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Review

The role of vitamin D deficiency in the pathogenesis of type 2 diabetes mellitus

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SUMMARY

Physical inactivity, poor nutrition practices and obesity contribute significantly to the development of T2DM, however increasing evidence suggests that vitamin D deficiency may play a role in the pathogenesis of T2DM. T2DM manifests as a result of insulin resistance, increased hepatic glucose production and β-cell failure. Vitamin D deficiency increases insulin resistance and decreases insulin secretion in humans and animal models. Conversely, vitamin D supplementation restores insulin secretion and decreases insulin resistance and plasma glucose in humans and animal models. Vitamin D metabolites are thought to play a role in increasing insulin sensitivity and facilitating insulin exocytosis. Vitamin D has also been shown to decrease inflammatory cytokines which play a role in insulin resistance and β-cell apoptosis. Human studies have shown an inverse association between dairy intake and the risk of T2DM. The inverse association between vitamin D and dairy intake and the risk of T2DM may be due to the fact that dairy products are high in more readily absorbable calcium and are often fortified with vitamin D. Vitamin D deficiency is positively associated with insulin resistance and T2DM; however more research is needed to understand this relationship.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a serious metabolic disorder that has become increasingly prevalent, not only in North America but throughout the developing world. The number of people with diabetes is expected to more than double by 2030 from 171 million to an astounding 366 million people worldwide, ninety percent of which will have T2DM.[1,2] The exponential increase of T2DM is a great cause for concern as it is no longer a disease found solely in adults, but has become increasingly evident in children as well.[3] If left untreated, T2DM can lead to a multitude of chronic microvascular and macrovascular conditions such as retinopathy, nephropathy, neuropathy and cardiovascular disease (CVD).[4] CVD is the leading cause of death in individuals with T2DM.[5]

The pathogenesis of T2DM remains unknown as there are many malfunctioning mechanisms that occur simultaneously which can contribute to the development of the disease.[6,7] The rapid rise in obesity that has occurred in recent years is thought to have contributed significantly to the rise in T2DM. The enormity of the T2DM epidemic and its sequelae emphasize the importance of finding ways to prevent and/or ameliorate the deleterious effects of this disease. In addition to genetics which predisposes individuals to developing T2DM, there are also many environmental factors which contribute greatly to its development; these include physical inactivity, poor nutrition practices and obesity; however increasing evidence suggests that vitamin D deficiency (as measured by serum 25-hydroxyvitamin-D_3 concentration) may also contribute to the pathogenesis of T2DM.[8–14] Therefore, the focus of this review will be on the role of vitamin D deficiency in the pathogenesis of T2DM.

2. Vitamin D-synthesis, structure and function

Vitamin D can be obtained either through dietary intake or produced endogenously. It is found in foods such as oily fish (salmon, sardines, mackerel), egg yolks and fortified milk and juice;[18] however dietary intake only accounts for about 30% of the vitamin D obtained.[19] The primary route via which people obtain

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FFA, free fatty acids; GLUT-4, glucose transporter-4; HOMA-IR, homeostasis model assessment of insulin resistance; HSL, hormone sensitive lipase; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL-6, interleukin-6; IR, insulin resistance; IRS, insulin receptor substrate; OGIS, oral glucose insulin sensitivity; RCT, randomized controlled trial; ROS, reactive oxygen species; RXR, retinoid X receptor; TNF-α, tumour necrosis factor-α; T2DM, type 2 diabetes mellitus; UVB, ultraviolet B; VDR, vitamin D receptor; VDRE, vitamin D response element; 1α(OH)ase, 25(OH)D_3-1α-hydroxylase; 1,25$(OH)_2D_3$, 1,25-dihydroxyvitamin-D_3; 7-DHC, 7-dehydrocholesterol; 25(OH)ase, 25-hydroxylase; 25 $(OH)D_3$, 25-hydroxyvitamin-D_3.

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vitamin D is through exposure to ultraviolet B (UVB) sunlight at wavelengths between 290–315 nm, occurring predominantly in the summer months (June–July) in the Northern hemisphere (latitude ≥ 42° N).[20,21] UVB sunlight activates 7-dehydrocholesterol [7-DHC], a pre-cursor synthesized from cholesterol and found within the skin.[22] The activation of 7-DHC and synthesis to pre-vitamin D_3 within the skin and its subsequent isomerization to the inactive form, vitamin D_3 (cholecalciferol),[15] produce the endogenous stores of vitamin D that, once hydroxylated twice, perform many integral physiological functions.[23] (see Fig. 1).

The vitamin D_3 which is obtained in the diet or through endogenous production is not biologically active.[15] In order for vitamin D_3 to become biologically active, it must receive two successive hydroxylations from the liver by 25-hydroxylase (25(OH)ase) to form 25(OH)D_3 (also known as calcidiol) and the kidneys by 25(OH)D_3-1α-hydroxylase (1α(OH)ase) to form 1,25 dihydroxyvitamin-D_3 (1,25$(OH)_2D_3$) (also known as calcitriol).[15,24] Once formed, 1,25$(OH)_2D_3$ must bind to its vitamin D receptor (VDR) which forms a complex with the retinoid X receptor (RXR).[15,23] The VDR has been identified in many cell types, including intestinal mucosal cells, immune cells (T and B cells), kidney cells and pancreatic β-cells.[15,25,26] The binding of 1,25$(OH)_2D_3$ to the VDR/RXR complex and subsequent binding to its specific DNA sequence known as the vitamin D response element (VDRE) leads to an increased expression of proteins, such as calbindin-D9K found in the intestine and calbindin-D28K found in pancreatic β-cells, thus facilitating calcium influx into these tissues.[27,28] Vitamin D, although traditionally classified as a vitamin, actually performs functions that are analogous to those of a hormone.[23] 1,25$(OH)_2D_3$ helps maintain calcium and phosphorous homeostasis by increasing calcium absorption by the intestinal mucosa, decreasing calcium excretion by the kidney, and promoting bone resorption when serum calcium falls to sub-optimal levels (<2.25–2.5 mmol/L).[1] 1,25$(OH)_2D_3$ also plays an integral role in preventing rickets and osteomalacia.[15] There has been much debate with regards to the levels of 25(OH)D_3 considered to be optimal; however maintaining serum 25(OH)D_3 levels of ≥80 nmol/L is thought to be ideal for healthy individuals; when levels drop below this value, calcium absorption is thought to be impaired and bone mineral density compromised.[22] Although serum 25(OH)D_3 concentrations of ≥80 nmol/L have shown to be efficacious in preventing many diseases associated with vitamin D deficiency, it is important to note that this is an arbitrary cut-off point, i.e., it may be sufficient for some individuals while grossly inadequate for others. These recommendations are based on data from individuals that do not spend a significant amount of time outdoors, and although they may be asymptomatic this does not mean that these recommendations are adequate for the general population; more research is needed to establish appropriate cut-off points for various populations.[22]

Although 1,25$(OH)_2D_3$ plays an important role in maintaining calcium homeostasis, there is evidence that it plays a role in immune function and more recently is thought to play a role in T2DM.[12,14–17,25,27,29–31] The most effective way of measuring vitamin D status is to measure serum concentration of 25(OH)D_3, not 1,25$(OH)_2D_3$; this is due to the rapid clearance rate of the latter.[23]

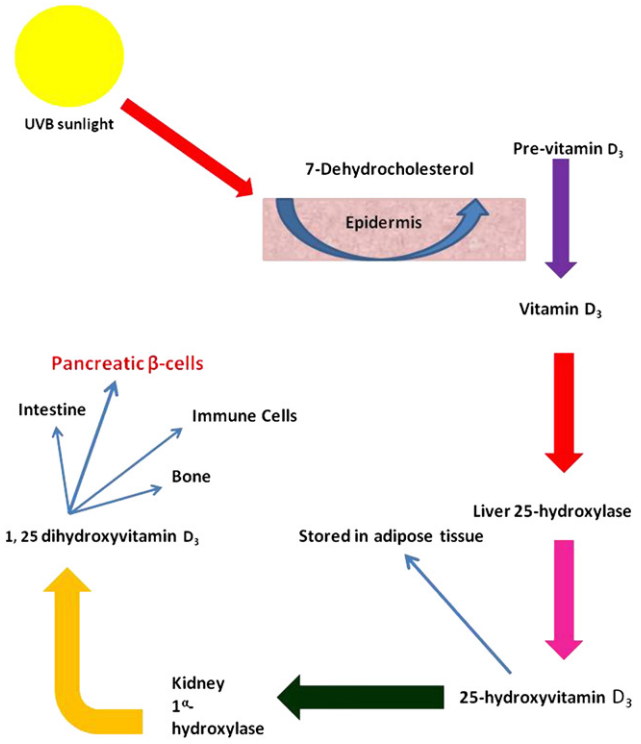

Fig. 1. *Vitamin D synthesis pathway* – Exposure to UVB sunlight activates 7-dehydrocholesterol (7-DHC), a pre-cursor structure made from cholesterol and found predominantly within the epidermis, to form pre-vitamin D_3. Pre-vitamin D_3 then isomerizes to vitamin D_3 which is then carried to the liver where it is hydroxylated by 25-hydroxylase and then the kidney by 25(OH)D_3-1α-hydroxylase to form the biologically active 1,25-dihydroxyvitamin-D_3 (1,25$(OH)_2D_3$). 1,25$(OH)_2D_3$ is now free to exert its effects by binding to its vitamin D receptor (VDR) in target tissues.

3. T2DM pathogenesis-insulin resistance

In a normoglycemic individual, in response to a rise in blood glucose, the β-cells of the islets of Langerhans, found within the pancreas, will synthesize and secrete insulin into the blood in a biphasic pattern.[32,33] Insulin, an anabolic hormone, works to build tissues by promoting glucose uptake and synthesis of glycogen, protein and triglycerides.[1] Glucose transporters-4 (GLUT-4) are responsible for glucose uptake into tissues which work to decrease blood glucose to an optimal level between 3.9 and 5.8 mmol/L; however this mechanism is impaired in individuals with T2DM. (see Fig. 2).[1,4]

The pathogenesis of T2DM is quite complex; it involves many different pathways, organs, tissues and hormones.[6,7] T2DM is a progressive chronic disease; it begins with insulin resistance, which leads to increases in hepatic glucose production and ends with β-cell failure.[4,7,34,35] Insulin resistance is defined as the inability of target tissues, such as skeletal muscle and adipose tissue, to respond adequately to the body's endogenous insulin secretions. As stated previously, the precise mechanisms responsible for the decrease in insulin sensitivity have not been elucidated; however some have implicated hyperglycemia or 'glucotoxicity' for the decrease in insulin sensitivity observed in T2DM.[36] Hyperglycemia is thought to exacerbate insulin resistance by further decreasing tyrosine phosphorylation while increasing serine and threonine phosphorylation of the insulin receptor, which has an inhibitory effect.[33] It has been estimated that there is a 50% decrease in insulin receptor autophosphorylation in individuals with T2DM, this may be due, in part, to hyperglycemia.[33] The decrease in insulin signalling observed in individuals with T2DM has also been shown in a study conducted by Cline et al. who found that insulin-stimulated glycogen synthesis was 80% lower in individuals with T2DM when compared to healthy controls.[37] Moreover, hyperglycemia has been shown to increase the production of reactive oxygen species (ROS), which are beneficial at low levels but detrimental at supra-physiological levels.[38] Hyperglycemia decreases the activity of pertinent antioxidant enzymes, such

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