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ROLE OF VITAMIN D IN DIABETES MELLITUS

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ABSTRACT: Diabetes Mellitus (DM), a global health care problem has been a burden to the socioeconomic society. The increasing incidence highlights the need for innovative approaches for the prevention and management, despite availability of various therapies for managing disease and its complications. There are several factors that seem to play a role in development of DM including genetic, lifestyle, environmental and nutritional conditions. Amongst nutritional factors, Vitamin D is likely to have an important role either in glycemic control or in attenuating diabetic complications. Vitamin D, an excellent marker of 'good' health has role in varied functions. Many of the epidemiologic studies have shown that vitamin D deficiency is associated with increased risk of chronic diseases such as cancer, cardiovascular disease, type 2 diabetes, autoimmune diseases and multiple sclerosis. Calcitriol (Vitamin D3) has reported to alter glycemic control and with some evidences pointing to its role in development of DM. Many studies done in past could not give conclusive association, hence benefit of supplementation of Vitamin D in DM patients need to be evaluated precisely.

INTRODUCTION: Type 2 Diabetes Mellitus (T2DM) is the commonly seen endocrine disorder characterized by hyperglycemia with absolute or relative insulin deficiency. As per the International Diabetes Federation, prevalence of DM in India has increased by 12-18 % in urban, 3-6 % in rural area over last 30 years.[1] By the year 2030, this significant global health care problem is estimated to affect 552 million individuals worldwide. [2] Although knowledge has been acquired on the etiology of diabetes, its precise etiopathogenesis is still under discussion.

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Recently inflammatory factors, reactive oxygen species and autoimmune reactions have strongly emerged as the major pathogenic factors for diabetes. [3]

Various therapies for type 2 diabetes and its complications have improved over the last few decades, but the increasing burden highlights the need for innovative approaches for the prevention and management of the disease.

Many risk factors play a role in etiopathogenesis and in glycemic control. To prevent development, sugar control, management of complications of DM, identification of environmental, easily modifiable risk factors (losing weight, physical activity) and use of simple natural remedies/supplements is the need of the hour in addition to existing therapy.

Achieving excellent Glycemic control is crucial in the management of diabetes as well as preventing the onset of serious and life threatening complications. Progressive beta-cell dysfunction and insulin resistance can make ant diabetic agents less effective; treatment adherence is only around 60% which could be attributed to painful injections of insulin or hypoglycemic episodes due to oral ant diabetic agents.

There are several factors that seem to play a role in its development including genetic, lifestyle, environmental and nutritional conditions. Amongst nutritional factors, Vitamin D is likely to have an important role either in glycemic control or in attenuating diabetic complications.

Adiposity and physical inactivity are strong risk factors for type 2 diabetes. Smoking, low consumption of fish or alcohol, general and central adiposity, physical inactivity are also associated with low 25-hydroxy Vitamin D concentration, an active metabolite of Vitamin D, used as a clinical indicator. [4]

Vitamin D, a fat soluble vitamin discovered in 1922 by McCollum is derived from sun exposure i.e synthesized in skin, diet including fish milk, yogurt, orange juice and cereals. [5] Hence Vitamin D deficiency could be attributed to either lack of sunlight exposure or insufficient dietary sources. It is a secosteroid synthesized in the skin by the action of ultraviolet irradiation from the sun related to bone metabolism and skeletal integrity as well. Its status is an excellent marker of 'good' health, including positive associations with young age, normal body weight and a healthy lifestyle.

It has been described as a wonder vitamin because of its possible benefits in diverse health outcomes like bone disease, coronary heart disease etc. Epidemiologic studies have shown that Vitamin D deficiency is associated with increased risk of chronic diseases such as cancer, cardiovascular disease, type 2 diabetes, autoimmune diseases, multiple sclerosis and type 1 diabetes mellitus too. [6]

Vitamin D deficiency and diabetes mellitus are two common conditions which are widely prevalent across all ages, races, geographical regions and socioeconomic conditions. The common risk factors for both conditions include American-African race, obesity, aging and low physical activity. [7]

Serum calcium levels, calcitriol (Vitamin D3) have reported to alter glycemic control and with some evidences pointing to their role in development of DM. [8] Few cross sectional studies have shown that low serum concentration of 25(OH) D3 have an association with impaired glucose tolerance and diabetes. [9-11]

Vitamin D is likely to improve insulin action directly by stimulating expression of the insulin receptors in peripheral tissues and enhancing its responsiveness for glucose transport. [12] Indirectly it could normalize extracellular calcium thus ensuring calcium influx through cell membranes to increase insulin secretion. [13] It may mediate activation of beta-cell calcium dependent endopeptidases to produce the cleavage of proinsulin to insulin. [8]

Systemic inflammatory mediators affecting Beta cells are also tackled by direct effect of Vitamin D on cytokines. Recently, Vitamin D has sparked widespread interest in the pathogenesis of diabetes and its complications. Evidences depict that its antioxidant effect has role in prevention of type 2 diabetes. [14]

The role of Vitamin D in DM is also suggested by a seasonal variation in glycemic control reported in patients with type 2 diabetes being worse in the winter which may be due to prevalence of hypovitaminosis D as a result of reduced sunlight. [13]

The clue towards the role of Vitamin D in DM has been provided by various facts. Presence of Vitamin D receptors on pancreatic β cells [15], expression of 1α hydroxylase activity at pancreatic β cells causing activation of Vitamin D. [16] Other evidences are presence of Vitamin D response element in human insulin gene promoter [17], Vitamin D receptor in skeletal muscle [18] and suppression of renin gene, increased transcription of insulin receptor genes by 1,25(OH)D.[19] Calbindin is activated by Vitamin D act as a

modulator of depolarization stimulated insulin release via regulation of intracellular calcium.

Protective effects of Vitamin D in diabetes may be due to its anti-inflammatory properties, its effects on calcium and phosphorus metabolism. [20] It plays role in the insulin sensitivity by regulating nuclear PPAR (Peroxisome proliferative activated receptor). [21] It also attenuates the expression of proinflammatory cytokines involved in insulin resistance such as interleukins, IL-1, IL-6, TNF-α, down regulates NF-Kb (Nuclear factor) activity. [22]

Additional evidence for a role of Vitamin D in type 2 diabetes comes from a large number of cross-sectional studies, which have generally reported an inverse association between Vitamin D status and prevalent hyperglycemia

Though epidemiological studies demonstrate an inverse association between low serum 25(OH) Vitamin D and glucose intolerance but some intervention trials using Vitamin D have produced mixed results [11, 12.]

Some of the observational longitudinal studies have shown an inverse association between the Vitamin D status 25(OH) D or self-reported Vitamin D intake and the development of type 2 diabetes. But some studies have revealed that glycemic control is independent of Vitamin D status.

Whether association between low 25(OH) D and DM is casual or not is yet to be proven.

Studies:

a. The Women's Health Initiative study, with sample of 33,951 women, did not observe any effect from Vitamin D in DM. [23] Major limitations with this study were, low vitamin D3 dose of 400 IU/day, less than ideal compliance; and the presence of contamination, since control subjects were able to take Vitamin 1991.[24]

b. In 1984, a study done by Nilas L showed that treatment with Vitamin D or its analogues at a dose of 2,000 IU/day did not change body weight or blood glucose level in postmenopausal women, but only 25 people were on this dose. [25]

c. The study by Forouhi et al. reported that the baseline serum 25(OH) D levels are inversely associated with glucose and insulin levels collected 10 years later. [26] Finnish cohort study attenuated after adjustment for confounders like obesity and low physical activity showed an inverse association between baseline serum 25(OH) D and 17-year risk of type 2 diabetes. [27]

Together, study done by Forouhi et. al and Finnish cohort study, provided strong evidence that low Vitamin D status predicts hyperglycemia.

d. Robert Scragg's commentary on Vitamin D and Type 2 Diabetes provides new prospective evidence that low levels of Vitamin D also predict hyperinsulinemia, and suggests that Vitamin D may act to prevent type 2 diabetes by decreasing insulin resistance, although it may also inhibit insulin secretion. [28] 2008

e. A post hoc analysis of a trial designed for bone-related outcomes, found that 700 IU/day of Vitamin D3 (combined with calcium) decreased homeostasis model assessment of insulin resistance in participants with impaired glucose tolerance but not in those with normal fasting glucose. [29]

f. With the aim to find unconfounded results, many investigators by using a Mendelian randomization approach, have examined previous observational studies to find causal associations of 25(OH)D with risk of type 2 diabetes. Unfortunately they were unable to confirm or refute causality because of small sample sizes, few included SNPs, or the absence of validation. Even issues like definite dose, need for combination treatment with calcium, compliance, and generalisability were not considered. [30-32]

g. The results of Mendelian randomisation analysis suggests that genetically predicted low concentrations of 25(OH) D were not

associated with risk of type 2 diabetes. This finding suggests that the association between 25(OH) D concentration and type 2 diabetes might not be causal (panel). [33]

h. A study done by Kostoglou-Athanassiou I. et. al showed that Vitamin D levels may have an inverse relationship with $HbA1_C$ and low levels of Vitamin D show a correlation to increased incidence of type 2 diabetes. Vitamin D supplementation should be considered in those with type 2 diabetes when clinically indicated. [34]

i. Using data from several studies covering thousands of people of European descent, Dr. Forouhi and colleagues investigated the link between levels of Vitamin D and risk of developing diabetes by examining the genes that control blood levels of Vitamin D. The researchers did not find any evidence of low Vitamin D causing type 2 diabetes, nor they found a link between the risk of developing type 2 diabetes and the different gene variants that control blood levels of Vitamin D. [35]

j. According to the article published in Lancet Diabetes & Endocrinology, October 2014 issue, the association between 25(OH)D concentration and type 2 diabetes is unlikely to be causal. Efforts to increase 25(OH)D concentrations might not reduce the risk of type 2 diabetes as would be expected on the basis of observational evidence. [36]

k. In a recent study, by de Boer et al examined the effect of calcium plus Vitamin D supplementation on the incidence of drug-treated diabetes in postmenopausal women and concluded that, calcium plus Vitamin D3 supplementation did not reduce the risk of developing diabetes over seven years of follow-up in this randomized, placebo controlled trial. [37]

l. Diabetes has been associated with several neurological disorders including reduced locomotor activity which in turn is associated with low concentration of Vitamin D. A study by K.T. Peeyush reported the altered expression of cholinergic and dopaminergic receptors in the central nervous system of STZ-induced diabetic rats. They further suggested that the altered expression of these receptors was brought back to control by the treatment with Vitamin D. [38,39]

m. A small, clinical study of 51 patients with type 2 diabetes (37 female) evaluated neuropathic complaints such as pain, burning, tingling, numbness, and throbbing sensations. Patients who were vitamin D deficient at base line were given cholecalciferol (D3) and re-evaluated at 3-month follow-up. Serum concentrations increased 67.4% from 18 to 30ng/ml, and were associated with significantly lower pain scores. [40]

These findings provide a confirmatory evidence for neuroprotective role of Vitamin D and represent a novel possibility for the better management of diabetic mediated complications.

n. Nurses' Health Study that included 83,779 women > 20 years of age found an increased risk of type 2 diabetes in those with low Vitamin D status. A combined daily intake of > 800 IU of Vitamin D and 1,000 mg of calcium reduced the risk of type 2 diabetes by 33%. [41]

It is possible that optimal levels of serum Vitamin D may be different for people at risk for developing diabetes, those with diabetes, and those without diabetes.

o. A Japanese study evaluating 581 diabetic patients and 51 nondiabetic ones showed a prevalence of hypovitaminosis D (< 20 ng/mL) of 75% with no differences between the type 2 diabetic patients and the control group. [41]

p. Von Hurst *et al*. supplemented the diets of nondiabetic overweight South Asian women with 4000 IU/d Vitamin D_3 for 6 months and found a significant improvement in insulin sensitivity compared with a placebo group. [42]

q. A study of 83,779 women with no history of diabetes over 2-4 years showed that a daily combined intake 0f 1200 mg of Ca and 800 IU of Vitamin D was associated with 33% lower risk of type 2 diabetes as compared with a daily intake of less than 600 mg of Ca and less than 400 IU of Vitamin .

DISCUSSION: Based on the results of the Diabetes Control and Complications Trial, hyperglycemia is an important contributor to the development of diabetic nephropathy in type 1 diabetes, and maintenance of euglycemia can prevent or delay progression of renal disease. Link between the observations that maintenance of euglycemia and blockade of the RAAS prevent or delay diabetic kidney disease remains entirely hypothetical. [43]

Since Vitamin D can enhance insulin sensitivity, suppress renin gene, it can be hypothesized to have an effect on diabetic control and better management of complications.

Dr. Neil Binkley gave a presentation at the Southern Regional Conference of the ADA in May of 2010. According to Binkley's report, diabetes is one of many diseases/conditions associated with low Vitamin D status. In fact, he hypothesized that low Vitamin D may play a role in the development of diabetes. Potential mechanisms underlying this association are supported by the following findings.[8, 44]

Vitamin D improves beta cell function
-Direct effect on insulin secretion
-1,25 (OH)2 D stimulates insulin release
-its supplementation restores impaired insulin secretion in Vitamin D deficient mice
-Indirect effect via calcium on insulin secretion
hypocalcemia is associated with impaired insulin secretion

Vitamin D is known to improve insulin action
-It stimulates expression of the insulin receptor
-It enhances insulin responsiveness for glucose transport.

Reducing hyperglycemic induced increase in renin levels in pancreatic β cells and blockade of renin-angiotensin activity has been proposed as a novel target for diabetes treatment. [45]

Role of Vitamin D in Inflammation:
It is currently recognized that t2DM is associated with systemic inflammation which has been linked to insulin resistance but elevated cytokines may also play a role in beta cell dysfunction by triggering beta cell apoptosis. Vitamin D may improve insulin sensitivity and promote beta-cell survival by directly modulating the generation and effects of cytokines**.** [46]

Nearly three decades have passed since the studies linking Vitamin D with insulin metabolism have begun, but none of them provide convincing conclusion. A well-designed clinical trial to evaluate the effect of Vitamin D supplementation on glycemia status and diabetes risk is urgently required to settle this question.

Deficiencies of previous studies need to overcome, which include

1. Confounding factor: Low physical activity, adiposity might confound the association substantially. Increased adiposity, lowers 25(OH)D concentration and increases the risk of type 2 diabetes as well. Measurements of confounders (eg, physical activity) are susceptible to errors and are not adequately controlled in epidemiological analysis
2.
3. Subclinical conditions such as liver disease can lower production of 25(OH)D as well as increase the risk of type 2 diabetes suggesting reverse causality(K), hence to be ruled out. [47]
4.
5. Lack of well-designed clinical trials- small sample size, lack of generalisability, poor compliance.
6.
7. Foods rich in Vitamin D may have an effect on glycemic status or replace other foods that might increase risk of type 2 diabetes. Uniform food habits should be part of study design.
8.
9. Definite dose proves to be helpful in DM is not yet defined. In particular, the Vitamin D dose given in such trials needs to be high enough—above 2,000 IU per day to raise blood 25(OH)D levels above 80

nmol/l because diabetes risk is lowest at this level. [48,49]

CONCLUSION: Although the role of Vitamin D in helping to regulate blood glucose remains poorly understood, many of the previous cross sectional studies have shown that Vitamin D status appears to play a role in the development and treatment of diabetes. It is possible that optimal levels of serum Vitamin D may be different for people at risk for developing diabetes, those with diabetes, and those without diabetes.

According to Danescu et al, "both animal and human studies support the notion that adequate Vitamin D supplementation may decrease the incidence of type 1 and possibly also of type 2 diabetes mellitus and may improve the metabolic control in the diabetes state. However, the exact mechanisms are not clear and need further investigation."[50]

Overall, observational longitudinal studies have shown an inverse association between the Vitamin D status (25(OH)D or self-reported Vitamin D intake) and the development of type 2 diabetes. In RCTs, Vitamin D supplementation did not show any beneficial effects on glycemic measures among persons with normal glucose tolerance but there were beneficial effects among patients with glucose intolerance or insulin resistance at baseline.

The challenge for health care providers and nutrition researchers is to determine whether Vitamin D deficiency actually causes or increases the incidence of certain diseases or whether, instead low levels of Vitamin D are simply coincidental given that the majority of the general population, regardless of disease, is likely to have insufficient levels of Vitamin D.

Since Vitamin D can enhance insulin sensitivity by various actions, suppress renin gene which is responsible for hyperglycemia induced complications, it can be hypothesized to have an effect on prevention, diabetic control and better management of complications.

Larger studies are needed to assess more precisely the potential causal association between 25(OH) D concentrations and risk of type 2 diabetes. If causality does exist, interventions such as sunlight exposure or increased Vitamin D intake (diet or supplementation) could provide a simple, inexpensive, and safe prevention strategy for type 2 diabetes.

Various short-term studies (follow up $\leq$ 3 months) suggested that Vitamin D supplementation has a positive impact on glycemic control and metabolic parameters such as insulin resistance and beta cell dysfunction.

However, the evidence was weak due to the low methodological quality of the studies. There was no significant effect on HbA1c, beta cell function and insulin resistance in the long-term studies (follow up > 3 months). There existed heterogeneity in the methodology of the studies, inclusion criteria, mode of supplementation of Vitamin D and the duration of follow up.

Large-scale trials with proper study design, optimal Vitamin D supplementation and longer follow up need to be conducted.

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