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Vitamin D, Type 2 Diabetic and Cardiovascular Disease: Myth or Reality?

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Introduction

In the last years a strong relationship has been described between diabetes and vitamin D. On the other hand, diabetes is a major cause of chronic renal disease which is associated with changes of the mineral metabolism, including vitamin D deficiency. Furthermore, it has been shown that vitamin D has pleiotropic properties, playing an important role at the cardiovascular system.

In this short article we describe the relations between vitamin D and diabetes, and we also summarize the facts connecting the deficiency of Vitamin D and cardiovascular disease, mainly in patients with renal disease.

Vitamin D and Diabetes

The mechanisms associated with diabetes mellitus (DM) are multiple and complex, being all interconnected, and this process is not yet fully understood. Recently some observational studies have reported the association between 1,25 dihydroxivitamin D3 receptors (VDRs) and type 1 and type 2 DM, glucose intolerance, sensitivity to insulin secretion and serum calcitriol levels [1-10].

The pathophysiology of type 2 diabetes is complex but we know that there is an involvement of changes in pancreatic β-cell function and tissue resistance to insulin. It is generally accepted that as the major hormone regulating calcium metabolism, 1,25 dihydroxivitamin D3 produces effects on the immune system and on the pancreatic β cells by facilitating insulin production [10].

The presence of 1,25-dihydroxyvitamin D3 receptors in the pancreas raises the possibility of a direct action of this vitamin in the synthesis, regulation and secretion of pancreatic hormones. It was recently reported the presence of 1,25 dihydroxivitamin D3-dependent-calcium-binding protein (DBP) in the pancreatic β cells and an additional factor in favour of the action of this vitamin in regulating the synthesis and secretion of insulin verified that 25-hydroxyvitamin D is converted to its active form, 1,25-dihydroxyvitamin D, in the pancreatic β cells through the action of the 25-hydroxyvitamin D-1α-hydroxylase [6,11].

Hypovitaminosis D is a risk factor for the development of type 2 diabetes and metabolic syndrome since it causes pancreatic β cell dysfunction and peripheral resistance to insulin action [12].

The mechanism by which 1,25 dihydroxivitamin D3 deficiency contributes to the onset of type 2 diabetes is not fully understood, and more studies are necessary to further examine this association; however, it is clear that pancreatic β cells dysfunction, resistance to insulin action and low-grade inflammation are important factors for the development of glucose intolerance and type 2 diabetes [13-15].

In both animal and human studies, it was described that pancreatic β cells dysfunction is associated with a state of 1,25 dihydroxivitamin D3 deficiency and that its supplementation contributes to the conversion of proinsulin into insulin [14-16].

Despite the evidence of a protective role of this vitamin in diabetes, it is unclear whether its deficiency is related to the several risk factors presented in this disease [17,18].

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Vitamin D and Cardiovascular Disease in Diabetes

Accumulating evidence suggests a strong association between low vitamin D levels with increased cardiovascular (CV) risk factors and cardiovascular disease (CVD) among type 2 patients, independently of traditional risk factors [19-22].

Some large observational studies like The Framingham Offspring Study and The Health Professionals Follow-up Study showed that the risk of cardiovascular events were significantly higher in those with lower levels of vitamin D [23].

The Third National Health and Nutrition Examination Survey III (NHANESIII) included more than 13.300 men and women older than 20 years, using a cohort that was followed for almost 9 years. Analyzing this population Martins et al. showed a strong association between vitamin D deficiency, defined as serum 25-hydroxyvitamin D concentrations ≤ 15 ng/mL, and cardiovascular disease risk factors (blood pressure, diabetes, overweight and hypertriglyceridemia) after adjustment for multiple variables [24].

Chonchol et al. observed that vitamin D deficiency is strongly and independently associated with manifest CVD in type 2 diabetic with mild kidney dysfunction [25]. We also found in a group of type 2 diabetic patients with chronic kidney disease, stages 3 and 4, that patients with higher carotid intima-media thickness had lower 25(OH)D3 levels [26] and that 25(OH)D3 levels were inversely correlated with the left ventricular mass index [27].

Active vitamin D has direct and indirect effects on CV system and may modulate key processes involved in the pathogenesis of CV disease [21]. The extra renal pool of 1α-hydroxylase seems to remain intact in kidney disease and the active form of vitamin D seems to work as a paracrine or autocrine hormone by binding to the vitamin D receptor which is present in many body cells, including, cardiomyocytes, vascular smooth muscle cells and endothelium [21,28,29]. The mechanisms through which vitamin D may modulate the development of cardiovascular disease has not been fully elucidated but several mechanisms have been proposed including

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vascular inflammation, plaque aggregation/thrombogenesis, impaired glycemic control, insulin resistence, endothelial dysfunction, vascular smooth muscle cell proliferation, impaired renin-angiotensin system regulation, cardiomyocite proliferation, vascular calcification, myocardial fibrosis and proliferation [29-31].

Vitamin D also regulates expression of collagen-degrading proteinases, including the matrix metalloproteinases, which are responsible for vascular wall and myocardium remodeling [30].
In spite of all these actions the PRIMO study did not show any benefit in terms of left ventricular hypertrophy regression in a group of patients with chronic kidney disease [32].

Vitamin D have an important role in renin synthesis reducing the activity of renin-angiotensin-aldosterone system that lead to a decrease blood pressure and a favorable effect on volume status [28-31]. Other antihypertensive effects of vitamin D are: PTH suppression, reno and vasculo-protective properties and anti-inflammatory and anti-diabetic actions [33].

Vitamin D has been recently showed to possess immunoregulatory properties and is deficiency has been linked to inflammation in heart and vascular wall that may be ameliorated with its correction down-regulating nuclear factor gene expression, activating anti-inflammatory cytokines (e.g. IL-10) and inhibiting pro-inflammatory markers like TNF-α and IL-6 [28,30,33].

Anti-atherosclerotic vitamin D effects may include inhibition of macrophage cholesterol uptake and foam cell formation, down regulation of vascular smooth muscle cell proliferation and migration, suppression of inflammation-triggered endothelial activation and expression of endothelial adhesion molecules [29,33].

Conclusion

There is a bulk of evidence connecting vitamin D, diabetes and cardiovascular disease in experimental models and also in human observational studies. However, it remains to prove, in a randomized controlled trial, the advantage of using Vitamin D or its analogues in patients with renal disease. Vitamin D has pleiotropic properties and in diabetic patients with chronic renal disease there is a myriad of factors contributing to the enormous cardiovascular risk observed. We think that it is realistic to conduct further studies to ascertain the usefulness of giving Vitamin D to our patients.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

All authors contributed towords the drafting of the manuscript.

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