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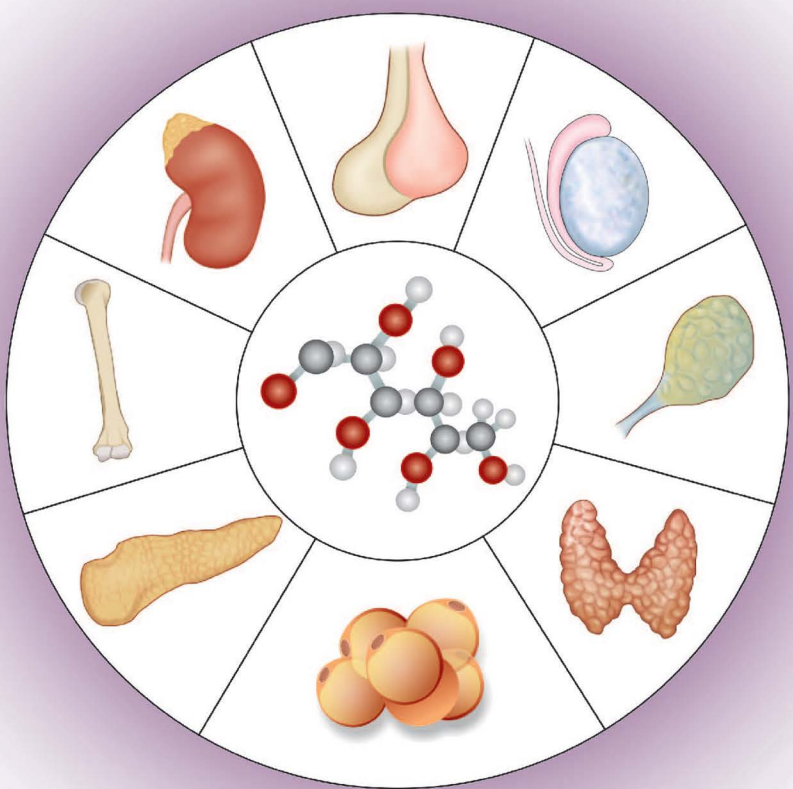
GLUCOCRINOLOGY

The Relationship between Glucose and Endocrine Function



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4
CHAPTER

Glucocrinology of Parathyroid and Bone Mineral Metabolism

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INTRODUCTION

The endocrine system is composed of glands that secrete hormones directly into circulation to regulate the function of distant target organs. Diabetes mellitus (DM) affects all organs in the body and one of the major focus of management of DM is the prevention, detection and treatment of this involvement of multiple organ systems. While a lot has been discussed about the involvement of cardiac, neurologic, renal, gastrointestinal and ophthalmic systems (the well-known micro- and macrovascular disease), relatively little is described about the relationship of endocrine system per se with DM. Glucocrinology is the study of medicine that relates to the relationship between glucose physiology and the endocrine system. In this chapter, we explore the bidirectional relationship between bone mineral metabolism and glucose homeostasis, in health and disease.

Bone Mineral Metabolism and Vitamin D/Parathyroid System

Bones provide strength and support for the body, and serve as an attachment for skeletal muscles. Bone is an extremely active organ at the metabolic level and is relevant in the regulation of several endocrine functions. Bones are the major source of calcium, act as a buffer against acidosis and adsorb toxins. Calcium, phosphate and magnesium are minerals vital to the functioning of all cells. Parathormone (PTH) and vitamin D (Vit D) are the major regulators of mineral metabolism. PTH and Vit D form a tightly controlled feedback cycle, PTH being a major stimulator of Vit D synthesis in the kidney while Vit D exerts negative feedback on PTH secretion. The major function of PTH and major physiologic regulator is circulating ionized calcium. The effects of PTH on gut, kidney and bone serve to maintain serum calcium within a tight range. PTH has a reciprocal effect on phosphate metabolism. In contrast, Vit D has a stimulatory effect on both calcium and phosphate homeostasis, playing a key role in providing adequate mineral for normal bone formation. Both hormones act in concert with the more recently discovered fibroblast growth factor 23 (FGF23) and

klotho, hormones involved predominantly in phosphate metabolism, which also participate in this closely-knit feedback circuit.

GLUCOSE PHYSIOLOGY IN RELATION TO BONE MINERAL METABOLISM

Calcium is an important second messenger in many intracellular processes, including both first-phase and second-phase insulin secretion. A rise in intracellular calcium is required for insulin release from β-cells by exocytosis. Functional impairment of voltage-gated calcium channels has been documented in individuals with type 2 diabetes mellitus (T2DM), which may mediate the insulin secretory defects.[1]

Calcium also affects the affinity and sensitivity of insulin receptor to insulin in target tissues, especially skeletal muscle. Intracellular calcium is involved in the insulin-stimulated glucose uptake into myocytes. In addition, the multiple hormones that regulate liver glycogenolysis, gluconeogenesis and glucose oxidation do so by calcium-signaling mechanisms.[2] Animal models of T2DM and obesity have demonstrated abnormal cellular calcium homeostasis.[2] Furthermore, abnormal intracellular calcium homeostasis may also be the link between insulin resistance (IR) and hypertension.

Role of Vitamin D in Glucose Homeostasis

Vitamin D is present in the body in several forms like cholecalciferol, ergocalciferol and calcitriol [1,25$(OH)_2$D], which is the active form which acts on the cells affecting transcription. Its primary role is ensuring adequate absorption of dietary calcium. Vit D exerts autocrine and paracrine effects such as direct intracellular effects via its receptors and the local production of 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3], especially in muscle and pancreatic β-cells. 1,25$(OH)_2$D also acts as a hormone causing immunomodulatory effect on gene transcription at the cellular level. Indeed, it can downregulate mechanisms connected with adaptive immunity, induce immunological tolerance and decrease autoaggression-related inflammation.[3] These properties provide the basis for a preventive and therapeutic role of Vit D.

Recent research suggests that Vit D also regulates metabolism, and influences both insulin secretion and insulin action. This has been depicted in Table 1. Vit D promotes pancreatic β-cell function via direct genomic action, regulating the transcription of target genes via Vit D responsive elements. Thus, it enhances insulin secretion and synthesis and promotes β-cell survival by inhibiting cytokine-induced β-cell apoptosis.[3] Further, Vit D regulates calbindin (a cytosolic Ca-binding protein in β-cells) and intracellular calcium. Hence, it acts as a modulator of depolarization-stimulated insulin release.[4] Calcium is needed for insulin secretion by β-cells. Vitamin D deficiency (VDD) or defects in activation/action and resultant hypocalcemia have been shown to be associated with reduced glucose-stimulated insulin secretion.

Chronic inflammation is one of the important factors responsible for IR and T2DM. Macrophages and dendritic cells express the enzymes vitamin D-25-hydroxylase and 1α-hydroxylase and can produce 1,25$(OH)_2$D.[3] Several studies have supported the role of Vit D and 1,25$(OH)_2$D as anti-inflammatory agents. The

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TABLE 1 **Effects of vitamin D [1,25(OH)$_2$D] on glucose homeostasis.**

	β-cell function	Insulin sensitivity
Rapid nongenomic effects	• Regulates intracellular calcium to modulate insulin release	• Increases insulin gene transcription and insulin synthesis • Anti-inflammatory effects • Reduces β-cell apoptosis by downregulation of Fas pathway • Increases calbindin that acts as a buffer for intracellular calcium—regulates intracellular calcium
Genomic effects	• Regulates intracellular calcium—improved insulin sensitivity • Reduces the activity of renin–angiotensin system by inhibiting secretion of renin	• Increases insulin receptor gene expression • Increases activity of PPARδ, improved fatty acid metabolism • Reduces expression of inflammatory cytokines

(1,25(OH)$_2$D: calcitriol; PPARδ: peroxisome proliferator-activated receptor delta)

regulation of serum calcium via PTH and 1,25(OH)$_2$D following changes in dietary calcium and obesity has been proposed to mediate the effects of Vit D on IR.

Its effect on insulin sensitivity could also be due to the regulation of intracellular calcium levels within a narrow physiological range. In addition, Vit D modulates the expression of insulin receptors in adipose tissue and skeletal muscle.[4] By activating peroxisome proliferator-activated receptor delta (PPARδ), it also plays a role in fatty acid metabolism. Vit D is also a negative regulator of the renin–angiotensin–aldosterone system (RAAS) and it suppresses renin formation from the kidneys. VDD has been associated with IR.

Role of Parathormone in Glucose Homeostasis

The role of PTH in glucose regulation is not completely clear. It increases the generation of 1,25(OH)$_2$D that influences both insulin secretion and sensitivity. However, high PTH as seen in primary or secondary hyperparathyroidism is associated with increased IR and greater prevalence of diabetes.

Parathormone in mice models have been shown to increase cytosolic calcium and impair insulin release through adenosine triphosphate (ATP)-dependent potassium channels. In addition, the rise in intracellular calcium also induces IR in target cells.[5] PTH stimulates cyclic adenosine monophosphate (cAMP) production in a calcium-dependent manner, and through activation of protein kinase C, it increases phosphorylation of insulin receptor substrate-1 (IRS-1). Resultant reduced expression of IRS-1 and glucose transporter 4 (GLUT4) are associated with decreased peripheral glucose uptake and IR.[5]

Role of Osteokines in Glucose Homeostasis

Bone is an important endocrine organ that secretes several bone-specific proteins with widespread effects.[6] The osteokines that have important metabolic effects include osteocalcin (OC) and osteoprotegerin.

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- *Osteocalcin*: OC is secreted by osteoblasts and stored in the bone extracellular matrix in its carboxylated form, which binds with high affinity to hydroxyapatite. Undercarboxylated OC is readily secreted into circulation. In the active undercarboxylated form, OC has been found to promote insulin expression and secretion via OC receptor on β-cells.[6] OC also stimulates insulin secretion indirectly by promoting the release of glucagon-like peptide-1 (GLP-1) in intestinal epithelial cells. Undercarboxylated OC also increases insulin sensitivity in muscle, adipose tissue, and liver and was found to increase glucose and fatty acid uptake in rodents.[6] The improvement in insulin sensitivity is mediated by means of upregulation of adiponectin, an adipokine that facilitates insulin sensitivity.
  Several cross-sectional studies of patients with T2DM have reported negative associations between higher serum levels of OC and fasting plasma glucose and hemoglobin A1c (HbA1c) and a higher risk for prediabetes and T2DM among individuals with lower baseline serum levels of OC. Weight reduction and aerobic exercise are associated with increase in OC levels[6]
- *Lipocalin-2*: The osteoblast-derived lipocalin-2 (LCN2) has been found to regulate appetite through hypothalamic action. This increase in LCN2 seems to contribute to postprandial satiety, as restoration of LCN2 levels in *Lcn2* null mice corrected the rebound hyperphagia induced by fasting.[7] The LCN2 levels are higher in normal weight individuals and lower in obese individuals. When rodents were administered by exogenous LCN2, they experienced reduced food intake, body weight and fat mass, along with improved glucose tolerance, insulin secretion and energy expenditure
- *Bone morphogenetic protein 7*: Osteocyte-secreted molecules such as bone morphogenetic protein 7 (BMP7) and sclerostin may also have a potential role in diabetes management. BMP7 has long been reported to reduce food intake and stimulate brown adipogenesis, thus improving energy metabolism.[7] BMP7 was positively linked with the insulin secretion index and fasting insulin, indicating that the protein may prompt insulin secretion and fasting insulin
- *Sclerostin*: Sclerostin has been shown to have positive associations with body mass index, fat mass and IR. Some studies have recorded elevated sclerostin levels in patients with impaired glucose regulation, type 1 diabetes mellitus (T1DM) and T2DM; although findings from other research on the topic have varied[7]
- *Osteoprotegerin (OPG)*: It is a glycoprotein of the tumor necrosis factor superfamily that prevents the binding of receptor activator for nuclear factor κB ligand (RANKL) to RANK, and inhibits osteoclastogenesis. OPG increases IR, inflammation, and proliferation of endothelial and vascular smooth muscle cells and may have a role in atherogenesis.[6] High serum OPG levels are associated with IR, metabolic syndrome (MS), and micro- and macrovascular complications in diabetes.

Effects of Insulin on Bone

Insulin is an osteogenic hormone. It was earlier regarded that the anabolic effects of insulin may be mediated due to its homology with insulin-like growth factor-1 (IGF-1). However, insulin acts via insulin receptors on osteoblasts, with increase in osteoblast differentiation and proliferation, glucose uptake and collagen formation.

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Thus, insulin results in an increase in bone mass.[8] It also reduces the expression of OPG and increases OC. With reduced OPG, differentiation of osteoclasts is increased. Resultant low pH in the resorption lacunae increases decarboxylation of OC, which has a positive effect on both insulin secretion and sensitivity.[8]

In addition, gastric inhibitory polypeptide (GIP) receptors are present in osteoblasts, osteoclasts, and osteocytes and it is believed to mediate postprandial reduction in bone resorption. Adiponectin also seems to influence bone by increasing proliferation of osteoblasts and reducing osteoclast formation. The net effect is an increase in bone mass.

While IGF-1 is a well-known anabolic agent in bone, evidence is beginning to accumulate that its homolog, insulin, also has some anabolic properties for bone. There is specific evidence that insulin may work to stimulate osteoblast differentiation, which in turn would enhance production of OC, the osteoblast-produced peptide that can stimulate pancreatic β-cell proliferation and skeletal muscle insulin sensitivity. It is uncertain whether insulin stimulates bone directly or indirectly by increasing muscle work and therefore, skeletal loading. We raise the question of the sequence of events that occurs with IR, such as T2DM. Evidence to date suggests that these patients have lower serum concentrations of OC, perhaps reduced skeletal loading and reduced bone strength as evidenced by microindentation studies.

GLUCOVIGILANCE IN VITAMIN D DEFICIENCY, PARATHYROID DISORDERS AND BONE DISEASE

After noting the glucocrinological considerations of bone mineral metabolism, it is clear that aberrations in bone mineral metabolism will warrant for vigilance for glycemic abnormalities.

Vitamin D Deficiency

Vitamin D deficiency has been linked to an increased risk of T1DM, T2DM and gestational diabetes mellitus (GDM).

- *Type 1 diabetes mellitus*: T1DM involves immune-mediated destruction of β-cells. Vitamin D receptor (VDR) is expressed in antigen-presenting cells (macrophages and dendritic cells) and activated T-cells. VDR is involved in the activation of several intracellular pathways involved in the proliferation, differentiation and function of cells of immune system (both innate and adaptive). $1,25(OH)_2D$ decreases the maturation of dendritic cells and also inhibits the release of proinflammatory cytokines, interleukin-12 (IL-12), IL-2, interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α). These immunomodulatory and anti-inflammatory effects of $1,25(OH)_2D$ can lead to the protection of target tissues, such as β-cells.[9]

  Vitamin D deficiency has been associated with an increased risk of T1DM in epidemiological studies. A higher incidence of T1DM has been reported in association with low sunlight exposure. At the same time, high doses of $1,25(OH)_2D$ were found to suppress insulitis and occurrence of hyperglycemia in T1DM nonobese mice.[9]

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Studies suggest that Vit D supplementation may reduce the risk of T1DM. Supplementation in early life was associated with a 33% reduced risk of T1DM in the European Diabetes (EURODIAB) study. In a meta-analysis of eight studies, Vit D supplementation of infants was associated with a 29% risk reduction, but maternal supplementation did not reduce the risk in offspring.[10] However, this is not substantiated by large prospective studies. Structural analogs of Vit D, that are not associated with risk of hypercalcemia or tissue calcification, are under exploration for their potential role in the prevention of T1DM and other autoimmune diseases and in immunomodulatory therapy following islet cell transplantation[10]

- *Type 2 diabetes mellitus*: There exists a positive relationship between 25-hydroxy-vitamin D [25(OH)D] levels and insulin sensitivity, and an inverse relationship with the risk of T2DM in cross-sectional studies. VDD is associated with obesity, IR, MS and T2DM. The Nurses' Health Study reported a 33% lower risk of T2DM in women with calcium intake of at least 1,200 mg and Vit D intake of 800 IU daily, compared to those with intake less than 600 mg and 400 IU, respectively. Higher calcium intake in Women's Health Study was also associated with lower prevalence of MS.[11]

  However, it is unclear whether VDD increases the risk of T2DM or occurs due to clustering of risk factors that increase the risk for both VDD and T2DM. Obesity is associated with increased sequestration of Vit D in adipose tissue. Poor dietary habits and sedentary lifestyle may also be contributory. Likewise, it is uncertain whether Vit D supplementation reduces the risk of diabetes.[12] Vit D has been shown to improve IR, reduce conversion from prediabetes to diabetes, and improve glycemic control in small studies. However, most of the studies done in this area are underpowered and there is lack of properly done randomized control trials.

  There is increasing evidence of an association of complications of T2DM with VDD, most notably with presence of diabetic peripheral neuropathy, diabetic kidney disease and macrovascular disease.[11] However, evidence that Vit D supplementation improves the risk of complications is lacking
- *Gestational diabetes mellitus*: VDD is common in pregnancy. Several studies have evaluated the potential role of Vit D supplementation in prevention of GDM. Observational studies provide conflicting evidence as to whether low serum 25(OH)D levels are associated with GDM. Two recent systematic reviews concluded that Vit D deficiency is associated with a higher risk of GDM.[13] Randomized controlled trial data remain limited. It will be important to understand whether supplementation with Vit D beyond what is contained in routine prenatal vitamins will prevent GDM or improve glucose tolerance for women with GDM.

To conclude, although hypovitaminosis D is a described risk factor for DM, a cause and effect relationship has not been determined. Moreover, there is insufficient evidence that Vit D supplementation reduces the occurrence or progression of diabetes and its complications. Therefore, at present, there are no specific recommendations for screening for DM in hypovitaminosis D.

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Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) has been associated with IR, MS, impaired glucose tolerance (IGT) and diabetes. The main reason for IR seems to be hypercalcemia though hypophosphatemia has been attributed by some. IR not only increases DM risk but also may contribute to hypertension seen in PHPT. A high prevalence of diabetes has been reported in patients with PHPT across several cohorts. About 8% cases of PHPT had DM, which was higher than normal population. In a cohort of 105 consecutive patients with primarily asymptomatic PHPT, 40% had IGT and 15% overt diabetes on oral glucose tolerance test, compared to 25% and 5% of controls, respectively.[14] However, a higher prevalence of diabetes was not reported in a series of 609 patients with PHPT except for elderly subgroup.[15] Another group reported reduction in fasting and postmeal plasma glucose levels following parathyroidectomy.[16]

Therefore, all patients with PHPT should be screened for diabetes, with fasting and postmeal plasma glucose or oral glucose tolerance test. Glycemic control may improve in some patients following reduction of PTH levels after parathyroidectomy.[17] This may necessitate reduction in antidiabetic medications, including insulin. Hence, it is important to monitor glucose levels in diabetic patients who are undergoing surgery for PHPT as doses of insulin or oral antidiabetic medications may need to be reduced following parathyroidectomy.

Multiple endocrine neoplasia type 1 (MEN1) syndrome is characterized by PHPT in more than 90% patients and pancreatic islet cell tumors in 60–70% of patients. Of these, 40% are β-cell tumors or insulinomas. Any unprovoked hypoglycemia in a PHPT patient should raise the clinical suspicion of insulinoma and MEN1. Monitoring fasting glucose and insulin level is a routine part of protocol of monitoring of MEN1 patients, most of whom have PHPT.

Hypoparathyroidism

Autoimmune hypoparathyroidism is more commonly associated with T1DM as a part of autoimmune polyglandular syndromes. Therefore, an attempt should be made to screen for other endocrinopathies in patients with hypoparathyroidism.

OSTEOVIGILANCE IN DIABETES

With current medical advances, people with diabetes have improved survival and recent studies have shown that both T1DM and T2DM are associated with a significantly increased risk of vertebral, hip and all nonvertebral fractures due to osteoporosis. Altered bone quality appears to correlate with long standing and poorly controlled DM, suggesting the skeleton be viewed as a target for diabetic complications.

The risk of hip fractures was reported to be increased in individuals with T2DM, both men [relative risk (RR) 2.8, 95% confidence interval (CI) 1.2, 6.6] and women (RR 2.1, 95% CI 1.6, 2.7). The association between hip fractures and diabetes was even stronger for T1DM (RR 6.3, 95% CI 2.6, 15.1).[18] There was a weak association of diabetes with fractures at other sites. Not only is the fracture risk higher in diabetic patients,

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fractures are associated with worse outcomes compared to nondiabetic individuals, such as delayed healing, wound infections, longer hospital stay, postoperative cardiac events and mortality.[19]

Factors Associated with Increased Fracture Risk in Diabetes

Several factors might influence the fracture risk in diabetes and these are discussed here and enlisted in Table 2.

As discussed earlier, diabetes has been associated with low Vit D levels that may impact long-term musculoskeletal health. In addition, hyperglycemia promotes adipogenesis rather than osteogenesis, impairs osteoblast growth, increases osteoblast apoptosis and inhibits osteoclastogenesis.[20] The sensitivity of osteoblasts and osteoclasts to insulin or hyperglycemia in individuals with T2DM, however, is undetermined. Osteoporosis is conventionally defined as low bone mass along with microarchitectural deterioration of bone. The bone disease correlates with levels of advanced glycosylation end products in diabetes. Indeed, longer disease duration and poor glycemic control are associated with greater risk.[20]

Both types of DM are associated with changes in bone turnover, but there are different patterns. Patients with T1DM have impaired osteoblastic bone formation, proven by low levels of bone-formation markers, like OC or alkaline phosphatase.[20] Most clinical studies investigating bone turnover markers (BTM) have reported lower bone turnover in T2DM. Bone resorption markers like C-terminal cross-linked

TABLE 2 **Pathogenesis of increased fracture risk in diabetes.**

	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Microarchitectural changes and bone strength	• ↓ cross-sectional bone area • ↓ volumetric BMD (trabecular bone) • Thin cortices and trabeculae • ↑ trabecular separation	• ↑ cortical porosity • ↓ bone material strength
Pathogenesis	• ↓ IGF-1 • Chronic hyperglycemia—accumulation of advanced glycation end products (AGEs) • Microvascular bone damage	• ↓ IGF-1 • Obesity (↑ adipokines, inflammatory factors) • Altered composition of marrow fat • Low-grade chronic inflammation • Chronic hyperglycemia—accumulation of AGEs • Microvascular bone damage
Bone turnover	• Impaired osteoblastic bone formation • Possibly increased bone resorption	• Decreased osteoblastic bone formation • Decreased bone resorption
Neuropathy	Increased risk of falls	Increased risk of falls
Pharmacological	–	Antidiabetic drugs—thiazolidinediones, SGLT-2 inhibitors

(BMD: bone mineral density; IGF-1: insulin-like growth factor-1; SGLT-2: sodium-glucose cotransporter-2)

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telopeptide (CTX) of type I collagen and tartrate-resistant acid phosphatase 5b (TRAP5b) and PTH, and bone formation markers like P-procollagen type 1 amino-terminal propeptide (P1NP) and OC, are all decreased in T2DM.[20] Some markers are lower in patients with T2DM than in those with T1DM as is shown in Table 3.

In addition, concomitant presence of celiac disease worsens bone health in T1DM.[21] Insulin therapy, especially in T1DM, is associated with increased bone mass, indicating bone anabolic effects of insulin or the normalization of bone remodeling due to glycemic control, correction of acidosis, or increased body weight.[22]

Other factors associated with poor bone quality and fracture risk include comorbidities and complications, such as chronic kidney disease, peripheral and autonomic neuropathy, visual impairment, and an increased risk of falls. Antidiabetic medications may also have an effect on bone health. PPAR-γ agonists like pioglitazone drive differentiation of mesenchymal stem cells toward adipocytes rather than osteoblasts and are associated with an increased risk of osteoporosis and fractures. Bariatric surgery for the management of obese T2DM also contributes to bone loss by augmenting nutritional deficiencies, sarcopenia, altered adipokines, sex hormones, and central signaling pathways. Therefore, bone density should be regularly monitored in postbariatric surgery patients.[23]

Prevention and Management of Fracture Risk in Diabetes

From the earlier discussion, it is clear that osteovigilance must be maintained in the diabetes clinic. A simple strategy would be to ensure adequate calcium and Vit D supplementation, nutrition and physical activity for optimal musculoskeletal health. Assessment of fracture risk using tools such as Fracture Risk Assessment Tool (FRAX) may be useful, but has been found to underestimate the risk of fractures in diabetic patients.[24]

TABLE 3 **Bone turnover markers in type 1 and type 2 diabetes mellitus.**

Bone markers in diabetes		T1DM compared with controls	T2DM compared with controls
Bone formation	Osteocalcin	↓	↓
	Alkaline phosphatase	↓	= ↑
	P1NP	↓	↓
Bone resorption	CTX	↓	↓
	TRAP5b	↓	↓
	Pyridinoline	↑	↓
	Deoxypyridinoline	↑	↓ =
	PTH	↓	↓
	Sclerostin	=	↑
	s-RANKL	↓ =	NA
	OPG	↓	↑

(CTX: C-terminal cross-linked telopeptide; NA: not assessed; OPG: osteoprotegerin; P1NP: procollagen type 1 amino-terminal propeptide; PTH: parathormone; s-RANKL: soluble receptor activator for nuclear factor κB ligand; T1DM: type 1 diabetes mellitus; TRAP5b: tartrate-resistant acid phosphatase 5b; =: no significant difference)

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Finally, since DM is associated with altered bone health and an increased risk of fractures, we have to be cautious about the effect that antidiabetic drugs may have on bone metabolism.[25] Table 4 summarizes the effects of various antidiabetic medications on bone health.

Fall prevention, optimization of glycemic control and management of comorbid conditions should be a priority. Impact of current therapies of osteoporosis on DM as well as their utility in DM-specific population has not been well-studied, though data of their efficacy has been largely reassuring. Bisphosphonates reduce the secretion of undercarboxylated OC, but did not have clinically meaningful effects on glycemic control in diabetic patients. Similarly, no negative effect on glucose levels or risk of diabetes has been reported with teriparatide or denosumab.[26]

TABLE 4 **Effects of antidiabetic medications on bone health.**

Antidiabetic medications	Effects on bone
Metformin	• Stimulates osteoblast differentiation through inducing AMPK/USF-1/SHP expression by increasing AMPK-dependent runt-related transcription factor 2 (RUNX2) expression • Protects MG63 osteoblast-like cells against hyperglycemia by promoting type 1 collagen, osteocalcin and alkaline phosphatase
Sulfonylureas	• Stimulate proliferation and differentiation of osteoblast through activation of PI3K/Akt pathways • Enhance the osteoblastic markers such as alkaline phosphatase and osteocalcin
Thiazolidine-diones	• PPARγ activation upregulates adipogenesis in the bone marrow and decreases osteogenesis by decreased stem cell differentiation into osteoblasts • Enhance osteocyte apoptosis and sclerostin level • Cause histomorphometric changes by affecting osteoblasts and osteoclasts
DPP-4 inhibitors	• Inhibit bone resorption markers such as serum CTX and improve bone loss
Glucagon-like peptide-1 receptor agonists	• Promote bone formation via Wnt signaling pathway • Dual regulatory action on bone turnover by attenuating bone resorption through elevation of receptor activator for nuclear factor κB ligand/ osteoprotegerin (RANKL/OPG) ratio and favors bone formation by increasing the expression of α-1 collagen, osteocalcin, alkaline phosphatase and RUNX2 • All in vitro effects with no reduction in fracture risk in large clinical studies
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	• Hyponatremia due to SGLT-2 inhibition may be associated with osteoporosis • Increase the bone resorption markers CTX, PTH, and decreases 25-hydroxyvitamin D
Insulin	• Improves fracture healing by enhanced expression of vascular endothelial growth factor (VEGF) • Anabolic effect on bone through increased IGF-1 and GLUT4 levels

(AMPK: AMP-activated protein kinase; CTX: C-terminal cross-linked telopeptide; DPP-4: dipeptidyl peptidase-4; GLUT4: glucose transporter type 4; IGF-1: insulin-like growth factor-1; PPARγ: peroxisome proliferator-activated receptor gamma; PTH: parathormone; SHP: small heterodimer partner; USF-1: upstream stimulatory factor-1)

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CONCLUSION

Vitamin D, PTH and calcium are intricately involved in glucose metabolism regulation. Vit D has direct effect on insulin secretion and sensitivity and also regulates glucose homeostasis through immune modulation. Role of osteokines in glucose metabolism is increasingly being identified. Due to its impact on β-cell function and insulin sensitivity, VDD has been linked with the development of T1DM and T2DM. Association of VDD with complications of DM has also been documented, but there is insufficient evidence to suggest that Vit D supplementation reduces the risk or improves glycemic control. PHPT has been associated with IR, MS, and T2DM and glycemic control may improve after parathyroidectomy. In addition, individuals with autoimmune hypoparathyroidism may have T1DM.

The fracture risk is increased in individuals with diabetes and is associated with poor bone microarchitecture. A heightened vigilance for bone health, osteoporosis and fracture risk is needed in diabetes care. Good clinical practice demands conscious vigilance of bone metabolism parameters in patients with DM and its complications. More research is clearly needed to understand the complex interaction between bone mineral health and glucose homeostasis. Such research may provide with opportunities to develop drugs that target both glucose metabolism and skeletal health.

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