

Calcium homeostasis in diabetes mellitus

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Diabetes mellitus (DM) is becoming a lifestyle-related pandemic disease. Diabetic patients frequently develop electrolyte disorders, especially diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. Such patients show characteristic potassium, magnesium, phosphate, and calcium depletion. In this review, we discuss a homeostatic mechanism that links calcium and DM. We also provide a synthesis of the evidence in favor or against this linking mechanism by presenting recent clinical indications, mainly from veterinary research. There are consistent results supporting the use of calcium and vitamin D supplementation to reduce the risk of DM. Clinical trials support a marginal reduction in circulating lipids, and some meta-analyses support an increase in insulin sensitivity, following vitamin D supplementation. This review provides an overview of the calcium and vitamin D disturbances occurring in DM and describes the underlying mechanisms. Such elucidation will help indicate potential pathophysiology-based precautionary and therapeutic approaches and contribute to lowering the incidence of DM.

Keywords: calcium, calcium channels, diabetes mellitus

Introduction

The vitamin D precursor 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) functions via genomic and nongenomic mechanisms in a numerous of cell types [9,34,53]. Moreover, the paracrine and autocrine modes of action of 1,25(OH)₂D₃ appear to be important in several cell types, including adipocytes and secretory cells in the pancreas, duodenum and kidney [24,25,27,48]. Vitamin D, dietary precursor of 1,25(OH)₂D₃, is often considered important nutrient for maintaining good health for preventing diseases [33]. In addition, 1,25(OH)₂D₃ has an important role in the regulation of cellular Ca²⁺ signaling, which is linked to cellular responses, signaling and secretion [46,47,50]. Sustained Ca²⁺ signals triggered by 1,25(OH)₂D₃ have been researched for the regulation of apoptosis, a process that can determine cell death in diseases such as obesity and type 2 diabetes (T2DM) [5,36,46,47]. Moreover, 1,25(OH)₂D₃-induced Ca²⁺ signals (Ca²⁺ oscillations) can regulate insulin secretion from pancreatic β-cells [51]. Vitamin D status has been linked to insulin resistance and T2DM in observational studies [56,62]. Vitamin D deficiency and dysregulation of vitamin D metabolism have been associated with an increased risk of obesity and T2DM;

however, the mechanism for an association between vitamin D and disease such as obesity and T2DM remains unclear [45,48,53]. In secretory cells, vitamin D has protective against apoptosis due to the transient and localized nature of the Ca²⁺ signals induced by 1,25(OH)₂D₃ [43]. Elucidation of the role of 1,25(OH)₂D₃ in the regulation of cellular Ca²⁺ signaling in obesity and T2DM may lead to the development of novel therapeutic and preventive modalities for these diseases.

The purpose of this review is to discuss the roles of calcium in the regulation of insulin secretion and insulin resistance, with an emphasis on signaling pathways that involve vitamin D-dependent cellular Ca²⁺ signaling.

Calcium and vitamin D metabolism and biological function including insulin secretion

It has been reported that 1,25(OH)₂D₃ can regulate insulin secretion from pancreatic β-cells [45,52]. The rapid increase in intracellular calcium ([Ca²⁺]_i) triggers insulin release. The role of 1,25(OH)₂D₃ in insulin secretion derives from its effects on Ca²⁺ influx, mobilization, and buffering in pancreatic β-cells [39]. 1,25(OH)₂D₃ induces rapid (within 5–10 sec), synchronous, sinusoidal [Ca²⁺]_i and oscillations in pancreatic β-cells, effects

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that are independent of glucose level [51]. In pancreatic β -cells, it has been suggested that organelles contribute only marginally to the dissipation of large cytosolic calcium increases [8]. Calcium clearance is mainly achieved by storage in the endoplasmic reticulum (ER) via the sarcoplasmic ER calcium ATPase (SERCA) channel and by excreting to the extracellular space via the plasma membrane calcium ATPase and $\text{Na}^+/\text{Ca}^{2+}$ exchanger [8]. In addition, $1,25(\text{OH})_2\text{D}_3$ stimulates Ca^{2+} influx through voltage-dependent Ca^{2+} channels and voltage insensitive Ca^{2+} channels as well as via Ca^{2+} mobilization from the ER stores through ryanodine receptors but not through the activation of IP3Rs [49]. The effects of $1,25(\text{OH})_2\text{D}_3$ on intracellular Ca^{2+} in pancreatic β -cells has been linked to plasma and ER membrane bound vitamin D receptors [17,35]. Pulsatile insulin release from pancreatic β -cells is related with frequency of Ca^{2+} oscillations. In the same mechanism, insulin release oscillations are proportional to the $1,25(\text{OH})_2\text{D}_3$ concentration [51,52]. The physiological significance of the $1,25(\text{OH})_2\text{D}_3$ effects on Ca^{2+} in pancreatic β -cells (Ca^{2+} oscillations) may be related to its regulatory roles of insulin secretion under steady-state glucose concentrations in blood, *e.g.*, during fasting when $1,25(\text{OH})_2\text{D}_3$ regulate insulin secretion by independent with glucose concentration.

Calcium and vitamin D supplementation attenuates symptoms of diabetes mellitus

Prospective studies have reported varying results regarding the association between calcium intake and risk of T2DM [10,40,60]. A large, prospective cohort study of 41,186 subjects found that higher calcium intake was not associated with the risk of T2DM. In contrast, those who consumed calcium supplements had a decreased risk of T2DM compared to the risk among non-supplement users [60]. However, among supplement users, there was no association between the amount or duration of calcium supplementation and a lower risk of T2DM [60]. Another large prospective study reported contrasting results with total calcium intake being inversely associated with incident T2DM. Those who consumed more than 1,200 mg/d calcium via diet and supplements had a 21% reduced risk of development of incident T2DM than the risk among those who consumed less than 600 mg/d. However, among subjects with a calcium intake via supplements only, there was an 18% lower risk of T2DM in those who consumed more than 500 mg/d than in those who consumed less than 250 mg/d [40]. A meta-analysis of these two prospective studies reported an 18% decrease in the risk of incident T2DM in the highest calcium intake group (661–1,200 mg/d) from the risk in the lowest calcium intake group (219–600 mg/d) [40,60]. Although some results from studies on calcium intake and risk of diabetes are conflicting, the results do indicate a potential link between the two. The optimal intake of calcium that can reduce the risk of T2DM has not yet been

determined; however, a meta-analysis has indicated that a calcium intake of more than 600 mg/d is desirable, while an intake over 1,200 mg/d is preferred [40]. In addition, vitamin D may influence both insulin secretion and sensitivity. The relationship between T2DM and vitamin D has been based on cross-sectional and prospective studies, although a conclusive relationship has not yet been described. Previous studies differ in their designs and in the recommended daily doses for vitamin D in non-skeletal diseases and DM patients [2,39,57]. Thus, large, well designed, and controlled studies on the potential role of vitamin D and calcium in the prevention and management of T2DM are required to clarify the relationship among calcium, vitamin D, and glucose homeostasis in T2DM.

Calcium-associated proteins and diabetes mellitus

Cytosolic calcium is used for insulin secretion in pancreatic β cells. Calcium channels in cytoplasm, ER, and mitochondria help to maintain intracellular calcium homeostasis. In an experimental type 1 DM (T1DM) model, there were changes observed in the expressions of calcium-associated proteins and the calcium channel. Several calcium transport-related factors (CALM, CaBP-9k, CALR, CANX, Cav1.2, and PMCA) have been evaluated [1]. The levels of CALM-2, CALM-3, and CaBP-9k become elevated after T1DM is induced in a mouse model [1]. With regard to cellular calcium-channel calcium, decreased expression of Cav1.2 and increased expression of PMCA indicate that the concentration of intracellular calcium is being gradually depleted. These results indicate that calcium metabolism of T1DM model is modulated by various calcium channels. In addition, the ER quality control genes CALR and CANX are downregulated by streptozotocin administration. Administration of streptozotocin can produce ER stress and apoptosis of pancreatic cells [1]. CALR and CANX are chaperone proteins that are involved in protein folding in the ER [13]. Dysregulation of ER calcium-transporters such as SERCA and IP3R could induce ER stress [13]. Disruption of calcium homeostasis by streptozotocin is associated with the ER. SERCA2a and 2b are both responsible for calcium influx from the cytosol to the ER. SERCA2b expression was significantly downregulated after streptozotocin treatment. In contrast, IP3R levels were upregulated by streptozotocin. The expression of these ER calcium-channel transporters implies depletion of the ER calcium pool, demonstrating that ER calcium concentrations are decreased by streptozotocin treatment, resulting in ER stress (Fig. 1).

Relationship between hypocalcemia and diabetes

Patients with DM have an increased risk of developing acute renal failure due to volume depletion [19]. Under conditions of renal failure, phosphorus cannot be excreted by the

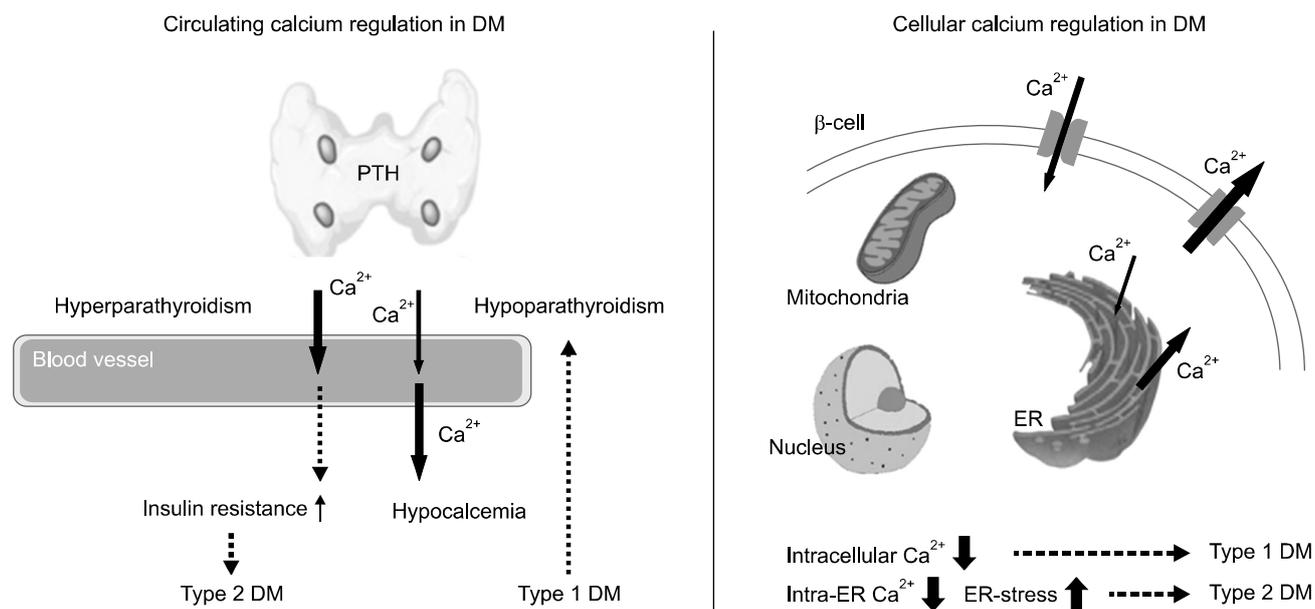


Fig. 1. Schematic summary illustrating the relationship between calcium and diabetes. Hyperparathyroidism is related to long-term insulin resistance and relative insulin insufficiency and can lead to overt diabetes mellitus (DM) or deterioration of glycemic control in established DM. Patients with DM have an increased risk for development of acute renal failure due to volume depletion. In particular, parathyroid hormone (PTH) secretion in DM patient tends to decrease. Disrupted calcium homeostasis facilitates renal failure. In DM patients, cellular calcium depletion occurs. In type 1 DM, not only is there diminishment of pancreatic β cells, but both intracellular and intra-endoplasmic reticulum (ER) calcium are depleted. In type 2 DM intra-ER calcium is depleted, which induces ER stress.

malfunctioning kidney, leading to hyperphosphatemia [28]. A hyperphosphatemic condition induces hypocalcemia by interfering in phosphorus excretion in the malfunctioning kidney [6]. In addition, phosphate binds ionized calcium and removes calcium from the bloodstream. Advanced chronic renal insufficiency may be associated with hypocalcemia due to hyperphosphatemia or low levels of blood vitamin D [28]. Like hyperphosphatemia, hypomagnesemia is another cause of hypocalcemia in diabetic patients [38]. Mg^{2+} depletion leads to hypocalcemia through impaired secretion of parathyroid hormone (PTH) or via bone and renal tubular resistance to the action of PTH [57]. Vitamin D deficiency and administration of diuretics such as furosemide administration may also induce hypocalcemia. DM patients have an increased prevalence of hypoparathyroidism [57]. Moreover, a small downward shift in PTH secretion in patients with T1DM, as well as decreased parathyroid gland responsiveness to hypocalcemia in DM patients, have been reported [22,44]. Ionized calcium binds to negatively charged sites on protein molecules. Therefore, hypoalbuminemia is associated with pseudohypocalcemia, which is a reduction in total serum calcium concentration even though there are normal ionized serum calcium levels [28].

Relationship between hypercalcemia and diabetes

The incidence of DM in primary hyperparathyroidism is approximately 8%, while that of primary hyperparathyroidism in DM is 1% [28]. Both values are about three-fold higher than the prevalence of each disease in the general population [58]. Hyperparathyroidism may be the result of long-term insulin resistance or insulin insufficiency, which leads to a DM condition or exacerbation of glycemic dysregulation in DM establishment [42,58]. An elevated intracellular free-calcium concentration via a decrease in normal insulin-stimulated glucose transport increases the requirement for insulin, makes over-produce and over-secrete of insulin, resulting in hyperparathyroidism-mediated insulin resistance [58]. Serum calcium level should be evaluated in diabetic patients because hyperparathyroidism has been linked to hypertension [21,58]. For T1DM patients, a high serum calcium level is a risk factor for autoimmune hyperparathyroidism associated with anti-calcium-sensing receptor autoantibodies [37]. Recently, a case of severe hypercalcemia [15 mg/dL (3.75 mmol/L)] with dehydration in diabetic ketoacidosis (DKA) was reported [29]. In DKA, which is a life-threatening complication of DM, a hypovolemic condition might be the most important causative factor for the occurrence of hypercalcemia [29]. Metabolic acidosis and bone

resorption decreases bone formation, and bone resorption is a process subsequent to severe insulin deficiency and metabolic acidosis [59]. As well as bone resorption, insulin growth factor-1 deficiency and hypophosphatemia are potential factors for hypercalcemia in DM [3,4,29,59]. In addition, medication such as thiazide diuretics for diabetic patients may result in hypercalcemia [18].

Classification of diabetes in dogs and cats

DM is a common disease in dogs and cats, although a full definition of DM in dogs has not been agreed upon. There are difficulties with developing such a definition due to the many different serum analyzers and glucometers used in veterinary medicine. In dogs, DM is commonly characterized by permanent hypoinsulinemia, and it resembles T1DM in humans [20,31] as there is no increase in c-peptide in response to insulin [20]. Moreover, DM in dogs requires exogenous insulin administration to avoid ketoacidosis [20,32]. Previous studies have reported that genetic and environmental factors are involved in the DM of dogs [12,15,16]. Dog leukocyte antigen haplotypes are involved in the increased risk of DM, and common alleles/haplotypes are observed in diabetes-prone breeds such as Samoyed and terriers [7]. Under hypoinsulinemic and diabetic conditions, dogs are sensitive to glucotoxicity [20]. In addition, as observed in humans, a variant of gestational diabetes is present in dogs [16]. In gestational diabetes in dogs, progesterone stimulates the production of growth hormone (GH) and increased GH leads to insulin resistance [16].

In contrast to dogs, the most common form of diabetes in cats is similar to T2DM in humans [26]. As in human T2DM, obesity in cats is major risk factors for DM [26,41,55]. Obesity in cats can alter the expression of several insulin-signaling genes, glucose transporters, and leptin resistant [30]. In healthy condition cats, islet amyloid polypeptide is a normal product of pancreatic β -cells and is stored in secretory vesicles with insulin. When insulin is secreted into the circulation system, islet amyloid is co-secreted with the insulin. In diabetic cats, islet amyloid is deposited in islets of the pancreas and can develop into islet glucotoxicity when exposed to prolonged hyperglycemia [41].

Relationship between unbalanced serum calcium level and diabetes in dogs and cats

The importance of calcium and vitamin D in calcium homeostasis and in the maintenance of skeletal health was indicated nearly a century ago [61]. In comparison with human retrospective studies and experimental studies with laboratory animals, the relationship between serum calcium level and DM is less fully described in veterinary research and animal retrospective studies [11,54]. Based on the small numbers of

available reports on dogs and cats, there is doubt about a connection between calcium and DM in dogs and cats as there are no reports connecting abnormal vitamin D metabolism with DM in dogs or cats. However, in dogs and cats with DM, there is an increased risk for the development of acute renal failure, which could develop into DKA. A severe form of DM is frequently accompanied by complications such as impaired renal function, malabsorption syndromes, acid-base disorders and cataract. Especially in renal failure with hypovolemic condition, there is an increased frequency of electrolyte abnormalities are lethal. Increased cell catabolism and severe hyperphosphatemia may occur in the presence of a malfunctioning kidney, resulting in hypocalcemia, which, in dogs, can result in an increased risk of cataract, a characteristic of the severe form of DM [14]. Hess *et al.* [23] demonstrated that serum total and serum ionized calcium levels were low in 221 diabetic dogs. Such results show that there is an apparent basis for a connection between an abnormal serum calcium level and DM in dogs. In dogs and cats, as in humans and laboratory animal models, the pancreatic islet insulin secretion mechanism is mediated by intracellular calcium ions. This suggests that administration of drugs to correct an abnormal blood calcium level could have a therapeutic effect in dogs and cats with DM and abnormal blood calcium levels.

Conclusion

Abnormalities related to homeostasis of calcium and vitamin D are common in diabetic patients and may be associated with increased morbidity and mortality. These abnormalities are particularly common in decompensated DM as well as in the presence of renal impairment or hypo- or hyperparathyroidism, which could result in impaired calcium homeostasis. Patients with DM often exhibit electrolyte disorders. The severe form of DM accompanies unbalanced electrolyte homeostasis in the body. Therefore, DM patients need strict control of blood glucose, which is of paramount importance in the prevention of blood calcium abnormalities. Successful management of DM and its associated disorders can best be accomplished by elucidating the underlying pathophysiologic mechanisms.

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Conflict of Interest

The authors declare no conflict of interests.

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