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Research Article

Association of Vitamin D Deficiency and Diabetes: Literature Review of Recent Research

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Abstract

Background: Vitamin D deficiency is ranked as a global problem affecting both developed and developing countries. The consequences of vitamin D deficiency was studied but still diabetes needs more focus to elucidate the risk and management of vitamin D deficiency related diabetes, however, It can be controlled by considering the risk factors involved.

Aim and Method: To stand on the latest research that links diabetes to vitamin D deficiency. Moreover, to discuss how to manage cases with vitamin D related diabetes'. We conducted a search in MEDLINE database in the last ten years using PubMed. Two independent reviewers reviewed the resulting papers and reviewed based on our inclusion criteria.

Results: Sixteen studies fulfilled our inclusion criteria. Based on our review, there was contradicting results whether vitamin D deficiency caused diabetes or not. However, all studies agreed that vitamin D intake enhanced the insulin sensitivity and blood glucose level. Furthermore, it slowed the progression to diabetes in prediabetics and post kidney transplants patients. A possible mechanism was explained as either genetics or its effect on insulin resistance.

Conclusion: The contradicting results on the deficiency of vitamin D and its relationship to diabetes has not been much researched.

Keywords: *Diabetes Mellitus; Fasting Hyperglycemia; Hyperglycemia; 1,25 Hydroxy D2; Vitamin D; Insulin Resistance*

Introduction

Vitamin D is one of the most essential components for human health. It is a fat-soluble vitamin. It has two forms either Vitamin D2 or Vitamin D3 [1]. However, the active form of the vitamin is 1,25 dihydroxy vitamin D3 [2]. It has a well-known function for maintenance healthy bones through enhancing the absorption of Calcium. Hence, it has a crucial role for bone metabolism. The primary source of vi-

tamin D is the sun; hence it is called sunshine vitamin [2]. Other sources of vitamin D include fatty fish which is rich in D3 and D2 which can be obtained through plants. The oral form of vitamin D is incorporated into the pathway of lipid transport. However, the vitamin D absorbed from the skin must pass first through hydroxylation and undergo renal activation to form the active form of vitamin D [2,3]. The active form performs a lot of physiological functions that is crucial for human health. It stimulates calcium and phosphorous absorption. It was evident that in cases of vitamin D deficiency, about half of the phosphorus are not absorbed and as much as 85% of calcium in diet is not absorbed [1-3].

Other reported physiological functions include inhibition of unnecessary cellular proliferation and controlling cellular differentiation. It was found to induce terminal differentiation [4-8]. It has anti-cancer effect through inhibiting angiogenesis [4-8]. It was found to have a protective effect against diabetes and hypertension [9,10]. It acts through stimulation of insulin secretion and inhibit renal angiotensin system [11,12]. Furthermore, it stimulates macrophage and cathelicidin production [13-17]. It was reported that 200 genes' expression are regulated through vitamin D which mediates its beneficial effect [14-17].

Vitamin D deficiency is a worldwide problem affecting one billion patients around the world [18]. It was defined as intake of vitamin D less than 0.8IU [19]. It was found that all ages are affected by deficiency even adults and pregnant women [20]. It is common in developed countries like Australia and other countries including Africa and India [18-21]. Even in United states where the food is fortified with vitamin D, it was found that 50% of children ages 1 - 5 and 70% of children ages 6 - 11 had low levels of active vitamin D [22,23]. It was estimated that vitamin D deficiency occurs in 30% of children and 60% of adults [22,23].

The risk factors for vitamin D deficiency includes race, obesity, lack of sun exposure and starvation. Race is considered one of the most important causes of vitamin D deficiency. It was found to affect sunrays absorption especially UV which is important for the pathway of vitamin D in the body. It was found that dark skinned patients need to sit for at least three to five times in the sun more than light skinned population. Fat malabsorption and intestinal pathology are also associated with Vitamin D deficiency [24,25]. Moreover, chronic diseases such as T.B, sarcoidosis and chronic granuloma had a high risk of vitamin D deficiency [24,25]. Hyperparathyroidism was associated with conversion of the vitamin D into inactive form [26,27]. In addition, drugs like anticonvulsants were associated with high metabolism of vitamin D [28].

Diabetes is one of the most investigated disease which occurs in vitamin D deficiency. It was found that deficiency of vitamin D is correlated with insulin resistance, obesity and fasting hyperglycemia. In a recent meta-analysis, it was found that the risk of diabetes mellitus was 43% lower when 25(OH)D was > 25 ng/mL (62 nmol/L) compared to 14 ng/mL (35 nmol/L). Furthermore, another study was associated with high risk of diabetes in patient with low vitamin D. Song., *et al.* also reported the protective effect of vitamin D [29].

The recent evidence needs more investigation, that's why, in this study, we are reviewing the last ten years of research into this area to unveil the latest results and direct the future research.

Methods

MEDLINE database was searched for studies in the last 10 years using PubMed. We used the MeSH (Medical Subject Headings) terms for vitamin D and diabetes. A manual search was conducted searching the references of the included studies and the related studies in PubMed. We also searched systematic reviews for any relevant papers. We only included human studies assessing the relationship between diabetes risk and vitamin D from 2009. We excluded conference papers, reviews, abstract only papers and books.

Two reviewers independently reviewed the found papers for fulfilling the inclusion criteria.

Results and Discussion

The databases search yielded 4531 paper; after title/abstract screening, we had 230 studies that fulfilled our inclusion criteria. Full text screening yielded sixteen studies that was included in our review. The studies fall under two categories; one that investigated vitamin D deficiency as a direct cause of diabetes, other studied the effect of vitamin supplementation on diabetes. Twelve studies investigated

the association between vitamin D and diabetes. One study assessed the relationship between insulin resistance and vitamin D deficiency. Three studies assessed the effect of vitamin D supplementation on the diabetic state.

Does vitamin D deficiency cause diabetes mellitus?

Twelve studies assessed the causal relationship between diabetes and vitamin D deficiency. A case control study in Australian population revealed that vitamin D levels were inversely associated with diabetes. They found that increase of vitamin D levels of 25 nmol/L was associated with 24% lower risk of type 2 diabetes [30]. Consistent with this study, it was found that low vitamin D was associated with diabetes mellitus. In this study, they conducted meta-analysis to see if the results of the analysis were consistent with the other studies [31]. The results of the meta-analysis revealed that the results were consistent with the previous literature [31]. Three other studies supported the same hypothesis and found that vitamin D deficiency was associated with higher risk of diabetes [32-35]. one of the studies illustrated that BMI abolished the risk of diabetes in case of vitamin D deficiency [34]. Another study assessed the risk of diabetes after kidney transplant. They assessed the time to development of diabetes based on the level of serum vitamin D. They found that vitamin D deficiency accelerated the development of diabetes in these patients [36].

A study that tried to explain the reason for positive association between vitamin D deficiency and diabetes found that vitamin D binding protein SNPs can illustrate the cause of this association. They found that these SNPs are absent in black and they did not have risk of diabetes on low vitamin D levels [37].

On the contrary to the previous studies, other studies found that the vitamin D deficiency was not associated with diabetes in elderly [38-41]. The common factor in all these studies that it studied the vitamin D deficiency in elderly.

Is insulin resistance a possible cause of action?

A study assessed the state of insulin resistance in a cohort of nondiabetic healthy participants for median follow-up period up to year and a half [42]. They assessed the levels of vitamin D and HOMA-IR. They found that per each 25 nmol/Litre increment of vitamin D, there was significant decrease in both HOMA-IR and fasting blood glucose. They found that hypertension increased the incidence of insulin resistance associated with vitamin D deficiency [42]. The same was found for overweight and obesity which were associated with significant increase of the risk of insulin resistance. Surprisingly, smoking and alcohol consumption decreased the risk of insulin resistance associated with vitamin D deficiency. Physical exercise was also associated with less risk of insulin resistance. The limitation of the study that they used HOMA-IR as a test for insulin resistance which is not the golden standard test. In addition, there were other confounders that was not mentioned in this study [42].

Will the intake of vitamin D enhance the glycemic status in diabetic patients?

Three studies assessed the effect of vitamin D intake on the glycemic control either in pregnancy in gestational diabetes mellitus, prediabetics or diabetes type II [43-45]. Asemi., *et al*. assessed the effect of vitamin D intake on the metabolism of carbohydrates, and lipids. The study divided the participants into two groups: one group received 50,000 IU vitamin D3 twice one capsule at the baseline and at day 21 of the intervention [43]. They found that increase in the blood level of serum vitamin D was associated with low fasting blood glucose and low serum insulin. There was also significant increase in the Quantitative Insulin Sensitivity Check Index indicating enhanced insulin sensitivity [43].

In case of the other study, they recruited participants with both diabetes mellitus and hypovitaminosis D [44]. The case group received calcirol 60,000 IU every week for first six weeks and then once every 4 weeks for six months. They found that HBA1C, fasting blood glucose and postprandial glucose was significantly decreased and they recommended vitamin D supplementation in cases of vitamin D deficiency as an adjuvant treatment [44].

A clinical trial on the prediabetics inferred that vitamin D deficiency was a direct cause of impaired glucose tolerance in these patients. They measured Fasting plasma glucose, 2-h oral glucose tolerance test plasma glucose, Homeostatic Model Assessment of Insulin Resis-

tance, and the rate of progression of glucose tolerance [45]. They found that there was increased insulin sensitivity, decreased fasting and post prandial glucose level. Furthermore, it slowed the progression of the prediabetes to the diabetic state [45].

ID	Country	Study design	Sample size	Purpose
Niromand/2019 [45]	Iran	RCTs	N = 162	Vitamin D supplementation as a treatment for diabetes
Heath/2019 [46]	Australia	Case control	N =1884	Vitamin D deficiency as a cause of diabetes
Upreti/2018 [47]	India	RCTs	N = 60	Vitamin D supplementation as a treatment for diabetes
Napoli/2016 [38]	USA	Prospective cohort study	N = 1939	Vitamin D deficiency as a cause of diabetes
Le Fur/2016 [36]	France	Prospective cohort study	N = 444	Vitamin D deficiency as a cause of diabetes
Pham/2015 [42]	Canada	Longitudinal study	N = 5730	Vitamin D deficiency as a cause of insulin resistance
Reis/2015 [37]	USA	Nested prospective cohort study	N = 10222	Vitamin D deficiency as a cause of diabetes
Schafer/2014 [40]	USA	Prospective cohort study	N = 5463	Vitamin D deficiency as a cause of diabetes
Veronese/2014 [41]	Italy	Population-based cohort study	N = 2227	Vitamin D deficiency as a cause of diabetes
Asemi/2013	Iran	RCTs	N = 54	Vitamin D supplementation as a treatment for diabetes
Afzal/2013 [31]	Denmark	Cohort study	N = 9841	Vitamin D deficiency as a cause of diabetes
Deleskog/2012 [35]	Sweden	Nested case-control study	N = 980 women, N = 1398 men	Vitamin D deficiency as a cause of diabetes
Forouhi/2012 [32]	United Kingdom	Nested case-cohort study	N = 1447	Vitamin D deficiency as a cause of diabetes
Gagnon/2011 [33]	Australia	Prospective study	N = 5200	Vitamin D deficiency as a cause of diabetes
Robinson/2011 [39]	USA	Nested case-control study	N = 5140 (postmenopausal)	Vitamin D supplementation as a treatment for diabetes
Grimnes/2010 [34]	Norway	Cohort study	N = 4157 non -smokers N = 1962 smokers	Vitamin D deficiency as a cause of diabetes

Table 1: *The characteristics of the included studies.*

Conclusion

There is still contradicting evidence if the vitamin D deficiency was associated with diabetes mellitus or not. However, vitamin D supplementation in prediabetics or in cases of diabetes mellitus was associated with better glycemic control and slow progression to higher glucose and insulin levels.

Conflict of Interest

None.

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