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Vitamin D and Type 2 Diabetes Mellitus: Indian Perspectives

Shilpa Balaji Asegaonkar*

Government Medical College, Aurangabad, India

***Corresponding author**: Shilpa Balaji Asegaonkar, Associate Professor, Government Medical College, Aurangabad, India, Tel: 919420763430; Fax: 912402402418; E-mail: sbasegaonkar73@gmail.com

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Abstract

Deficiency of vitamin D is emerging as one of the important nutritional risk factors for development of insulin resistance (IR) and Type 2 Diabetes Mellitus (T2DM). It is also observed to be associated with poor glycemic control and progression of complications among diabetics. In India, in spite of adequate sunlight exposure throughout year, several reports documented prevalent finding of deficiency of vitamin D. With the context of rising surge of T2DM and hypovitaminosis D among Indians, relation between vitamin D and T2DM and related studies have been reviewed in the present article.

Vitamin D plays important roles in the metabolism of glucose. It directly stimulates insulin secretion from beta cells of pancreas. It increases intracellular calcium levels, which attenuates insulin synthesis. Also it improves insulin sensitivity in peripheral muscle and fats cells. T2DM is a state of chronic low-grade chronic inflammation and being anti-inflammatory in nature, vitamin D exerts beneficial effects on glycemic control and prevention of complications.

Current data about vitamin D status in T2DM is based on small sporadic studies from different regions of India. Researchers have reported conflicting results about the association of hypovitaminosis D with development of T2DM and its complications. This warrants an urgent need of population based; large sample sized prospective studies to prove the role of vitamin D in every stage, from prevention to management.

Keywords: Type 2 Diabetes Mellitus; Vitamin D; Prediabetes; and Insulin resistance

Background

Type 2 Diabetes Mellitus (T2DM) is the most prevalent chronic metabolic disorder worldwide. It is caused due to impaired glucose tolerance caused by Insulin resistance and beta cell failure. T2DM is the significant cause of premature morbidity and mortality imposing enormous socioeconomic burden globally [1]. As per the current prevalence and trend of T2DM, International Diabetes Federation (IDF) predicted 592 millions people will have T2DM by 2035 worldwide [2]. Prevalence of T2DM is escalating at rapid pace in India due to westernization of lifestyle. As per IDF report, the prevalence of T2DM will increase to 101.2 million by 2030 among Indians [3].

Several etiological factors including genetic, environmental, lifestyle and nutritional have been implicated in the causation of T2DM. One of the important emerging nutritional risk factors recognized for the development of insulin resistance (IR) and T2DM is deficiency of vitamin D. Also it has been proposed to be associated with worsening of glycemic control and progression of complications among T2DM individuals [4]. In spite of adequate sunlight exposure throughout year, several studies documented deficiency of vitamin D as most prevalent finding among Indians [5]. With this context of rising surge of T2DM and hypovitaminosis D among Indians, relation between vitamin D and T2DM and related recent studies published from India have been reviewed in the present narrative review article.

Skeletal manifestations of vitamin D deficiency are well known. But recently, the evidences have shown hypovitaminosis D as a risk factor in the causation of various noncommunicable, metabolic disorders. Numerous research studies documented association of insufficiency/deficiency of Vitamin D with T2DM. Beneficial effects of administration of vitamin D in improving insulin sensitivity among diabetics are also reported. But whether supplementation of vitamin D prevents development of T2DM and its complications is not confirmed due to inconsistent results from clinical trials. Differences in race, body mass index, glycemic status, and exposure to sunlight, inadequate dose, and low compliance could be the possible reasons for such discordance observations. Baseline low levels of vitamin D, poor glycemic control and insufficient post hoc analysis power may also be probable factors for such results [6,7].

Vitamin D plays important roles in the metabolism of glucose. It directly stimulates insulin secretion from beta cells of pancreas. It increases intracellular calcium levels, which attenuates insulin synthesis. Also it improves insulin sensitivity in peripheral muscle and fats cells. T2DM is a state of chronic low-grade chronic inflammation. Because of anti-inflammatory nature, vitamin D exerts beneficial effects on glycemic control and helps in prevention of complications of T2DM [8].

Vitamin D and T2DM: An Indian Scenario

India is facing concurrent epidemics of T2DM and hypovitaminosis D due to urbanization and industrialization. Despite of adequate sunshine throughout the year, hypovitaminosis D is commonly seen among Indians across all age groups in urban as well as rural regions. It is associated with IR which progress towards T2DM and its subsequent complications. Indian researchers investigated association of vitamin D deficiency with IR, T2DM, glycemic control and progression of

complications among diabetics. After extensive literature search on PubMed and Google scholar search engine, Indian studies evaluating association of vitamin D with T2DM were selected in the present review. One of the most important limitations among these studies is small sample size. Hence these studies could not reach the statistical significance. But vitamin D deficiency has been identified as an independent adjunctive risk factor for T2DM. Following papers were studied to evaluate the relation of vitamin D status with T2DM among Indians (Table 1).

Authors and reference number	Study design	Number and characteristics of Subjects	Main outcome
Kotwal et al. [9]	Case control	102 newly detected and similar controls. North Indian subjects	81% cases and 67% controls had deficiency. 16.2% diabetics and 2.5% controls had severe deficiency. Mean vitamin D in cases 18.81+/-15.18 vs 28.26 +/- 18.89 in controls (p<0.000) Significant negative correlation with fasting blood glucose and HbA1c.
Dutta et al. [10]	Cross sectional	157 prediabetes subjects, 42 T2DM and 28 healthy controls.	Severe deficiency (<10 ng/ml) in 14.65, 7.14% in diabetics and control. Deficiency/insufficiency in 73.25% prediabetes, 66.6% diabetes, 78.7% healthy subjects. Vitamin D<10 ng/ml inversely correlated with highest IR-HOMA2IR 2.04+/-0.26, r=0.33 p 0.008. Positive correlation with insulin sensitivity QUICKI r 0.39, p 0.002. No correlation with estimated beta cell mass.
Mukherjee [8]	Cross sectional	Group 1- 48Group II- 46 T2DM with HbA1C<7% controlsGroup III- 56 T2DM with HbA1c>7%Participants-Odisha	Significant deficiency in-group III (p<0.001). Negative correlation of vitamin D with HbA1c- poor glycemic control (r=-0.96)
Sheth et al. [11]	Prospective Cross sectional	429 T2DM and 483 healthy control urban western India	Deficiency in both groups without any statistically significant difference. No association with HbA1c and HOMA-IR in both groups. (p 0.057, 0.257 vs 0.675, 0.647)
Mohpatra [12]	Case control	68 controls and 68 T2DM with and without complications from Odisha	More deficiency in complicated DM (mean 13.14+/-1.45) than uncomplicated (19.94+/-2.4) and controls (mean 33+/-3.3). Inverse association of vitamin D with HbA1c (r=-0.883, p<0.001)
Bid et al. [13]	Case control	100 T2DM, 160 controls North Indians to study Vitamin D receptor (VDR) gene polymorphism and risk of T2DM	VDR gene polymorphism in combination with genotypes FfBbTt and FFBbtt associated with increased risk of T2DM. But there was no significant difference in rest of genotypes and VDR gene polymorphism with cases and controls.
Chaudhari et al. [14]	Case control study	Total- 155 subjects Non-diabetic (39), only T2DM (46) Pulmonary Koch's with (40) and without T2DM (30).	Severe deficiency of vitamin D in pulmonary Koch's only (93.5%), Koch's with T2DM (87.5%), only T2DM (80.5%- mean 19.42+/-11.32) and healthy (61.5% mean 29.47%). P<0.001 Non-significant difference statistically.
Daga et al. [15]	Case control	72 newly diagnosed youth onset (<25 years) type 1 DM (13) and T2DM (58) and healthy controls	Severe deficiency in T1DM than T2DM. Mean vitamin D cases- 7.8+/-1.2 ng/ml, controls- 16.64 ng/ml (p value 0.26) 91.1% cases and 58.5% normal individuals were deficient. No correlation of vitamin D levels with clinical and biochemical parameters, HbA1c.
Doddamani [16]	Cross sectional	Newly diagnosed cases of T2DM (n=50)	70% patients had vitamin D <20 ng/ml. (p<0.001) Inverse correlation with HbA1c and fasting plasma glucose. (p – 0.006, <0.001 respectively)
Bajaj et al. [17]	Case control	74 T2DM cases and 70 age and sex matched healthy normoglycemic controls	Deficiency of vitamin D in 13.51% of diabetics and 28.57% in controls. statistically significant inverse correlation betweem vitamin D and total cholesterol (-0.279) and low density lipoproteins (-0.297).
Latha [18]	Cross sectional	51 T2DM and 51 healthy controls	vitamin D positively associated with high density lipoproteins (r=0.697) and inversely with fasting blood sugar and triglycerides (at p<0.01 r=-0.79, -0.435 respectively) among cases.
Tandon et al. [19]	Cross sectional	312 Post-menopausal women evaluated for deficiency of vitamin D	Results failed to establish correlation of vitamin D deficiency with existence of T2DM may be due to small sample size Correlation between vitamin D deficiency and raised blood glucose was non-significant (p=0.324).
Kumar et al. [20]	Cross sectional	50 T2DM cases categorized into 3 groups according to vitamin D levels.	Significant deficiency in cases in relation to age of onset (p<0.001), HbA1c (p-0.006), blood sugar (p-0.001) while difference in relation to BMI and duration of T2DM (p-0.109, 0.666 respectively) non-significant.

Table 1: vitamin D status with T2DM among Indians.

Seth et al. could not establish role of deficiency of vitamin D in glycation of hemoglobin and IR, although deficiency was prevalent in individuals with and without T2DM [11]. Niti Agrawal et al. investigated association of serum hydroxyvitamin D with markers of

IR among postmenopausal women. They found inverse correlation between vitamin D and BMI (r=-0.234 p- 0.047) and HOMAIR (r=-0.237 p-0.047). On adjustment of BMI, association with HOMAIR was lost statistical significance [21]. Deep Dutta et al. found statistically significant inverse correlation of vitamin D with IR (HOMA2IR 2.04+/- 0.67 r 0.33) and positive correlation with Insulin sensitivity (QUICKI r=0.39, p-0.002). People with severe deficiency had highest IR. But no correlation could be observed between vitamin D and estimated beta cell mass. The study reported worsening of IR in Indians with prediabetes [10]. In Indian Diabetes prevention program-1 study, 18% annual risk of progression of prediabetes to diabetes has been reported [22]. So longitudinal prospective studies with intervention of supplementation of vitamin D are strongly warranted among Indian population.

Vitamin D and T2DM

Active metabolite of Vitamin D (1, 25-dihydroxy vitamin D3) is involved in normal endocrine function of pancreas. Vitamin D and VDR complex play role of transcription factor in regulating secretion of beta cells function of insulin secretion [14]. Kota supplemented vitamin D to pulmonary tuberculosis patients with uncontrolled diabetes. They reported improval of glycemic control after supplementation suggesting that vitamin D could be an adjunct therapy in tuberculosis patients with T2DM [21-23].

Hypovitaminosis D is commonly seen in obesity, which is most important cause of prediabetes. In obesity, adipose tissues store 25-hydroxy vitamin D making it biologically unavailable resulting in depletion of calcitriol and rise in PTH. This in turns increases intracellular calcium in adipocytes stimulating lipogenesis with subsequent weight gain and impaired glucose intolerance [24] Deficiency of vitamin D favors systemic inflammation and worsens glycemic control among diabetics enhancing their cardio-metabolic risk [25]. Shore-Lorenti et al. performed systematic review of literature and found moderate level evidence for association of sunlight exposure with T2DM [26].

Action of vitamin D and its active metabolite, 1,25-di(OH)-vitamin D has been well recognised as an important regulator of bone health and calcium homeostatsis. It is a part of "Calcium-Vitamin D-Parathyroid hormone" endocrinal axis. Apart from extra-skeletal functions, it regulates around 200 genes function. Since last decade, its role in the causation of various cardio-metabolic disorders, IR, T2DM and malignancies has been widely studied. Inadequate direct exposure to sunlight, increased skin pigmentation, environmental pollution, obesity and malabsorption have been proposed as possible reasons for vitamin D deficiency in India even though it's tropical country [27]. There is steep rise in prevalence of T2DM by 10-fold in urban as well as rural parts of India. Sedentary lifestyle and high intake of refined carbohydrates have been identified as important predisposing factors [28]. Decreased physical activity is also one of the causes for hypovitaminosis D. So it's a common factor in etiology of both, T2DM and vitamin D deficiency. Physical exercise would improve vitamin D status as well as prevent development and progression of T2DM [29]. Vitamin D modulates expression of insulin receptors genes and insulin secretion. So it's a new ray of hope in the management of T2DM. Possible mechanisms to find link between hypovitaminosis D and T2DM have been investigated by researchers. Activation of vitamin D receptor and calcium homeostasis impair beta cell function of pancreas causing IR and its subsequent effects [30].

Conclusion

Current data about vitamin D status in T2DM is based on small sporadic studies from different regions of India. Researchers have reported conflicting results about the association of hypovitaminosis D with development of T2DM and its complications. This warrants an urgent need of robust evidence from population based; large sample sized prospective studies to prove the role of vitamin D in every stage of T2DM, from prevention to its management. Supplementation of vitamin D for prevention of T2DM, and its complications, halting progression from prediabetes to T2DM, and improving glycemic control is of utmost importance. If these roles could be established by statistically significant findings, vitamin D will remain at the cornerstone of T2DM management and prevention of morbidity and mortality. It could minimize enormous socioeconomic healthcare burden.

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