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ASSOCIATION OF SERUM VITAMIN D LEVELS IN EARLY AND LATE DIABETES – A REVIEW

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REVIEW ARTICLE

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Abstract

Diabetes mellitus is one of the common chronic conditions, which affects millions of people around the world. It is associated with many problems, including micro and macrovascular abnormalities, which not only impair the quality of life significantly but also increase mortality. There has been widespread interest in the pathogenesis and prevention of vitamin D-related diabetes. Vitamin D deficiency has become increasingly recognized all around the world in recent years. Above and beyond its classical role as a regulator of calcium and phosphorous metabolism and bone mineralization, vitamin D facilitates the secretion of insulin from the beta cells of the pancreas to increase glucose uptake by the peripheries and decrease systemic inflammation. Thus, vitamin D deficiency has been found to have a vital role in the pathogenesis of diabetes mellitus. Vitamin D deficiency is known to be associated with glucose intolerance, insulinemia, insulin resistance, and obesity. The majority of patients with diabetes mellitus may have low serum vitamin D levels. Vitamin D supplementation has been shown to reduce insulin resistance in diabetes mellitus. The normal serum level of vitamin D and the range of related factors are still essential to carry out an extensive investigation to conclude a risk factor. In anticipation of that, it is probable to conclude that maintenance of serum vitamin D levels holds benefits in diabetic disorders, and researchers have to be duty-bound to attempt to attain them.

INTRODUCTION

Diabetes mellitus is a syndrome of chronic hyperglycemia due to insulin deficiency, resistance or both. The disease is classified into two forms, one affecting young individuals, type 1 diabetes mellitus (T1DM), with a shorter life span and the other affecting obese and older individuals, type 2 diabetes mellitus (T2DM). It is also described the relation of diabetes to hereditary factors, obesity, lifestyle and dietary habits. Ever since, the treatment of diabetes has taken a long road, with the advent of various forms of insulin and also oral hypoglycemic agents. According to Seshadri et al. [1], by the year 2025, it is estimated that around 380 million individuals would be affected by diabetes worldwide. At present, in India, 41 million individuals are affected by diabetes, which is suspected to increase to 70 million by the year 2025 [2]. Even though significant understanding has been acquired on the etiology of diabetes, its precise etiopathogenesis is still under debate. Reactive oxygen species (ROS), autoimmune reactions and inflammatory factors have emerged as major pathogenic effectors for diabetes. Evidence suggests that a significant association was observed between serum vitamin D levels and diabetes, metabolic syndrome, chronic heart disease (CHD) and insulin resistance. It is observed that vitamin D plays an important role in glucose

intolerance and insulin resistance [3,4,5,6]. Vitamin D receptors (VDR) are present in the colon, pancreas, and immune cells [7,8]. Vitamin D has a widespread effect in the pathogenesis and prevention of diabetes, as it is found to regulate calcium homeostasis, which in turn improves insulin exocytosis. It has been reported that vitamin D also improves glucose tolerance [9]. However, studies suggest a relationship between vitamin D status and the incidence of T1DM [10] or T2DM [11]. From clinical trials, it is evident that vitamin D supplementation exerts a positive effect on the status of diabetes; in heterogeneous patient populations, it has been tried with a wide range of vitamin D types and dosing regimens to manage diabetes [12,13,14,15,16].

VITAMIN D AND ITS METABOLISM

Calciferol (Vitamin D) is an important micronutrient with hormone-like action, vital for bone mineralization and calcium and phosphorous metabolism. Sunlight (UVB radiation) is the main source of vitamin D in humans, while a minute amount is contributed by diet. There are two major forms that have similar metabolism but differ in their side-chain structure; classified as ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). Vitamin D3 is synthesized in the skin of humans and is also absorbed via diet. The sources of vitamin D3 include animal-based foods like fish oil, whereas sources of vitamin D2 include plant-based diet [17]. Both forms of vitamin D are absorbed along with dietary fats by the small intestine in humans [18]. It is first metabolized in the liver to 25-hydroxy vitamin D (25(OH)D), a major metabolite in circulation and therefore measured in the serum levels. The second hydroxylation occurs in the kidney by the enzyme 25-hydroxy vitamin D-1(alpha)-hydroxylase to 1,25-hydroxy vitamin D, which is the active form and exerts its effects by means of steroid hormone nuclear receptors. VDR is present in various other tissues like immune cells, brain, prostate, breast, colon and pancreas. In addition, some of these tissues and cells express the enzyme 25-hydroxy vitamin D-1(alpha)-hydroxylase. The vitamin D storage levels depend mainly on its bio-availability via absorption. On average, vitamin D half-life is around three weeks in plasma [19]. Recent evidence in various studies demonstrates its impact in a lot of disorders like cancers (Hodgkin's Lymphoma, Prostrate, Colon, Pancreatic and Breast), cardiovascular and respiratory illnesses, autoimmune diseases (Multiple Sclerosis) and infections [20].

ROLE OF VITAMIN D IN INSULIN RESISTANCE

The onset of diabetes may be due to low levels of vitamin D. The level of vitamin D has a major role in developing insulin resistance, with the subsequent decline in β-cells that results in diabetes [21,22]. In adipose tissue, vitamin D has a role in controlling cell signaling pathways and gene transcription to improve the onset of insulin resistance in usual circumstances [23]. However, the majority of its actions are mediated through genetic factors. During adipogenesis, vitamin D has a role in inhibiting the differentiation of adipocytes by the mitogen-activated protein kinase signaling pathways [24] and Wnt/β-catenin [23,25]. It is also reported to control lipogenesis and lipolysis. Vitamin D can act through a non-genomic pathway [26]. Obesity-driven insulin resistance leads to the development of diabetes [27,28], with the consequence of a decrease in the capability of insulin to maintain glucose homeostasis between the liver and other tissues [29]. It is reported that vitamin D has a major role in the expression of insulin receptors, which thereby helps in sustaining the insulin signaling pathway [30,31]. Studies suggest that decreased levels of vitamin D lead to an increase in Ca^{2+} concentration, which results in the onset of insulin resistance by reducing the number of insulin receptors and decreasing the glucose transporter-4 (GLUT4) activity [32]. Obesity-associated inflammation also leads to the onset of insulin resistance [28,33,34,35]. There are reports available for the role of vitamin D in regulating chemokines and cytokine release, which affects the reduction in monocyte chemotaxis [36,37]. Vitamin D plays an important role in reducing adipocyte formation [38]. The ROS formation is considered to be a possible factor for inducing insulin resistance [33]. Regulation of ROS levels plays a key role in maintaining the stability of cell signaling pathways. Literature reports show that vitamin D plays a vital role in regulating ROS levels by controlling the expression of cellular antioxidants [39,40]. It is also found that vitamin D regulates the epigenetic modifications that might lead to diabetes [41]. Supplementation of vitamin D has been shown to decrease insulin resistance through which might cause fatty liver, and the consequences lead to T2DM. Insulin resistance and fatty liver are particularly closely related. Vitamin D supplementation resulted in increased serum 25-hydroxy vitamin D [25(OH) D] in non-alcoholic fatty liver disease [42].

VITAMIN D AND EARLY DIABETES (T1DM)

T1DM is an autoimmune disorder mainly characterized by decreased or absent secretion of insulin in the β- cells of the islets of Langerhans of the pancreas. One of the fastest-growing diseases all over the world is diabetes [43]. According to the national database of the USA, it is found that the prevalence of T1DM had reached 1.5 cases in every 1000 children and teenagers as of the year 2002 [44]. A lot of studies reveal that there is a significant association of T1DM with vitamin D deficiency [45,46,47,48]. A range of 15% to 90.6% prevalence of T1DM due to vitamin D deficiency is reported from different studies [46,49,50]. Studies prove that vitamin D is important in protecting the islets of Langerhans to improve insulin production [51,52]. Many studies have been performed correlating vitamin D

supplementation with the risk incidence of T1DM. A daily dose of 2000 IU of vitamin D proved to reduce the risk around 78% in developing T1DM in the Finnish population [53]. T1DM is mainly associated with the imbalance in the pro and anti-inflammatory cytokines, especially interleukins and tumor necrosis factor-alpha (TNF-α) [9]. Increased secretion of inflammatory cytokines plays a significant role in damaging the β-cells of the islets of Langerhans. The increase in cytokines and other pro and anti-inflammatory markers is due to the triggering of the immune system, particularly the activation of T and B lymphocytes along with dendritic cells, natural killer cells, and macrophages. It was observed that these cells possessed the vitamin D receptor on their surface, which triggered the researchers to investigate the role of vitamin D as an immune modulator [54]. In the beginning, increased concentration of vitamin D in the system will trigger immune cells, particularly macrophages and dendritic cells responsible for the secretion of the 1α-hydroxylase enzyme that converts vitamin D2 to vitamin D3, the metabolically active molecule [55]. Vitamin D3 has the potential to activate the T-cells and antigen-presenting cells (APC's), which play a crucial role in stimulating the immune cascade. It is also found from the studies conducted by Jeffery et al. [56] that vitamin D3 and interleukin-2 (Secreted by dendritic cells and Macrophages) have a synergistic role in decreasing the activity of T-cells, thereby acting in an anti-inflammatory role, which in turn helps to reduce the risk of T1DM. Apart from the above, it is also found that vitamin D3 directly interacts with the VDR and nuclear factor κB (NF-κB), which interferes with the transcription of IL-12 [1].

VITAMIN D AND LATE DIABETES (T2DM)

In the last two decades, clinical research studies on the fundamental biochemical mechanism proposed for the management of vitamin D an age-related decay in various steps of vitamin D action, [57] which includes synthesis of vitamin D in skin, the proportion of converting pro-vitamin D to its active form, and the response of target tissues (e.g., bone) as well as reduced skin exposure to UV-B [58]. The elevations of parathyroid hormone (PTH) and alkaline phosphatase are observed due to vitamin D deficiency in the elderly population [59]. It is proposed that vitamin D has a key role in insulin resistance and pathology of β-cell functioning in T2DM [60,61]. The deficiency of vitamin D increases serum PTH level, which, in turn, increases insulin resistance in peripheral tissues. While a low vitamin D level induces secondary hyperparathyroidism, increased PTH levels are also associated with diabetes. An observational study of 494 women undergoing serial metabolic characterization revealed that reduced vitamin D levels with increased PTH levels were an independent predictor of β-cell dysfunction, insulin resistance, and glycaemia [62]. Vitamin D regulates pancreatic β-cells and the function of the systolic calcium-binding protein, calbindin, and acts as a modulator of depolarization stimulated insulin secretion via regulation of intracellular calcium [63]. In the diabetic animal model, it is observed that vitamin D deficiency affects pancreatic insulin secretion [52]. T2DM is mainly caused by insulin resistance and altered insulin secretion. It is observed that environmental factors like seasonal changes [54] and physiological changes, especially in women, lead to T2DM. Studies suggest that a recommended dose of vitamin D supplementation did not reduce the risk of T2DM over several years of follow-up; however, authors suggested that higher doses of vitamin D might be required to affect diabetes risk [64]. In view of this result, an observational study conducted by Nurses Health Study, women with the highest calcium and vitamin D intake had a 33% lower risk of T2DM incidence than women with the lowest calcium and vitamin D intake [65]. Still, there is a lack of knowledge for differentiating the cause of T2DM either by vitamin D deficiency on beta-cell function or on insulin resistance.

CONCLUSION

In this current retrospective review, the vitamin D supplementation may have been counterproductive because hypo-vitaminosis of vitamin D is one of the prevailing problems worldwide, especially for people residing at higher altitudes where the probability of exposure to sunlight is low. In the last 20 years, vitamin D and its actions have come to the forefront of the clinical scenario, with a role in avoiding autoimmunity against beta cells, insulin resistance and improving health. Yet, as already stated, there is still a demand for further research to clarify the promising clinical use of vitamin D in the prevention and treatment of diabetes.

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