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Systematic Review

The Relationship of Vitamin D Deficiency to Prediabetes and Diabetes Control - A Systematic Review

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Abstract

The relationship between serum vitamin D levels and glucose metabolism has been studied in-depth and described in various scientific works.

This systematic review of published literature, further analyzing this relationship, was conducted and included meta-analyses, case control studies, randomized clinical trials, cross-sectional and prospective cohorts.

The review only included literature from 2013 to 2024, and analysis validates the established outcome of many investigations that low vitamin D levels correlate with the existence of prediabetes and type 2 diabetes mellitus, in a reverse association. However, most authors agree that the evidence remains inconsistent and needs to be subjected to further investigations.

Keywords: *Diabetes Mellitus (DM); Prediabetes; Diabetes Control; Vitamin D Deficiency*

Introduction

Diabetes mellitus (DM) is a very important global health problem, with significant economic, morbidity and mortality implications.

In 2021, data from the International Diabetic Foundation (IDF) and the World Health Organization (WHO) estimate there are approximately 537 million people living with the condition [1], and accounts for an age-standardized prevalence close to 7%.

Vitamin D deficiency (VDD) is defined as a serum vitamin D level below 50 nmol.L [2], with a worldwide and geographical variation, ranging from 50% to 80% [3]. Some scholars have considered VDD a pandemic [4] due to its global spread and prevalence.

Physiology and pathophysiology of prediabetes and diabetes

The regulation of glucose metabolism is the function of Insulin, a hormone produced by the beta cells in the pancreatic islets.

Prediabetes (PD) and Diabetes mellitus (DM) are characterized by varying levels of insulin resistance (IR). While the full mechanism of IR remains an enigma, it has been succinctly described by [5] as "the state of reduced responsiveness of insulin-targeting tissues to

physiological levels of insulin". The criteria for the diagnosis of DM rely on various blood sugar levels, which could be determined by fasting levels ≥ 126 mg/dl, 2-hour post prandial levels ≥ 200 mg/dl or Hemoglobin A1c levels ≥ 6.5 [6]. For PD, the serum fasting glucose and glycosylated hemoglobin levels used to determine diagnoses are 100 - 125 mg/dl and 5.7 - 6.4 respectively [7].

Physiology of vitamin D production and metabolism

Vitamin D is a fat-soluble prohormone synthesized by the skin when exposed to solar ultraviolet rays and also obtained from dietary ingestion. However, it takes a combined action of the liver and kidneys to convert this inactive D3 (Cholecalciferol) to the active form, calcitriol (1,25, Dihydroxyvitamin D).

The 25 hydroxyvitamin D [25 (OH) D] is the circulating form of the hormone that is used for assays to determine vitamin D status. Most of the effects of vitamin D metabolism are found in the regulation of the calcium/phosphorus balance, as well as bone mineralization [8]. Therefore, rickets (in the pediatric population) and osteomalacia (in the adult population) are common health manifestations from significantly low levels of serum vitamin D. At the molecular level, these effects are mediated via a nuclear receptor/transcription factor called the vitamin D receptor (VDR) and because it is autoimmune based, it has been postulated that some subclinical inflammation of the end organs is involved [9], and this increases oxidative stress and angiotensin II levels in the microvasculature [10,11] in diabetic patients. The corollary to this was the diabetic improvement noted by mitigating oxidative stress-induced pancreatic beta cell dysfunction with vitamin D supplementation [12].

The common pathway

Whereas it has now been established that vitamin D is primarily involved in maintaining skeletal well-being through the regulation of calcium and phosphorus metabolism [8], other medical conditions have been associated with its deficiency, and include DM, PD, metabolic syndrome and non-alcoholic hepatic steatosis. For DM and PD, this involvement is at the molecular level and thought to be from the expression of inflammatory cytokines and genetic transcription mechanisms in the pancreatic beta cells with hypovitaminosis D [13]. This interaction increases the insulin resistance (IR) that is necessary to maintain glycemic homeostasis [14] and the recent discovery of 1-alpha-hydroxylase, an enzyme-activating vitamin D in pancreatic beta cells [14] has laid more credence to this theory.

Following their systematic review and meta-analysis [15], these authors concluded that there was a reverse association between serum vitamin D levels and DM2 in adults, but this relationship was not remarkable with prediabetes. A similar nonlinear, inverse relationship between hypovitaminosis D and increased risk of infections in diabetic patients was observed in a retrospective cohort study by [1] and a systematic review by [16].

Several factors impact the transition from prediabetes to type 2 diabetes mellitus. The effects of using vitamin D supplements to prevent this transition have been the subject of many clinical trials and the results are disappointingly inconsistent [17]. This finding was also confirmed by a randomized placebo-controlled trial [18] and a pre-specified secondary analysis [19], which showed some benefits of vitamin D/Calcium supplementation on pancreatic beta cell function in PD subjects with low vitamin D levels. They suggested further studies to confirm any therapeutic advantages. A retrospective analyzed study of 332 diabetic subjects [20] concluded that 25 (OH) D is an independent risk factor impacting IR and that supplementation with vitamin D in patients with DM was beneficial in improving glycemic control. In a study of 5310 subjects that investigated the independent risk factors behind the transition from a normal population to PD to DM, the authors found clinical prediction models to provide "basis for the prevention and management of prediabetes and diabetes" [21]. These risk factors include age, weight (recorded as BMI), urinary glucose, serum protein and liver transaminase levels. A prospective cohort study of a large (18,594) Mediterranean subject base to determine the effect of vitamin D in the development of type 2 DM [22], suggested that higher levels of vitamin D levels at baseline may be associated with lower risks of developing type 2 DM.

A cross-sectional study of 325 diabetic subjects [23] using continuous glucose monitoring (CGM), showed a significant reduction in 25 (OH) D with increasing HbA1c levels, and differences were observed with glycemic variability metrics, like age, duration of disease, lipid profile, albumin, creatinine and GFR values. An especially interesting cross-sectional study [24], revealed that reduced vitamin D levels were associated with increase in prevalence of PD in males, but not in females. However, this gender-specific disparity only occurred in vitamin D levels less and equal to 35 nmol/L and not observed at levels above 35 nmol/L.

Even in non-human studies, some investigators [25] noted that prediabetic wistar rats responded with improved glycemic control parameters when given vitamin D3.

Role of vitamin D supplementation in glycemic homeostasis

While the primary therapeutic regimen for managing DM does not traditionally include vitamin D supplementation but having established the reverse association between serum vitamin D levels and PD/DM, the question becomes if it can help regression to normal glucose regulation. This was tested in a randomized clinical trial [26] with 2424 participants, which concluded that indeed, vitamin D supplementation was associated with a lower risk of developing DM as well as an increased likelihood of normal glucose regulation. This conclusion was corroborated by a meta-analysis by [27], where they investigated the mechanism of vitamin D against metabolic syndrome. They found significant reductions in fasting glucose and triglyceride levels and some improvement in insulin homeostasis with vitamin D supplementation. This conclusion was similarly reached from a RCT with a 6 month follow up [11] where dose-dependent vitamin D supplementation in diabetic subjects was found to reduce the HbA1c levels over the 6-month period under study.

In their analysis of 3 RCTs [28], these authors determined that there was a significantly reduced risk of developing DM when prediabetic subjects were administered vitamin D.

In a systematic review and meta-analysis [29,30], the investigators found that vitamin D supplementation drastically improved IR in diabetic subjects, especially when given in higher doses for short periods.

However, in their literature review [31] concluded that even though there was positive response in glycemic improvement in DM when subjects were administered vitamin D, it was only relevant in type 1 and not in type 2 DM. Vitamin D exerts these protective functions against complications of hyperglycemia via its anti-inflammatory, anti-oxidant and immune-modulatory effects [32].

Although the primary objective of this review is to analyze the literature pertaining to the effects of or relationship between vitamin D supplementation and the outcomes of PD and DM, some studies have shown great potential in the adjunctive management of other non-skeletal conditions as well [33]. This case study demonstrated the efficacy of instituting vitamin D supplementation that resulted in rapid clinical improvement in a patient with reactive airways dysfunction syndrome (RADS). A case report and literature review [34] analyzed the effect of vitamin D deficiency in the setting of multiple sclerosis (MS) and concluded that the risk of developing MS can be ameliorated by maintaining optimal serum vitamin D levels in the healthy population.

A HIPAA-compliant cross-sectional study of 202 subjects from our outpatient clinic following verbal consents (160 diabetics and 42 prediabetics) from January 2021 to September 2024 was reviewed.

89 of them showed an inverse relationship with HbA1c levels, while 48 had normal HbA1c. The rest did not have serum vitamin D levels for review.

Conclusion

The molecular basis for the actions of vitamin D in various target organs has been shown to have an anti-inflammatory and reduction in oxidative stress response to various diseases. Most of the investigators highlighted in this review have come to this conclusion based on the relationship between vitamin D levels and the outcomes of glucose homeostasis in PD and DM, but also caveat that more studies should be continued to fully understand if any causal relationships exist. Based on this, it may be concluded that vitamin D supplementation helps to regulate glycemic control in patients with PD and DM and should be used as an adjunct to the primary treatment of these conditions.

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