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VITAMIN D DEFICIENCY EFFECTS UPON DIABETES MELLITUS AND ITS CARDIOVASCULAR AND RENAL CHRONIC COMPLICATIONS

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Abstract

Vitamin D was proved to have multiple non-skeletal actions, its receptor being expressed by almost every tissue, consequently proper levels being necessary for their optimal functioning. Although biologically inactive, 25(OH)D is the most abundant circulating form of vitamin D and it has been accepted as the functional indicator of vitamin D status. During the last decades, vitamin D insufficiency reflected by circulating 25(OH)D levels less than 20 ng/ml, tends to have a pandemic expansion, affecting almost 50% of the population worldwide. Diabetic patients' diet must assure an optimal macro- and micronutrients intake, an adequate vitamin D level being, therefore, required. Some of the observational studies have found an inverse association between insulin resistance and vitamin D status. Vitamin D involvement in type 2 DM was also supported by the seasonal variation in glycemic control, which was worse in the winter in some of the studied patients, partly determined by the low vitamin D status in the winter. When discussing the protecting effect of vitamin D against type 1 DM, it was concluded that more clinical trials are needed in order to ascertain the dose and the duration of the vitamin D supplementation. There appears to be a relationship between vitamin D deficiency and the development of type 2 DM and its chronic complications (cardiovascular events and CKD). Vitamin D and its analogs have proved their importance in preventing renal injury in diabetic nephropathy and, therefore, in reducing cardiovascular mortality in these patients.

keywords: *vitamin D status, type 2 diabetes mellitus, chronic kidney disease, cardiovascular risk*

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Introduction

Discovered at the beginning of the 20th century for its role in calcium metabolism and adequate bone status, vitamin D (both vitamin D2 and D3) was proved to have multiple non-skeletal actions, its receptor being expressed by almost every tissue, consequently proper levels being necessary for their optimal functioning [1, 2]. Unlike other vitamins, only 10-20% of our vitamin D has dietary sources (fish, eggs or vitamin-D-fortified milk), the vast majority originating from the conversion of 7-dehydrocholesterol to vitamin D3 (cholecalciferol) in the skin, process which is UVB-induced [3]. Vitamin D, whether from the diet or the skin, is then converted to 25-hydroxyvitamin D (25(OH)D) by vitamin D-25-hydroxylase, in the liver. Although biologically inactive, 25(OH)D is the most abundant circulating form of vitamin D and it has been accepted as the functional indicator of vitamin D status [1, 2]. In order to activate the vitamin D receptors (VDR) located in the cell nucleus, this metabolite must be converted to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), in the kidney, by 25-hydroxyvitamin D-1α-hydroxylase [1]. This represents 25(OH)D's endocrine pathway, as $1,25(OH)_2D$'s primary target is the intestinal mucosa, regulating calcium transport system in order to adapt to varying calcium intakes [2]. But 25(OH)D has an autocrine pathway as well, which consists in its intracellular conversion to $1,25(OH)_2D$ by 1-a-hydroxylases, process that takes place in many other cells such as epithelial cells (breast, colon, lung, skin and prostate) and cells of the immune system [2].

During the last decades, vitamin D insufficiency reflected by circulating 25(OH)D levels less than 20 ng/ml [4], tends to have a pandemic expansion, affecting almost 50% of the population worldwide [3, 5], which is not surprising when considering the main factors that affect the 25(OH)D serum level: the dietary intake (both food and supplements) and the sun exposure (which depends upon the season, the latitude, the air pollution, the skin pigmentation as well as sunscreen application) [3, 6].

Taking into consideration that hypovitaminosis D was proved to be an independent risk factor for total mortality in the general population [3, 7] and the findings of a meta-analysis published in 2007, that vitamin D supplementation was associated with a significant decrease in mortality [3, 8], we have purposed to summarize vitamin D's involvement in diabetes mellitus (DM), as well as its importance in chronic kidney disease and cardiovascular diseases, both major DM chronic complications.

Vitamin D and the Risk of Diabetes Mellitus

Over the last decades the relationship between vitamin D deficiency and DM became the subject of many studies. Some of them tried to explain the potential mechanism through which vitamin D status determines beta cells function. Firstly, it was demonstrated the expression of the VDR and 1alpha hydroxylase in these cells. Furthermore, vitamin D seems to improve beta cell function, having both a direct and an indirect effect on insulin secretion. The former was supported by studies showing: impaired insulin secretion in VDR deficient mice; reduced insulin secretion in vitamin D deficiency; supplementation of vitamin D restores insulin secretion in animals and the

fact that $1,25(OH)_2D$ stimulates insulin release [9, 10], as summarized in table 1, while the latter is potentially exercised via a calcium effect on insulin secretion [9, 10], as explained in table 2.

Table 1. Direct effects of vitamin D in type 2 DM [adapted from 10]

Improvement in pancreatic beta cell function	Evidence
Effect on insulin secretion	Presence of specific vitamin D receptors in pancreatic beta cells. Expression of 1-α-hydroxylase enzyme in pancreatic beta cells. Impaired insulin secretory response in mice lacking functional VDR. Presence of the vitamin D response element in the human insulin gene promoter. Transcriptional activation of the human insulin gene by 1,25-OHD. Vitamin D deficiency impairs glucose-mediated insulin secretion from rat pancreatic beta cells in vitro and in vivo. Supplementation with vitamin D restores insulin secretion in animals.
Effect on insulin action	Inverse association between 25-OHD levels and sarcopenia. Presence of vitamin D receptor in skeletal muscle. Vitamin D stimulates the expression of insulin receptor and enhances insulin responsiveness for glucose transport in vitro. Vitamin D directly activates a transcription factor implicated in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue.

Table 2. Indirect effects of vitamin D in type 2 DM [adapted from 10]

Improvement in pancreatic beta cell function	Evidence
Effect on insulin secretion	Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes. Regulation of calcium flux in the pancreatic beta cell via regulation of calbindin, a cytosolic calcium-binding protein.
Effect on insulin action	Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium influx through cell membranes.

After analyzing many observational studies on the association between vitamin D and calcium status and type 2 DM, Pittas et al. [10] made public their conclusions. They observed that some studies reported an association between vitamin D deficiency and impaired glucose-mediated insulin release. Furthermore, vitamin D supplementation led to an improvement in insulin release. They have also noticed an association between low vitamin D level and decreased insulin sensitivity in some of the cross-sectional studies analyzed. Some of the observational studies have found an inverse association between insulin resistance and vitamin D status. Vitamin D involvement in type 2 DM was also supported by the seasonal variation in glycemic control, which was worse in the winter in some of the studied patients, partly determined by the low vitamin D status in the winter.

Many of the studies regarding the association hypovitaminosis D – type 2 DM were conducted on women. One of them, the Nurses` Health Study, has found DM relative risk to be 0.87 (P trend=0.04) when the highest and the lowest vitamin D supplementation, 800 IU respectively 400 IU, were compared [11, 12].

In the EURODIAB study, it was found a decrease in the risk of developing type 1 DM with vitamin D supplementation [11, 13], but when discussing the protecting effect of vitamin D against type 1 DM, it was

concluded that more clinical trials are needed in order to ascertain the dose and the duration of the vitamin D supplementation [11, 14].

Diabetes is known to lead to a series of long term micro- and macrovascular complications, the chronic kidney disease and the cardiovascular disease being only two of them. Vitamin D deficiency seems to be associated with these conditions, both in patients with diabetes and in the general population, although the vast majority of studies were conducted on non-diabetic patients.

Vitamin D deficiency and the Cardiovascular Risk

Many studies tried to demonstrate an association between hypovitaminosis D and cardiovascular disease. Some of them concluded that vitamin D plays a role in hypertension, coronary artery calcification and heart disease [15].

A recent meta-analysis [15] that summarized the evidence on the effect of vitamin D on cardiovascular outcomes, after studying 51 eligible trials, could not demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D. The authors were interested in vitamin D`s involvement in the cardiovascular mortality and other three major cardiovascular events: myocardial infarction, stroke and peripheral vascular disease. The analysis of the 51 studies demonstrated that vitamin D has a nonsignificant and potentially trivial role in cardiovascular mortality reduction. Meta-analysis of the eligible studies for myocardial infarction and stroke (6 studies for each) showed no significant effect of vitamin D on these conditions. The authors also analyzed vitamin D`s effect on cardiovascular risk factors (blood pressure, serum lipids and glucose levels) and concluded that vitamin D did not significantly affect any of them. The authors of this meta-analysis concluded that when discussing vitamin D as an intervention, opposed to a blood level, it did not demonstrate a significant effect on death, myocardial infarction, stroke, blood pressure, lipid profile and blood glucose values.

Vitamin D and the Chronic Kidney Disease as a Cardiovascular Risk Factor

Chronic kidney disease (CKD) is associated with increased cardiovascular risk and mortality [16], to such an extent, that Ronco et al. [17] defined the term cardiorenal syndrome (CRS). This includes a variety of acute or chronic conditions, where the primary failing organ can be either the heart or the kidney. When CKD is the primary condition, we speak of type 4 CRS (chronic renocardiac syndrome). In the CKD patients the $1,25(OH)_2D$ deficiency appears due to the reduction/absence of kidney α1-hydroxylase, which causes parathyroid hyperplasia and increased parathyroid hormone (PTH) [16, 18]; the consequent hyperparathyroidism and hyperphosphatemia represent important mortality risk factors in these patients [16, ref 4=17, 7=18].

Hence, studies have showed that vitamin D treatment is associated with a reduced rate of cardiovascular events and mortality [16, 19, 20]. But the studies also underlined the side effects of calcitriol treatment (hypercalcemia and hyperphosphatemia), which are associated with a risk of cardiovascular calcifications [16]. Both calcitriol and vitamin D analogs are known as VDR activators, but in comparison

to calcitriol, vitamin D analogs (e.g. paricalcitol), due to less bone resorption and intestinal absorbtion, cause less hypercalcemia and hyperphosphatemia [16, 21, 22]. The use of VDR has the following effects: suppression of PTH, inhibition of the rennin-angiotensin system by inhibiting rennin synthesis, decreased vascular calcification and atherosclerosis, prevention of cardiovascular diseases, reduced hospitalization and mortality, preservation form cellular senescence, improved endothelial function, reduced tubular interstitial fibrosis, and reduced inflammatory status [16].

Observational studies suggest that VDR systemic activation may have important effects on cardiovascular system and may lead to a decrease mortality in patients with chronic kidney disease [16, 20]. Vitamin D and its analogs seem to be important in preserving the cardiovascular system and reducing vascular calcification [CKD].

Another distinctive clinical sign in patients with CKD is albuminuria/proteinuria. Even though a decrease in glomerular filtration rate (GFR), especially when eGRF<60ml/min/1.73m^2, is correlated with an increase in cardiovascular disease incidence, patients with normal eGFR but with a degree of albuminuria/proteinuria are also at risk of developing CVD [23, 24, 25]. VDR activators were proved to reduce proteinuria in these patients independent of concomitant use of agents that block the rennin angiotensin system, as was demonstrated by Agarwal et al. [16, 26] in three double-blind, randomized, placebo controlled studies in patients with chronic kidney disease stage 3 and 4.

Zeeuw et al. [16, 27] and Zhang et al. [16, 28] also proved that blockade of the rennin angiotensin system with a combination of vitamin D analogs and rennin angiotensin system inhibitors effectively prevents diabetic nephropathy and it may be associated with better renal protection [16].

Conclusions

There appears to be a relationship between vitamin D deficiency and the development of type 2 DM and its chronic complications (cardiovascular events and CKD). Vitamin D and its analogs have proved their importance in preventing renal injury in diabetic nephropathy and, therefore, in reducing cardiovascular mortality in these patients. Future intervention studies using these analogues will answer many questions still not responded when discussing vitamin D: “what are the optimal levels of serum 25(OH)D?”, “do they vary for prevention of various disorders?”

At the moment, according to the most recent practical guideline on evaluation, treatment, and prevention of vitamin D deficiency [29], vitamin D supplementation it is recommended at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances. Treatment with either vitamin D2 or vitamin D3 was recommended for deficient patients, but there was not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D for its role in diabetes, CKD and cardiovascular disease prevention.

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