mineral and bone metabolism are common sequelae of CKD.

The risk of developing moderate to severe CKD (stages 3b, 4 and 5) is eight times greater in women and twelve times greater in men with type 1 diabetes than in people without diabetes (Hippisley-Cox and Coupland, 2010). Similar to diabetes and osteoporosis, the risk of developing CKD increases with age.

Clinical expression of mineral and bone disorders in CKD (CKD–MBD) is often asymptomatic until late in its course. Abnormalities in bone turnover and mineralisation can result in osteitis fibrosa cystica

(brown tumours; *Figure 4*), adynamic bone disease, osteomalacia and secondary hyperparathyroidism caused by phosphate retention, decreased calcium and 1,25-dihydroxy(OH) vitamin D (calcitriol) concentration, and uraemic osteodystrophy. These conditions increase the risk of fractures due to changes in bone quality. While abnormalities in calcium and phosphate levels are detected even at CKD stages 1 and 2, the clinical significance of these abnormalities is unclear. Hence, management is focussed on optimising calcium and phosphate levels in CKD stages 3, 4 and 5.

Factors affecting falls risk

People with diabetes are at increased risk of falls and this is multifactorial due to advancing age, diabetes complications, hypoglycaemia and high BMI (*Figure 3*).

Peripheral neuropathy

The ABC health study showed that individuals with type 2 diabetes who develop fractures are more likely to have peripheral neuropathy, cerebrovascular disease and falls compared with people with diabetes without fractures (Strotmeyer et al, 2005). Cortical bone mass is reduced in the feet and hands in severe diabetic peripheral neuropathy and may predispose to metatarsal fracture and diabetic Charcot's osteoarthropathy (Cundy et al, 1985), which can cause foot deformity and gait disturbance, further increasing fracture risk by increasing falls. People with diabetic peripheral neuropathy are more likely to fall when compared to age-matched controls. While the underlying causative factors are not entirely understood, reduced muscle strength and stability (Handsaker et al, 2014) and foot deformity are likely to be contributing factors.

Retinopathy

The Blue Mountain Eye study showed that, in people with diabetes, there was a significantly increased risk of proximal humerus fracture associated with diabetic retinopathy, cortical cataract, longer diabetes duration (>10 years) and insulin treatment (Ivers et

Page points

1. People with diabetes are at increased risk of falls and this is multifactorial due to advancing age, diabetes complications, hypoglycaemia and high BMI.

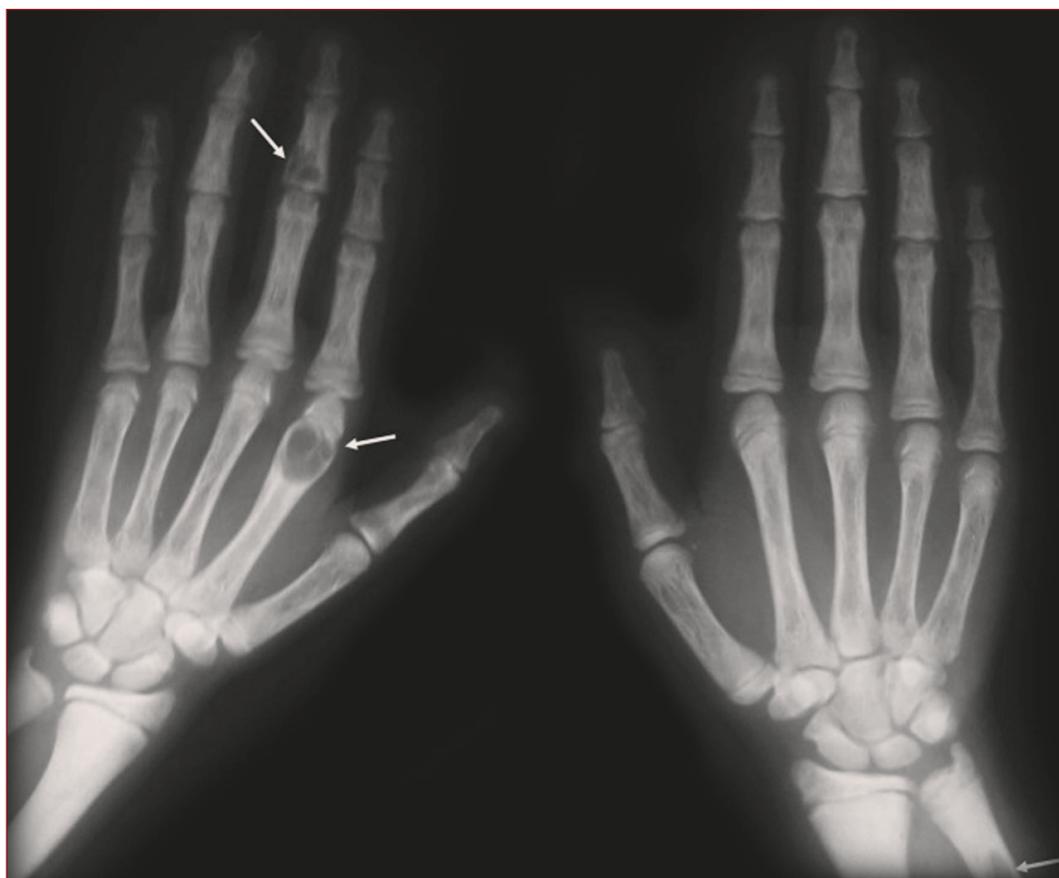2. Individuals with diabetic retinopathy or cataracts, or both, with reduced visual acuity are prone to falls.

Figure 4. Brown tumours of the hands in an individual with hyperparathyroidism (Gaillard, 2008).

al, 2001). Individuals with diabetic retinopathy or cataracts, or both, with reduced visual acuity are prone to falls. Thus, the attendant increased risk of falls contributes to greater risk of fracture.

Obesity
In total, 90% of people with type 2 diabetes are overweight or obese. Obesity is commonly thought to have a protective effect on bone as BMD tends to increase with load bearing associated with being overweight. In post-menopausal women, obesity increased the risk of fractures at the humerus and ankle while decreased the risk at the hip, pelvis and wrist (Gonnelli et al, 2014). Fewer data are available for men. The reasons for site-specific fractures in obesity could be related to fat padding protecting the hip and pelvis and a tendency to fall backwards or sideways rather than fall forward on outstretched arm leading to wrist fracture. Obesity is also associated with decreased bioavailability of vitamin D due to distribution in the subcutaneous tissue leading to vitamin D deficiency, another risk factor for osteoporosis. Hence, in spite of increased BMD, obesity is associated with increased risk of fracture at particular sites, which is likely to be due to the pattern of fall and vitamin D deficiency.

Hypoglycaemia
There is a higher incidence of fragility fracture in people who experience hypoglycaemic events (Signorovitch et al, 2013). Intensive glycaemic control (HbA$_{1c}$ 42 mmol/mol [<6%]) achieved with insulin treatment has been associated with increased risk of falls (Schwartz et al, 2008). Though it can be inferred that intensive glycaemic control could cause more hypoglycaemic events, Schwartz et al (2008) did not investigate a relationship between hypoglycaemia and falls risk. It is intuitive, however, to speculate that with frequent hypoglycaemic episodes contributing to loss of consciousness, falls risk would increase. Thus, hypoglycaemia-induced falls with underlying low bone density in diabetes would increase risk of fragility fracture.

Secondary causes for osteoporosis associated with diabetes
Type 1 diabetes can be associated with other autoimmune conditions such as coeliac disease, hypothyroidism and Graves' thyrotoxicosis.

About one-third of people with coeliac disease have osteoporosis and may be at a higher risk of fractures. Both hyperthyroidism and over-treated hypothyroidism are associated with lower BMD and increased risk of fracture (Mirza and Canalis, 2015). Hypogonadotrophic hypogonadism (low gonadotropins and low testosterone) is found in 25% of people with type 2 diabetes. Low testosterone levels in men are associated with low BMD and hypogonadism is a recognised cause of osteoporosis, but there are no reliable data available on fracture rates in people with type 2 diabetes and hypogonadism (Dandona and Dhindsa, 2011). Though epidemiological observational studies have shown associations between vitamin D deficiency and type 1 and type 2 diabetes, the evidence is inconclusive (Suzuki et al, 2006; Tahrani et al, 2010), as it is for many associations between suboptimal vitamin D and major health outcomes.

Anti-diabetes medication
Thiazolidinediones
Expression of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is increased in diabetes. This induces adipogenesis and inhibits osteogenesis (Botolin and McCabe, 2006; Montagnani and Gonnelli, 2013). Thiazolidinediones (pioglitazone and rosiglitazone) are PPAR-gamma agonists that are commonly used in the management of type 2 diabetes. They improve insulin sensitivity through their action on adipose tissue and liver by increasing glucose utilisation and decreasing glucose production. Thiazolidinediones, through their action on PPAR-gamma, enhance the effect of inhibiting osteoblast formation and increase risk of fracture in type 2 diabetes.

Both pioglitazone and rosiglitazone are associated with increased fractures in women but not in men. A meta-analysis by Zhu et al (2014) reported this risk as independent of age and with no clear association with duration of treatment. Thiazolidinedione use was associated with significant changes in BMD and increased fractures not only in the upper and lower limbs but also at the lumbar spine and femoral neck (Zhu et al, 2014). The benefit of improving glycaemic control versus the risk of fracture should be assessed carefully on an individual case basis, especially in post-menopausal women, before commencing treatment with pioglitazone in type 2 diabetes.

Incretin-based medicines

Glucagon-like peptide 1 (GLP-1) agonists are recommended in the management of obese people with type 2 diabetes and their effect on the risk of bone fractures is beginning to be established. In a meta-analysis of RCTs, liraglutide was associated with significantly reduced risk of fracture and exenatide was associated with an elevated risk of incident bone fractures (Su et al, 2015). Protective effects of dipeptidyl peptidase-4 (DPP-4) inhibitors on bone have also been reported in a recent meta-analysis. These data should be interpreted with caution as the trials included in the meta-analysis were not sufficiently long to assess fracture risk and the effect on bone was not assessed as a primary end-point (Monami et al, 2011). The effects of DPP-4 inhibitors and GLP-1 agonists on bone health need to be confirmed with well-designed RCTs.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors

In October 2015, the US Food and Drug Administration (FDA; 2015) issued a warning for the SGLT2 inhibitor canagliflozin relating to increased risk of hip fractures and fractures of the lower spine. More evidence is needed to ascertain if this is a drug class effect.

Insulin

One large longitudinal study, using a German database of over 100 000 people with type 2 diabetes in general practice found non-significant increase in risk of fracture in people on basal insulin (glargine, insulin detemir and NPH insulin) compared to oral hypoglycaemia agents (Pscherer et al, 2016). This could possibly be due to increased insulin-induced hypoglycaemia-related falls as discussed above, rather than direct effect of insulin on the bone. In the absence of RCT data at present, there is no clear evidence to suggest that insulin increases the risk of osteoporosis or fracture.

Management

There is no specific guideline for the management of bone disorders in diabetes. Investigations and treatment of osteoporosis should be based on patients' absolute risk of fracture taking into consideration age, gender, menopausal status, personal and family history of fractures, body weight, falls risk,

thiazolinediones use and associated secondary causes of osteoporosis.

Fracture risk assessment based on FRAX (for type 1 diabetes) or QFracture (for type 1 and type 2 diabetes) help predict the risk of fracture and the need for BMD measurements and treatment with anti-resorptive medications. FRAX could underestimate fracture risk in type 2 diabetes. Type 2 diabetes is not an explicitly recognised risk factor included in the risk assessment tool and BMD in type 2 diabetes can be normal or elevated in spite of increased fracture risk. As BMD does not predict fracture risk in renal osteodystrophy, it need not be performed routinely in CKD stages 3–5 in the presence of CKD-MBD (Kidney Disease: Improving Global Outcomes [KDIGO] CKD-MBD Work Group, 2009).

Bone mineral disorders in CKD can be identified early by detecting decreasing serum calcium, phosphate and vitamin D concentrations, and increasing serum parathyroid hormone (PTH) concentrations. The KDIGO clinical practice guideline suggests monitoring for serum calcium, phosphorus, 25-hydroxy vitamin D deficiency and PTH routinely for CKD stages 3–5 with the frequency of monitoring based on stage, rate of progression and whether specific therapies have been initiated (KDIGO CKD-MBD Work Group, 2009). PTH and bone alkaline phosphatase can be used to evaluate CKD–MBD.

Anti-resorptive agents such as bisphosphonates can be used as first-line agents to treat osteoporosis and high fracture risk in diabetes and in CKD stages 1, 2 and 3 (estimated glomerular filtration rate [GFR] >30 mL/min/1.73 m^2) in the absence of abnormal bone mineral markers. The effect of drug treatment should be reviewed after 5 years for alendronate and after 3 years for intravenous zolendronic acid with a view to making a decision regarding a drug holiday or continuing or switching treatment. No studies have specifically looked at optimal treatment for people with fractures where thiazolidinediones have been implicated.

Screening for coeliac disease with tissue transglutaminase antibodies (TTG) is recommended at the time of diagnosis of type 1 diabetes and if a young adult with type 1 develops intestinal or extra-intestinal symptoms consistent with coeliac disease (NICE, 2009). Annual screening for thyroid status is also recommended. Screening for hypogonadism

Page points

1. There is no specific guideline for the management of bone disorders in diabetes. Investigations and treatment of osteoporosis should be based on patients' absolute risk of fracture, such as age, gender, menopausal status, personal and family history of fractures.

2. Fracture risk assessment based on FRAX (for type 1 diabetes) or QFracture (for type 1 and type 2 diabetes) help predict the risk of fracture and the need for bone mineral density measurements and treatment with anti-resorptive medications.

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1. Bone mineral disorders in chronic kidney disease can be identified early by detecting changes in calcium, phosphate, vitamin D and parathyroid hormone levels.

2. HbA$_{1c}$ targets should be individualised, and less stringent control should be the aim for people at risk, to avoid hypoglycaemia, especially in the frail or elderly who are at risk of falls.

3. Regular weight-bearing exercise helps prevent bone loss, improves muscle strength and, by improving flexibility and balance, decreases the likelihood of falls and fracture.

in people with type 2 diabetes and replacing with testosterone if found deficient is also recommended (Dandona and Dhindsa, 2011).

Good glycaemic control and blood pressure control delays the progression of microvascular complications, which are associated with increased risk of falls and fracture. HbA$_{1c}$ targets should be individualised and less stringent control (HbA$_{1c}$ <64 mmol/mol [8%]) should be aimed for to avoid hypoglycaemia, especially in the frail or elderly who are at risk of falls.

Lifestyle changes

Patients should be advised to stop smoking and reduce alcohol intake as these are recognised risk factors for osteoporosis. They should be encouraged to have a healthy diet with adequate calcium and vitamin D. Vitamin D replacement in people with deficiency is as recommended for the general population (National Osteoporosis Society, 2013).

Regular weight-bearing exercise helps prevent bone loss, improves muscle strength and, by improving flexibility and balance, decreases the likelihood of falls and fracture. Weight-bearing exercises, such as walking, climbing stairs and dancing for 30 minutes a day, 5 days a week, is recommended to improve bone density.

Conclusion

Diabetes and osteoporosis are increasingly prevalent diseases. Diabetes is an important clinical risk factor for osteoporosis and fracture, and as clinicians it is important to remember this association when managing people with diabetes. Diabetes-related complications, hypoglycaemia and obesity could increase the risk of falls and fragility fracture. HbA$_{1c}$ targets should be individualised taking into consideration age, frailty, diabetes complications and falls risk.

While there is much to learn regarding the associations between diabetes, osteoporosis and fractures, it is important to recognise the value of performing a multifactorial fracture risk assessment, including falls risk. Tools are available to conveniently assess this risk and measurement of BMD by performing a DXA scan may provide additional useful information to help target those patients who are most at risk of fracture with appropriate fracture prevention drug therapies. The value of lifestyle

modification to address fracture and falls risk cannot be underestimated. It is also convenient that the lifestyle modifications required to optimise bone health very much overlap with the lifestyle guidance that is offered to optimise the management of the underlying diabetes and obesity. It is important, where possible, to ensure that our messages to patients pertaining to lifestyle factors are aligned and overlap as much as possible, rather than conveying different sets of instructions for different disease areas. This is where diabetes and osteoporosis management from a self-help perspective very much align. ■

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