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Vitamin D Deficiency, Obesity and Diabetes

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Abstract

Obesity and type 2 diabetes mellitus (T2DM) are main chronic diseases harming human health. Although the association between obesity and T2DM is well established, the molecular mechanism is still unclear. Accumulating evidence suggests vitamin D plays a role in the development of these diseases. Vitamin D is a necessary nutrient for humans. People usually do not pay attention to supplementing vitamin D, since vitamin D can be produced when their skin is exposed to the sunlight. Nevertheless, even in highly sunny regions, vitamin D deficiency exists, suggesting vitamin D deficiency is a global problem. Vitamin D deficiency has previously been considered only to influence bone metabolism. Accumulating evidence counters this opinion. *In vivo* studies have revealed that vitamin D deficiency reduces insulin secretion capacity of the islet beta cells in pancreas. Moreover, epidemiological studies have demonstrated that vitamin D deficiency is closely related to obesity and increased risk of T2DM. This review introduces the current work on vitamin D, obesity and diabetes.

Key words: Adipocyte, Insulin resistance, Insulin secretion, Vitamin D, T2DM.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) have become main chronic diseases that harm human health not only in developed countries but also in developing countries. With improvement of living standards and lifestyle changes, the number of diabetic patients is increasing dramatically. It is estimated that by the year 2020 there will be approximately 300 million people affected by T2DM, most of which will occur in developing countries (1). In China, the number of people affected by T2DM is 92.4 million, which was estimated by a recent study using the Oral Glucose Tolerance Test (OGTT) in 46,239 adults from 14 provinces (2). A large patient base will adversely influence both the medical insurance system and people's social life. Therefore, obesity and diabetes are not only a health problem but also a social problem worldwide.

Control and treatment of obesity and diabetes must be based on the understanding of their development mechanisms, which remain unclear. However, over the past few decades, research has revealed a number of factors closely correlated with obesity and diabetes. Among them, the role of vitamin D is gaining more and more attention.

Source and metabolism of vitamin D

Vitamin D is a necessary nutrient for human health. Previously, vitamin D supplementation was only used to prevent rickets. Hence, vitamin D was considered only to participate in the formation and development of bone. However, recent studies have revealed that vitamin D also plays a crucial role in nerve, reproduction, immunity and the endocrine system (3). Vitamin D comprises two categories: vitamin D_2 and vitamin D_3. Vitamin D_3 is the main form in humans (4) and activates vitamin D receptor (VDR) which is a nuclear receptor expressed nearly ubiquitously.

Humans get vitamin D via the sun and through their diet. When people are exposed to sunlight, solar ultraviolet B radiation penetrates the skin and converts 7-dehydrocholesterol to previtamin D_3, which is rapidly converted to vitamin D_3 that enters the circulation. Most vitamin D_3 is transported in the blood by binding to vitamin D binding protein (DBP) (85%-88%) or albumin (12%-15%). In the diet, vitamin D mainly comes from animal derived food, such as salmon and cod liver oil.

Vitamin D via sun-exposed skin and from the diet has no biological activity and must be transported to the liver, where it is metabolized by 25-hydroxylase to 25-hydroxyvitamin D (25-(OH)D_3), which is the major circulating metabolite and a determinant of a patient's vitamin D status. However, 25-(OH)D_3 has little biological activity and needs to be transported to the kidney for further hydroxylation to its active form, 1,25-dihydroxyvitamin D (1,25-$(OH)_2D_3$).

Vitamin D and obesity

Obesity is a major risk factor for T2DM (5). Abundant studies have revealed that adipocyte dysfunction plays a key role in the development of obesity. Interestingly, researchers discovered that vitamin D is stored in adipocytes, which regulate its levels by storing and releasing vitamin D. And vitamin D level is significant inversely related to BMI (6), indicating vitamin D deficiency is related to increased body fat (7). These studies support that lower vitamin D level increases the risk of obesity. Another groups also confirmed this conclusion, finding an inverse association between vitamin D levels and excess weight (8, 9). Moreover, Wortsman *et al.* discovered that not only the vitamin D level but the bioavailability of vitamin D also decreased in obesity

(10). Conversely, high vitamin D intake reduces diet-induced obesity (11). Although the specific mechanism of how vitamin D influences lipogenesis is still not clear, some groups have discovered a few clues: Duque *et al*. reported 1,25-$(OH)_2D_3$ directly suppresses the expression of peroxisome proliferator-activated receptor γ2 (PPARγ2), which promotes lipogenesis and differentiation of 3T3-L1 preadipocytes (12). In addition, Lee *et al*. identified a novel 1,25-$(OH)_2D_3$ response element in the promoter region of insulin-induced gene-2 (Insig-2), showing 1,25-$(OH)_2D_3$ stimulates the expression of Insig-2, which inhibits lipogenesis and blocks differentiation of preadipocytes (13). These findings suggest 1,25-$(OH)_2D_3$ may also control fat deposits via these key factors.

Vitamin D and diabetes

In addition to being risk factors for obesity, abnormal insulin secretion and insulin resistance are closely correlated with the development of diabetes. Some studies have also revealed a relationship between vitamin D and these factors.

Vitamin D and insulin secretion

Accumulating evidence demonstrated vitamin D stimulates the islet β cells to secrete insulin through its active form 1,25-$(OH)_2D_3$ (14). It is believed that vitamin D might regulate insulin signal transduction and glucose-induced insulin secretion by this pathway. Studies on ob/ob mice indicated that vitamin D deficiency reduces insulin secretion and that supplementing with vitamin D increases insulin levels (15). Previous work confirmed the presence of vitamin D receptor (VDR) in pancreatic islet β cells and showed impaired insulin secretion in mice lacking functional VDR (16). These data suggest vitamin D regulates insulin secretion via VDR. Moreover, Bland *et al*. found pancreatic islets express 1α-hydroxylase, which catalyzes 25-$(OH)D_3$ to 1,25-$(OH)_2D_3$, suggesting the local production of 1,25-$(OH)_2D_3$ is an important autocrine link between vitamin D status and insulin secretion (17). Furthermore, an epidemiological study showed vitamin D deficiency increases the risk of metabolic syndrome (18). All these data support vitamin D is involved in the regulation of insulin secretion.

Vitamin D and insulin resistance

Insulin resistance is also a major risk factor for T2DM. Some groups have reported that vitamin D levels are inversely related to glycated hemoglobin (HbA1c) (19) and insulin resistance (20, 21). Moreover, OGTT data from non-diabetic patients revealed an inverse association between vitamin D and insulin resistance, implying vitamin D deficiency increases the risk of insulin resistance (22). Currently, India has the largest number of diabetic patients in the world. Although India has enough sunshine, Indians tend to have low vitamin D levels, which has been suggested to lead to high risk for insulin resistance and obesity in Indians (23).

Skeletal muscle and liver are key metabolic tissues and have a close relationship with insulin sensitivity and glucose tolerance. Consequently, skeletal muscle and hepatic insulin resistance are also presumed to be chiefly responsible for the development of T2DM. It is worth noting that both these tissues express VDR, meaning vitamin D plays a role in them (24, 25). However, the specific mechanism by which vitamin D influences insulin sensitivity is complicated. Maestro *et al*. identified a vitamin D response element in the insulin receptor gene promoter, discovering that 1,25-$(OH)_2D_3$ stimulates its transcription and enhances insulin response (26). These findings demonstrate vitamin D directly regulates insulin signaling. On the other hand, accumulating evidence indicates obesity and diabetes actually are conditions associated with chronic low level inflammation. Since NF-κB is able to stimulate many pro-inflammatory cytokines, its activation aggravates insulin resistance. Researchers have discovered 1,25-$(OH)_2D_3$ downregulates activation of NF-κB and vitamin D deficiency is associated with increased inflammation, suggesting vitamin D also has its effects through anti-inflammatory actions (21, 27).

Vitamin D status and type 2 diabetes

Researchers are paying more and more attention to the role of vitamin D in T2DM. Many studies have demonstrated there is an association between plasma 25-$(OH)D_3$ levels and T2DM (28). Data from the Third National Health and Nutrition Examination Survey (USA) indicates lower 25-$(OH)D_3$ increases the risk of T2DM (29). Analysis of the blood glucose and vitamin D levels of diabetic patients showed an inverse association between 25-$(OH)D_3$ and T2DM (30). Interestingly, there is a seasonal difference in the effect of vitamin D on blood glucose. This may be partly attributed to the lower vitamin D levels in winter (31). Moreover, vitamin D levels in the diabetic population are significantly lower than in the non-diabetic population. Therefore, researchers have proposed vitamin D levels should be monitored in diabetic patients (32).

Other studies have investigated the prediction of T2DM based on vitamin D levels. After a follow-up period of 17 years, Mattila *et al.* found people with higher vitamin D levels had a 40% lower risk of T2DM compared to those with lower vitamin D levels (33). Another study after a follow-up period of 22 years indicated women have lower serum vitamin D levels than men and the incidence of T2DM in men is 72% less than women (34). These data suggest higher vitamin D levels prevent incidence of T2DM.

Conclusions

Because humans can synthesize vitamin D when exposed to sunlight, it had been previously thought vitamin D deficiency would be unlikely. However, even in the sunniest regions of the world, vitamin D deficiency is common. In Qatar, which is highly sunny, researchers demonstrated 68.8% of children had vitamin D deficiency (35). Moreover, studies in other countries also shown 30 to 50% of the population have lower than normal vitamin D levels (36-39). These data reveal vitamin D deficiency has become a global health problem. Due to the differences of diet, Asians tend to get less vitamin D from food compared to westerners. Therefore, Asians may be at especially high risk of vitamin D deficiency than westerners. Undoubtedly, this situation is more

serious in diabetic patients (40). We consider the work introduced here is just the beginning in this field. More work remains to be done to clarify the role of vitamin D in the development of obesity and T2DM.

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