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Short Review

A Short Review on Potential Extra-skeletal Benefits of Vitamin D with Special Reference to Type-2 Diabetes mellitus

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ABSTRACT

Vitamin D, the "sunshine vitamin" mainly benefits bones and muscles. Over the past few decades, it has generated lot of interest in scientific community regarding its extra skeletal health benefits. These benefits range from neurodegenerative diseases to metabolic conditions, cardiovascular disease, lung infection and cancer. The present short review will highlight its extra skeletal beneficial health effects in particular the present thinking on vitamin D and diabetes mellitus.

KEYWORDS: Sunshine vitamin, Eldecalcitol, Cholcalciferol, Pre-diabetes, Insulin Resistance

INTRODUCTION

Vitamin D has been incriminated as the main factor promoting growth and fitness of bones as well as cognitive health. Over the past few decades, interest has been generated for its extra skeletal health benefit. There are many clinical situations which have been linked to Vitamin D deficiency states. Interestingly but really alarming, Vitamin D deficiency has become a common biochemical finding. It is difficult to trace the exact cause of Vitamin D deficiency, but the two important mechanisms are the possibilities. Firstly, the vitamin is not found in a lot of commonly eaten food and secondly, the primary source, the sun, its exposure may be limited depending upon the living conditions and social upbringing.

Extra-skeletal Health Benefits of Vitamin D

Vitamin D and Respiratory Infections

The role of vitamin D has been linked to respiratory illness including COVID-19. Preliminary research data found that Vitamin D supplementation may be beneficial in preventing the common respiratory illness. In a systemic review and meta-analysis, it was found that Vitamin D supplementation protected against the respiratory tract infection without side effects. The patients, in whom the Vitamin D levels were very low, benefited most[1].

As far as the connection between Vitamin D levels and COVID-19 is concerned, it is still not authenticated. However, in an unpublished study by researchers at North Western University in Chicago, observed that countries with high prevalence of Vitamin D deficiency had higher rates of COVID-19 mortality rate. Vitamin D has been known to play a role in immune system and there are Vitamin D receptors on immuno competent cells. Vitamin D deficiency therefore, may increase the body`s susceptibility to infection and its supplementation is therefore beneficial.

Vitamin D and Psychiatric illnesses

Vitamin D is also nicknamed as "sunshine vitamin" and conditions like seasonal affective disorder and depression are linked with its deficiency.

In a study (Sunshine Study) conducted on women with type 2 diabetes who had significant depressive symptoms and were administered 50,000iu of Vitamin D weekly for six months. The result obtained was, that there was a significant ($p<0.001$) decrease in depression and anxiety along with improvement in mental health[2].

A strong association was found between vitamin deficiency and schizophrenia in a systemic review and meta-analysis from 19 observational studies[3].

Vitamin D and risk of dementia including Alzheimer disease was assessed in more than 1600 elderly people without dementia at the start of the study. Comparing the Vitamin D levels in those who had normal values and those with low levels; it was observed that people with low levels of vitamin D had a 53 percent more risk of developing all-cause dementia. On the other hand, those were severely deficient had a 125 percent increased risk of developing dementia. People with lower levels of Vitamin D were 70 percent more chance to develop Alzheimer`s disease specifically, while severely deficit individuals had more than 120 percent chance to develop this neurodegenerative disorder of elderly[4].

Prostate Cancer Risk and Vitamin D Levels

In a meta-analysis of 21 relevant publications including 11,941 cases and 13,870 controls, it was revealed that a significant 17 percent increased risk of prostate cancer for the study subjects with higher levels of Vitamin D[5]. On the contrary, previous study reported earlier, found a link between low levels of Vitamin D and aggressive prostate cancer in African American and European men.

Vitamin D and Breast Cancer

Besides prostate cancer, a link has also been seen with Vitamin D deficiency and breast cancer. A review published in 2018 found that most of the studies support that there is an inverse association between the level of Vitamin D and the risk of breast cancer[6,7].

Erectile Dysfunction and Vitamin D Levels

A small study conducted on 143 patients with varying severity of erectile dysfunction (ED) to assess their Vitamin D levels. They found that the men with severe ED had significantly lower Vitamin D levels than the men with mild ED. Furthermore, it was interesting that this combination of ED with low level of Vitamin D was more frequent in patients with arteriogenic etiology, suggesting that low levels of Vitamin D may increase ED by promoting endothelial dysfunctions[8].

Vitamin D Deficiency and Cardiovascular Diseases

Literature reviewed points towards the relation between Vitamin D and heart problems. It may be a potential risk factor for health problems related to heart disease including hypertension, atherosclerosis, diabetes and stroke. However, it still not established whether Vitamin D supplementation will reduce the cardiac risk.

A recent study, conducted on Vitamin D supplementation and development of cardiovascular events, indicated that Vitamin D supplementation might reduce the incidence of major cardiovascular events, but absolute risk difference is small. However, it can also not be concluded that Vitamin D administration does not alter the risk of cardiovascular diseases[9].

Vitamin D and Diabetes

The exponential increase of T2DM is a great cause for concern and if left untreated, T2DM can lead to a multitude of chronic microvascular and macrovascular conditions such as retinopathy, nephropathy, neuropathy and cardiovascular disease (CVD)[10]. The enormity of the T2DM epidemic and its sequelae emphasize the importance of finding ways to prevent and/or ameliorate the deleterious effects of this disease. In addition to genetics which predisposes individuals to developing T2DM, there are also many environmental factors which contribute greatly to its development[11]. A plausible explanation of pathophysiology of T2DM is a requisite to understand the relationship between Vitamin D status and T2DM before reviewing the evidences for their association.

PATHOGENESIS OF TYPE 2 DIABETES:

In a normoglycemic individual, in response to a rise in blood glucose, the β-cells of the islets of Langerhans, found within the pancreas, will synthesize and secrete insulin into the blood[12]. A malfunctioning of the feedback loops between insulin action and insulin secretion results in abnormally high glucose levels in blood[13]. T2DM is a progressive chronic disease; it begins with insulin resistance, which leads to increases in hepatic glucose production and ends with β -cell failure[14,15].

In the case of β-cell dysfunction, insulin secretion is reduced, limiting the body's capacity to maintain physiological glucose levels. On the other hand, IR contributes to increased glucose production in the liver and decreased glucose uptake both in the muscle, liver and adipose tissue[16].

T2DM pathophysiology involves at least seven organs and tissues, including the pancreas, liver, skeletal muscle, adipose tissue, brain, gastrointestinal tract, and kidney (Figure 1). Reduced sensitivity to insulin (i.e., impaired insulin-mediated glucose disposal or insulin resistance) in liver, muscle, and adipose tissue, and a progressive decline in pancreatic β-cell function leading to impaired insulin secretion, eventually result in hyperglycemia, the hallmark feature of T2DM[17].

VITAMIN D AND T2DM:

Synthesis of 1, 25-Hydroxyvitamin D:

When the skin is exposed to solar ultraviolet B radiation (wavelength, 290 to 315 nm), 7-dehydrocholesterol is converted to pre-vitamin D3, which is rapidly converted to Vitamin D3 (cholecalciferol). Vitamin D from the skin and diet is then transported in the blood by circulating vitamin D-binding protein (DBP, a specific binding protein for Vitamin D and its metabolites in serum).

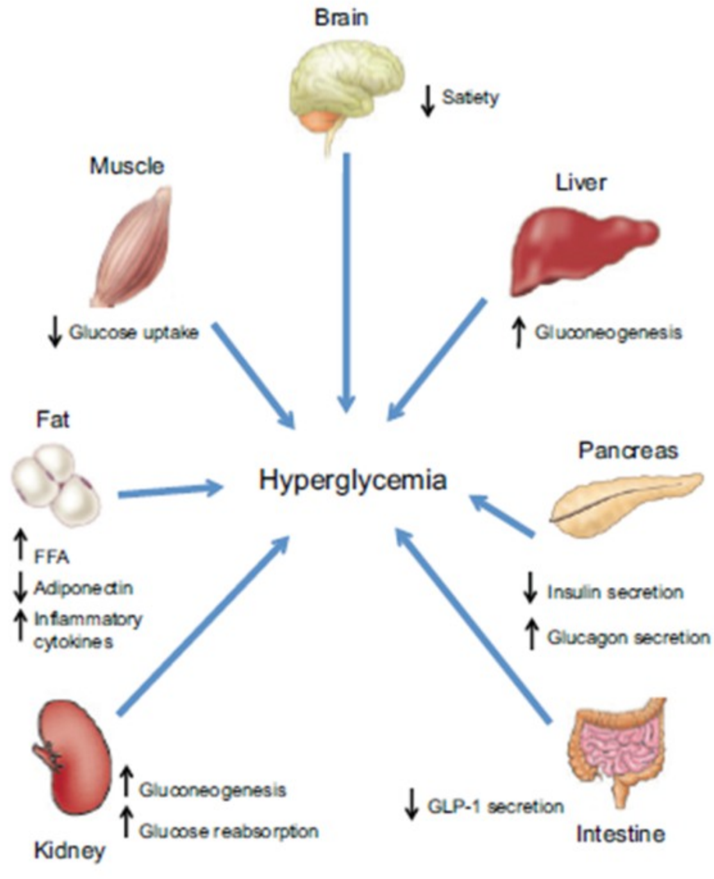

Figure 1: Multi-organ and tissue pathophysiology of type 2

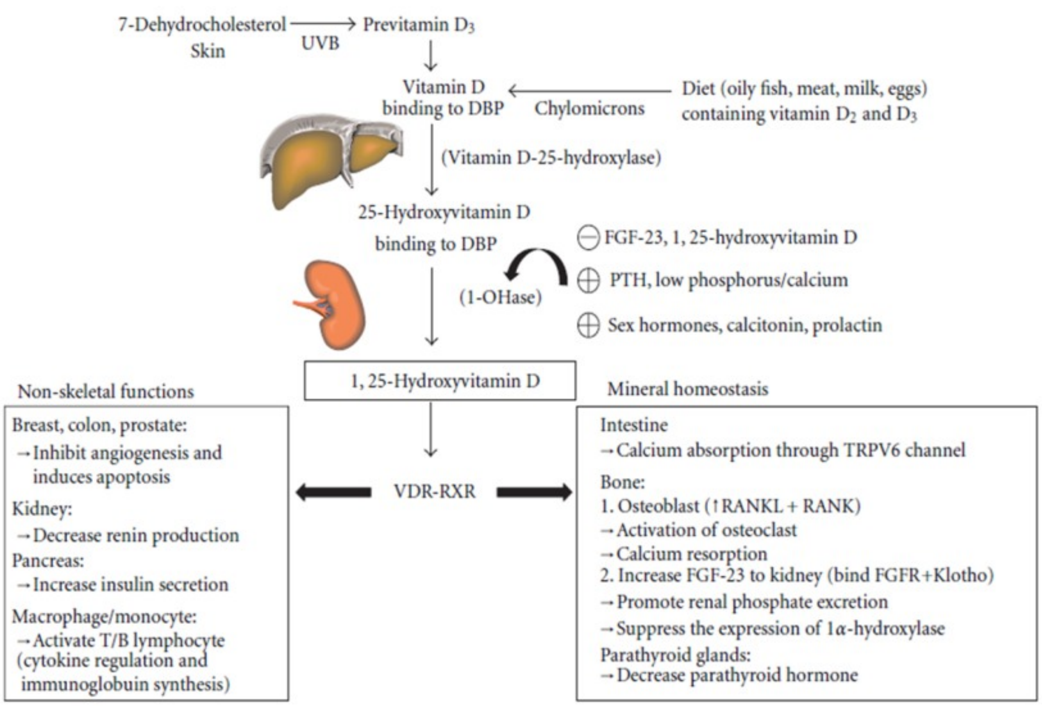

Figure 2: Synthesis and Metabolism of vitamin D in the regulation of mineral homeostasis and Non-skeletal functions.[18]

Link between Vitamin D Deficiency and Insulin Resistance:

Vitamin D has been proposed to play an important role and to be a risk factor in the development of insulin resistance and the pathogenesis of type 2 DM by affecting either insulin sensitivity or β-cell function, or both[19].

In keeping with the notion that T2DM cannot manifest without β-cell failure, it is important to examine the role of Vitamin D metabolites (i.e., 1, 25(OH) 2D3) in pancreatic β-cell function. Vitamin D is reported to be essential for insulin secretion from pancreatic β–cells[20] in both in vitro and in vivo studies[21,22,23]. The mechanisms by which Vitamin D acts on insulin secretion are thought to be both direct and indirect; in particular, the direct effect of vitamin D on insulin synthesis and secretion is suggested by the demonstrated binding of the active form 1, 25(OH) D to the vitamin D receptor on β-cells, by the identification of vitamin D response elements in the human insulin gene promoter[24], and by the transcriptional activation of the human insulin gene caused by 1, 25(OH) D25. Instead, the indirect effects of Vitamin D on β-cell secretory function seem to be mediated by alterations in calcium flux through the β-cell membrane, as suggested by a study conducted by Beaulieu *et al.*[26].

Another plausible explanation given is based on low-grade inflammation characterized by increase in circulating cytokines, which is one of the hallmarks of T2DM. High amounts of circulating inflammatory cytokines, such as TNF α and IL-6, contribute significantly to insulin resistance in muscle and adipose tissue[27]. To help establish a protective role for vitamin D and its respective metabolites against T2DM, **Riachy et al.** examined the effects of 1,25(OH)2D3 on human islets in the presence of cytokines and found that islets incubated with cytokines and 1,25(OH)2D3 were protected against apoptosis compared to those incubated with cytokines alone[28]. Moreover, the identification of the VDRE in the insulin receptor gene promoter has also helped establish a role for 1, 25(OH) 2D3 in increasing insulin sensitivity by increasing insulin receptor gene expression[24]. Furthermore, Vitamin D3 supplementation has been shown to reduce inflammatory cytokines such as IL-6 and TNF-a, which play a significant role in inducing insulin resistance[29].

Following chart summarize the role of Vitamin D deficiency in Insulin Resistance and hence, Diabetes as per the evidences available from literature:

Role of Vitamin D Deficiency in Insulin Resistance	Study Reference
Inherited gene polymorphisms • Including DBP, VDR, and CYP1alpha gene polymorphisms • Disturbance of Vitamin D transport, action, and production	18,30,31
Immuno-regulatory function • Activating innate and adaptive immunity • Enhancing dendritic cell maturation and macrophage differentiation, and cytokine release • Enhancing T-cell proliferation Releases of IL-12, IL-2, INF-γ, and TNFα (destruction of the β-cell)	18,32-34
Inflammation • Upregulation of NF-κB and inducing TNFα proinflammatory actions • Downregulates IκB-α by decreasing mRNA stability and increasing IκB-α phosphorylation. • Enhancing the expression of TLR2 and TLR4 protein and mRNA in human monocytes, reducing the release of cytokines	24,27-29,35
Other molecular actions of vitamin D to alter glucose homeostasis • Low calcium status: hypocalcemia can lower glucose-stimulated insulin secretion in β-cell • PTH level: elevating PTH reduces glucose uptake by liver, muscle and adipose cell • Obesity: Vitamin D deficiency can increase adiposity, and increasing sequestration of Vitamin D in adipose tissue TLR2 and TLR4 protein and mRNA in human monocytes, reducing the release of cytokines	18,36,37

In order to assess the correlation between Vitamin D levels and diabetes mellitus, many prospective case control and cross-sectional studies have been conducted throughout India as well as the globe. In India, results have been reported from Kolkata, Eastern India, Tirupati from south and Rajasthan from the west. Other studies have been reported from Kenya, Saudi Arabia, Korea, Brazil and Riyadh. Many reviews and meta-analysis of randomized controlled trials have also been published with different population and subsets of patients.

REVIEW OF STUDIES

A prospective case control study found out the Vitamin D status in newly detected T2D patients. One hundred and two, newly detected T2D patients and similar number of age, body mass index (BMI), and gender matched healthy controls without diabetes were studied. Overall 25HD, was lower (mean ± SD, 18.81 ± 15.18 ng/ml) in patients with T2D as compared to healthy controls (28.46 ± 18.89 ng/ml). Severe VDD (25HD of < 5 ng/ml) was seen in 16.2% of patients with diabetes and 2.5% of control subjects. Conclusion was drawn that the mean serum 25HD was significantly lower in people with diabetes compared with controls[38].

To determine the prevalence of Vitamin D deficiency in Asian Indians with Type 2 diabetes mellitus (T2DM) living in north India a study was conducted on a total of 92 patients with T2DM and were compared with nondiabetic patients (n = 92) matched for age, gender, BMI, waist circumference and total body fat. The average concentration of serum 25(OH) D3 was significantly lower for T2DM patients as compared with non-diabetic patients. Severe vitamin D deficiency was significantly more prevalent among T2DM patients (57.6%) than the non-diabetic patients (33.3%). The average concentration of serum 25(OH) was significantly lower for diabetic males than diabetic females (9.07 ± 6.7 vs. 12.6 ± 7.6, p = 0.02). Conclusion was made that the prevalence of severe Vitamin D deficiency among Asian Indians living with T2DM in a metropolitan city of north India was greater than those without T2DM and this difference was statistically significant[39].

The occurrence of Vitamin-D insufficiency/ deficiency among Pre-diabetics and the relationship between Vitamin-D status and insulin resistance was also addressed in a study carried out on 157 pre-diabetics along with 42 diabetics and 28 controls attending department of Endocrinology and Metabolism, Institute of Postgraduate Medical Education & Research, (IPGMER) and SSKM hospital, Kolkata, India.It was estimated that out of 157 subjects Vitamin-D deficiency/ insufficiency was 73.25% (n=115), 66.6% (n=28) and 78.57 % (n=22) in individuals with pre-diabetes, diabetes and controls respectively. A statistically significant inverse correlation was observed between Vitamin D and insulin resistance (HOMA2-IR; r=-0.33, P=0.008); and a positive correlation with measures of insulin sensitivity (QUICKI, 1/fasting insulin). Conclusion was drawn that Vitamin-D deficiency/insufficiency may play role in the development or worsening of insulin resistance in pre-diabetic individuals[40].

In a cross-sectional study conducted in a Tertiary Care Hospital of Eastern India, the prevalence of Vitamin D deficiency in new onset type 2 diabetes mellitus as well as the association between 25 hydroxy vitamin D with insulin resistance and insulin secretion was explored. The study was carried out for a duration of 18 months over 120 newly diagnosed cases of type 2 diabetes which were compared with 120 non-diabetic healthy controls. Results showed that there was significantly lower vitamin D level (p< 0.001) in cases (mean =24.91± 14.58 ng/ml) as compared to controls (mean=41 ± 28.33 ng/ml). 30% subjects (n=36) and 29.16% (n=35) were having insufficient Vitamin D levels among cases and controls respectively. Similarly, 30% (n=36) and 19.16% (n=23) were deficient among cases and controls respectively. As per the revealed results conclusion was drawn that 25(OH) D had significant negative association with insulin resistance[41].

Prevalence of hypovitaminosis D among type 2 diabetic patients at Kenyatta National Hospital in Nairobi, Kenya was determined through a cross-sectional study. A total of 151type 2 diabetic patients on follow-up were recruited. Results reported that the mean Vitamin D level was 31.40 ng/ml (±23.22). Vitamin D deficiency was found in 58 study participants (38.4%). The study brought out that population on a long-term follow-up for diabetes, there was high prevalence of vitamin D deficiency. This forms a basis for further management of patients with poor glycemic control[42].

Across sectional study investigated the prevalence Vitamin D deficiency in male patients with T2DM. 1145 patients with T2DM attending the Diabetes centre at King Fahad Armed Forces Hospital, Saudi Arabia between January 2018 and December 2018. The prevalence of different Vitamin D status were; 55.6% deficient, 27.3% insufficient and 17.0% sufficient. Vitamin D deficient patients have statistically significant higher HbA1c than patients with vitamin insufficiency or sufficiency (8.3 ± 2.0 vs. 7.7 ± 1.7 vs. 7.4 ± 1.7 respectively, p<0.0001). Moreover, Vitamin D deficient patients have statistically significant lower 25(OH) D than patients with vitamin insufficiency or sufficiency (34.3 ± 8.9 vs. 60.6 ± 7.2 vs. 100.3 ± 23.0 respectively, p<0.0001). The mean 25(OH) D was upward as age advanced with highest frequency of VDD was found in the sixth decades. Conclusion revealed that the prevalence of VDD in male patients with T2DM was high[43].

A cohort study explored the association between 25-hydroxy vitamin D and type 2 diabetes (T2D) risk. 1080 nondiabetic Korean subjects based on the presence of one or more risk factors for T2D, including obesity, hypertension, dyslipidemia, and/ or family history of T2D were recruited for the study and followed up for 5 years. Anthropometric and biochemical indicators, HOMA2-IR, and the insulinogenic index (IGI) were measured. Results revealed that 0.5% had a serum 25(OH) D deficiency, 51.6% had an insufficiency and 38.0% had a sufficiency. Out of 1080 participants, 97 (9.0%) developed T2D over 32.3 6 15.6 months of observation. The incidence rates of T2D (Hb A1c ⩾6.5%) came out to be 15.9%, 10.2%, and 5.4% in the 25(OH) D-deficient, insufficient, and sufficient groups, respectively (P < 0.01). It was concluded that independently of known risk factors, Vitamin D metabolism play a role in pathogenesis of T2D[44].

Blood levels of Vitamin D3 and its association with type 2 DM in rural ethnic population was assessed in a cross- sectional study undertaken from February 2018 to January 2019 at Multidisciplinary Research Unit of Agartala Government Medical College. A total of 208 ethnic subjects were recruited in this study using multistage sampling technique. 65% prevalence of Vitamin D3 insufficiency was observed as per the reported results. It was revealed that out of 208, 136 subjects had blood Vitamin D3 insufficiency while 72 subjects were with sufficient amount of Vitamin D3 level. The findings of this study also suggested a much higher prevalence of Vitamin D3 insufficiency in the age range of 51–61 years[45].

A prospective study was carried out in D. Y. Patil University, School of Medicine for a duration of 1 year to assess the correlation of Vitamin D deficiency with T2D and metabolic risk factors in Indian population. A total of 144 subjects were recruited for the study, out of which 74 were diabetic and 70 were non-diabetic controls. Analysis of the data revealed that 13.51% of the diabetics to be Vitamin D deficient as compared to 28.57% deficient among the non-diabetics. This study found out an inverse relation between Vitamin D and serum cholesterol ($p=0.01$) and it was also statistically significant for Vitamin D and low-density lipoprotein ($p=0.01$)[46].

In another study conducted in 2017, the association between serum Vitamin D levels and glycemic control markers in type 2 DM patients was analysed. 80 diagnosed subjects of Type 2 DM reporting to Endocrinology and Metabolism outpatient department of Sri Venkateswara Institute of Medical Sciences, Tirupati were included in the study. Subjects were divided into two groups; n=38 (with Vitamin D >20 ng/mL - Vitamin D non-deficient) and n = 42 subjects with Vitamin D ≤ 20 ng/ mL (Vitamin D deficient). Results revealed that there was no significant association between Vitamin D and markers of glycemic control- FBS, PPBS, HbA1c and Insulin resistance[47].

The relationship between Vitamin D levels and ages of type 2 diabetes individuals was assessed in a descriptive-analytical study conducted on 101 type 2 diabetes patients. The mean age of the subjects was 61.25 ± 11.75 years. Out of 101 diabetic patients, 72 individuals suffered Vitamin D deficiency which is 71.3%. Findings of the study suggested that serum Vitamin D levels of type 2 diabetic subjects were significantly correlated with their ages ($r = 0.282$, $P = 0.004$)[48].

Another study determined the vitamin D status among type 2 diabetics and examined the association of Vitamin D status with level of glycemic control. Subjects were divided into 3 groups- group I consisting of 48 healthy controls, group II having 46 patients with DM history of more than five years and HbA1c levels < 7% and Group III comprising of 56 patients with DM history of more than five years and HbA1c levels > 7%. Results of the study showed that diabetic patients had lower Vitamin D levels in comparison to healthy individuals and the value further decreases in patients with poor glycemic control (HbA1c >7%). It was also concluded that there was significant negative correlation between HbA1c and Vitamin D levels (r= -0.94 and -0.97 respectively)[49].

Prevalence of Vitamin D deficiency and its correlation with diabetes among menopausal women was also evaluated in a cross sectional one year analysis. A total of 312 Post-menopausal women were recruited in this study. Fasting blood glucose levels were used to analyse any Correlation between raised blood sugar levels and Vitamin D deficiency among postmenopausal women (PMW). Although results have shown high Vitamin D deficiency (53.35%) among the study population but it failed to show any statistical significant association between Vitamin D deficiency and existence of diabetes. Conclusion was made that statistical correlation between Vitamin D deficiency and existence of diabetes was not significant because of the small sample size[50].

The effect of Vitamin D supplementation on glycemic control and insulin resistance in Type 2 Diabetes Mellitus was explored in a Pre-post Intervention Trial. Fasting and postprandial blood samples were collected from the 300 known cases of Type 2 Diabetes mellitus and controls, which were further divided into 2 groups- Group I (subjects with normal Vitamin D level >20ng/ ml), no Vitamin D supplementation was given, whereas Group II (with decreased Vitamin D level <20 ng/ml), oral supplementation of Vitamin D, 60,000IU/week for 4 weeks was given. Results showed that prevalence of Vitamin D deficiency (< 20 ng/mL) in type II diabetes individuals was 30%. It was revealed that after supplementation to the Vitamin D deficient Diabetic group there was a significant decrease in Fasting plasma glucose (p-value 0.0028). Also, a statistically significant decrease was observed in Fasting serum insulin levels ($p < 0.0031$) and insulin resistance (p=<0.0001) after 4 weeks of Vitamin D supplementation. The Conclusion was drawn that Vitamin D supplementation in Diabetics could be beneficial in management of Type 2 DM[51].

Correlation between Vitamin D level and glycemic control in type 2 diabetics was investigated in a study conducted on 50 type-2 diabetes patients attending Medicine OPD and Geriatric OPD in PBM Hospital Bikaner Rajasthan. Result of this study revealed an inverse between Vitamin D level and HBA1c which meant Vitamin D status is inversely related to glycemic control. The conclusion was made that Vitamin D deficiency is prevalent in type 2 diabetes mellitus patients. Hence, supplementation of Vitamin D can improve their glycemic control which can further reduce the complication of diabetes[52].

The status of Vitamin D among type 2 diabetes mellitus patients was investigated in a systematic review including 12 Saudi studies. There were nine cross-sectional studies, two randomized case-control studies and one study whose design was not mentioned. In 10 studies14,373 T2DM patients participated and in the remaining studies there were 272 T2DM patients and 273 controls. Results showed that the prevalence of Vitamin D deficiency varied in a range of37.6% to 80% among the included studies. Four studies found that HbA1c was higher among T2DM patients with Vitamin D deficiency than patients without deficiency of the vitamin. On the contrary three studies found a negative correlation between HbA1c and Vitamin D deficiency, where HbA1c was higher among T2DM patients without Vitamin D deficiency. It was concluded that the prevalence of Vitamin D deficiency was high among T2DM patients especially among older patients[53].

Predictors of hypovitaminosis D in patients with type 2 diabetes mellitus patients were identified in a cross-sectional study on 108 patients recruited from Endocrinology outpatient clinic, Brazil. Results of the study revealed that the overall prevalence of hypovitaminosis D was 62% (39.8% insufficient and 22.2% deficient). In this study p = 0.02), dyslipidemia (OR 6.50, p < 0.01) and obesity (OR 2.55, p = 0.07) emerged as independent predictors of Vitamin D deficiency. HbA1c (r = −0.22, *p* = 0.03) showed significant inverse linear correlations with vitamin D levels. Based on these results conclusion was made that future studies are needed to evaluate whether vitamin D replacement would help reducing cardiovascular outcomes[54].

The impact of Vitamin D on glycemic control in patients with type 2 diabetes mellitus was analysed in a study conducted on 128 diabetic patients. Based on HBA1c values patients were divided into two groups: good glycemic control (HbA1c ≤ 7%) and poor glycemic control (HbA1c>7%). In this study Vitamin D deficiency rate was found to be 98.3%. Although there were high level of Vitamin D deficiency, results of this study indicated that Vitamin D was not significantly associated with glycemic control in type 2 diabetes mellitus subjects. (P value >0.05)[55].

The hypothesis that low 25(OH) D levels are associated with poorer glycemic control in diabetes mellitus (DM) patients was investigated in a prospective observational cohort study carried over 1000 type 1 and type 2 diabetes patients reported to outpatient clinics of a tertiary centre in Riyadh. Baseline HbA1c and vitamin D levels were recorded prior to supplementation and after a period of 9 months of supplementation with vitamin D. Results of the study revealed a total of 73.1% of patients having 25 (OH) D deficiency. HbA1c levels were found to be inversely correlated to 25 (OH)D levels (r = -0.14 (P=< 0.0000002). it was observed that the mean HbA1C dropped down to 7.70 form 10.55 after Vitamin D supplementation to the patients. It may be concluded based on the findings of this study that advising regular check on Vitamin D levels and correcting any deficiency would result in better blood glucose control[56].

A cross-sectional study conducted in 2016 investigated serum 25-hydroxy Vitamin D level in diabetic patients and compared it to the normal individuals. Study was conducted on a total of 106 subjects, 75 of those were free of diabetes while 31 were type 2 diabetics. Results have shown that the prevalence of Vitamin D deficiency (<50 nmol/l) was 88.87% in diabetic and 92% in normal subjects respectively which meant that level of Vitamin D was 8% lesser in diabetics in comparison to non-diabetics. However, the mean serum level of Vitamin D was not significantly different between the two groups (P=0.788). There was significant positive association of Vitamin D level with age in subjects with normal glucose levels[57].

A review paper published in 2011 summarized the relation between Vitamin D and diabetes and discussed the mechanism of action of vitamin D and its implications on health. Two main forms of Vitamin D: ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3) were clinically understood, highlighting the mechanism and dietary recommendations. 2-step process of conversion in the liver and kidney for both the forms was explained. Also, authors discussed binding of active form, 1, 25-dihydroxyvitamin D to Vitamin D receptors (VDRs). This mechanism explained why diabetics having pre-existing liver and kidney are amenable to high risk of Vitamin D deficiency. Supported by observational and experimental evidence, it was concluded that Vitamin D status appears to play a role in the development as well as treatment of diabetes and reasonable supplementation of Vitamin D can possibly reduce incidence of diabetes mellitus[58].

Over the past decade, Vitamin D deficiency has been linked to an increase risk for a number of extra skeletal conditions including type to diabetes. Its antidiabetic properties have been hypothesized to be by regulating insulin secretion or its sensitivity, its anti-inflammatory effect as well as down-regulation of elevated parathyroid hormone which impair insulin secretion[59-62]. Conflicting results also suggest its role in glucose homeostasis.

Many cross-sectional studies have highlighted that insufficient Vitamin D levels was associated with type 2 diabetes and its complications[63-65]. Also low levels of Vitamin D have been observed in obesity and metabolic syndrome- the two predisposing situations for the development of diabetes[66].

Prospective cohort studies have revealed inverse association between serum 25-OH-Vitamin D and future risk of type 2 diabetes, hyperglycemia, insulin resistance and diabetic complications[67-69]. On the contrary, a meta-analysis of four prospective cohort studies suggested no association between Vitamin D and type 2 diabetes[70].

Intervention Studies

Many intervention studies conducted so far to evaluate the effect of Vitamin D supplementation on glycemic control have shown conflicting results[71-75]. Many previous meta-analyses had methodological limitations and the findings were inconsistence[76-79].

A recent systemic review and meta-analysis of randomized controlled trials on the issue of Vitamin D supplementation and its effect on glycemic control in diabetic patients found that Vitamin D supplementation may be beneficial for reduction of fasting glucose, HbA1c and insulin resistance in patients with type 2 diabetes with deficient Vitamin D status. This significant effect was especially prominent when Vitamin D was given in large doses for a short period of time[80].

Present thinking

Recently a study published highlighting that supplementation of vitamin D reduces the risk of type 2 diabetes in people with pre-diabetes. It was a systemic review and meta-analysis from three randomized clinical trials. All three trials included in analysis were randomized, double blinded and placebo controlled. Three formulations of Vitamin D were tested: Cholecalciferol 20,000iu (500 mcg) weekly, Cholecalciferol 4,000iu (100 mcg) daily or Eldecalcitol 0.75 mcg daily against placebos[81].

The results showed that Vitamin D significantly reduced the risk of developing frank diabetes by 15 percent in adjusted analysis. The three year absolute risk reduction was 33 percent. There were no differences in the rate ratios for adverse events related to vitamin D such as kidney stones, hypercalcemia and hypercalciuria as compared to placebo.

The absolute risk reduction is small when compared with the risk reduction seen with intensive life style change (58%) and with metformin administration (31%) [82]. However, when these data are extrapolated to the 374 million adults throughout the word who are pre-diabetics suggests that this simple Vitamin D supplementation could delay the onset of diabetes in more than 10 million people.

CONFLICT OF INTEREST: None

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