Role of vitamin D deficiency in type 2 diabetes: Association or coincidence?

ABSTRACT
Background. Vitamin D has received considerable attention for its possible role in myriad of clinical conditions especially non-communicable chronic diseases. However, it is the role in the pathogenesis of type 2 diabetes (T2DM), which has generated a lot of enthusiasm to unravel the association between the two.

Aim. To determine the prevalence of hypovitaminosis D and its relation with the glycemic control in T2DM patients attending a tertiary care hospital in Kashmir.

Methods. A total of 108 cases of T2DM and 101 healthy controls aged between 35-65 years were investigated in this study. 25-hydroxyvitamin D (25OHD), glycosylated hemoglobin (HbA1c) and fasting serum insulin levels were determined using standardised and automated assays. Insulin resistance (IR) and beta-cell function (B) were estimated by the homeostasis model assessment (HOMA).

Results. The mean serum level of 25OHD was significantly lower in T2DM group compared to controls (20.55 ± 12.27 vs 27.62 ± 5.32 ng/mL; P = 0.001). The prevalence of hypovitaminosis D was significantly higher in patients with T2DM (79.5% vs 62.7%; P = 0.031).

Overall 51.1% and 28.4% patients with diabetes and 41.2% and 21.6% controls had vitamin D deficiency and insufficiency respectively. Vitamin D was found to have a significantly positive association with serum fasting insulin level and HOMA-B in both cases (P = 0.019), (P = 0.026) and controls (P = 0.022), (P = 0.008) respectively. Prolonged glycemic control as determined by HbA1c demonstrated a significant inverse correlation with vitamin D level in both cases (r = -0.225; P = 0.035) and controls (r = -0.373; P = 0.007).

Conclusion. We conclude that vitamin D deficiency (VDD) is a very common health problem and is relatively more common in patients with T2DM. There is an inverse association between vitamin D and glycemic control. Vitamin D status thus appears to affect glucose homeostasis. Vitamin D screening and supplementation is a plausible way to mitigate the impact of VDD on glucose homeostasis in T2DM. (Clin Diabetol 2021; 10; 2: 188–194)

Key words: vitamin D deficiency, type 2 diabetes mellitus, HOMA-IR, HOMA-B

Introduction
India, one of the fast growing economies of the world is witnessing rapid growth of diabetes cases owing to improved socioeconomic conditions and is estimated to harbor second largest diabetes population of over 77 million in 2019 in the world, which is expected to increase to 134 million in 2045 [1]. Urbanisation of lifestyle parameters and availability of affordable food items, have resulted in escalating prevalence of diabetes not only in urban dwellings but also in rural India. Like rest of India, in valley of Kashmir also, the prevalence of T2DM has shown a substantial increase from 1.89% (1.98% in males and 1.77% in females) in 2000, to 6.31% (7.15% in urban and 5.5% in rural) reported in a study published in 2015 [2, 3]. This enormous increase in prevalence of diabetes mellitus (DM) and its associated complications has emerged as a major health concern in relation to increased morbidity, mortality and impaired quality of life associated with the disease [4, 5]. The epidemic
proportions of the disease and its sequelae makes it imperative to study and find out the modifiable risk factors associated with DM and to address these factors to mitigate the impact of deleterious effects of this disease. Apart of non modifiable genetic predisposition there are many environmental factors including physical inactivity, obesity and poor dietary habits which contribute greatly to its development. However, in the recent years role of vitamin D, as modifiable risk factor for DM has come under careful scrutiny with studies suggesting a possible link of VDD in the pathogenesis of T2DM [6, 7].

Vitamin D, a fat soluble vitamin synthesized in the skin has been found to have myriad of roles in health and disease, with studies implicating its role in pathogenesis of number of chronic diseases including heart disease, autoimmune diseases, type 2 diabetes, many cancers and infectious diseases. High prevalence of DM in areas of significant VDD has generated lot of enthusiasm in unravelling the relationship between the two. The biological evidence implicating potential influence of vitamin D on insulin secretion and sensitivity include the presence of specific vitamin D receptor in pancreatic cells and target organs including skeletal muscles and adipose tissues in addition to expression of 1-α hydroxylase enzyme in pancreatic cells [8–10].

The present study aimed to find the prevalence of VDD in patients with T2DM attending a tertiary care hospital in Srinagar, Kashmir and to examine whether 25OHD has any clinically significant influence on glycemic control (HbA1c) and insulin resistance (HOMA-IR) in patients with T2DM.

**Aims and objectives**

To determine the prevalence of hypovitaminosis D in patients with T2DM and its correlation with glycated hemoglobin (HbA1c), a marker of glycemic control.

**Material and methods**

**Study setting**

This was a cross-sectional analytical study carried out in the Department of Medicine at Government Medical College, Srinagar after obtaining ethical clearance from institutional ethics committee. The study was carried out over a period of 18 months from November 2017 to May 2019. The study was done according to the principles expressed in the Declaration of Helsinki. A written informed consent was obtained from all the subjects, in the language that was understandable to the patient and their attendant.

**Study population and sample size**

A total of 108 cases of T2DM and 101 healthy controls aged between 35–65 years attending the OPD and wards of this hospital were included in the study.

**Inclusion criteria**

Cases: All patients aged 35–65 years with T2DM on oral anti-diabetic medication who gave informed consent.

Controls: Apparently healthy individuals aged 35–65 years who gave informed consent.

**Exclusion criteria**

Diabetic patients below 35 years or above 65 years, subjects with T1DM or other forms of diabetes, pregnant women, patients with chronic diseases including chronic liver disease or alanine aminotransferase > 5 times upper reference limit, renal insufficiency (glomerular filtration rate < 30 mL/min), diarrhoeal or malabsorption state and tuberculosis.

**Methods**

25-hydroxyvitamin D level was assayed using the chemiluminescent method. HbA1c assay was performed on the autoanalyzer (Abbott GmbH & co. kg Max-Planck-Ring 2. 65205 Wiesbaden, Germany) based on the turbidimetric inhibition immunoassay (TINIA) of hemolyzed blood samples and the hexokinase method was employed for assay of fasting plasma glucose. Enzyme-linked immunosorbent assay was used to determine the fasting serum insulin levels. Serum calcium, phosphorus, albumin and creatinine were measured using standardized and automated assays. Insulin resistance (IR) and beta-cell function (B) were estimated by the homeostasis model of assessment-insulin resistance index (HOMA-IR) and the homeostatic model of assessment-beta (HOMA-B) respectively. Higher HOMA-IR value indicates greater IR, and a lower HOMA-B value indicates greater β-cell dysfunction.

HOMA-IR is defined as the product of fasting serum insulin (µU/mL) and fasting plasma glucose (FPG) (mmol/L) divided by 22.5. A score of > 4 defined IR [11].

HOMA-B insulin secretion (IS) defined as the product of twenty and fasting insulin (µU/mL) divided by FPG (mmol/L) minus 3.5. A score of < 100 defined reduced IS (B) [11].

Serum levels of 25OHD were classified endocrine society guidelines into deficient (< 20 ng/mL), insufficient (≥ 20 to < 30 ng/mL) and normal (≥ 30 ng/mL). Subsequently, for this study, we considered all 25OHD values of < 30 ng/mL as hypovitaminosis D both in cases and controls.

**Statistical analysis**

Data was first entered into Microsoft Excel. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 25.0 software from IBM Corporation, NY, United States. The statistical
techniques used for analyzing this data were independent student t-test and one-way ANOVA with multiple range tests. Wherever applicable, an appropriate non-parametric test like Mann Whitney, Kruskal Wallis and other tests were used. A P-value of less than 0.05 was considered significant.

Results

A total of 108 cases comprising of 51% male (n = 55) and 49% female (n = 53) and age matched 101 controls comprising of 60.8% males (n = 61) and 39.2% females (n = 40), were included in this study. Demographic and laboratory characteristic of the study population is shown in the Table 1.

The mean age and BMI of cases and controls at presentation was 48.28 ± 9.53 years vs 48.12 ± 9.35 years and 25.60 ± 3.59 kg/m² vs 22.58 ± 1.78 kg/m² respectively. The prevalence of hypovitaminosis D was significantly higher in patients of T2DM compared to controls (79.5% vs 62.8%; P = 0.031). Overall 51.1% and 28.4% patients with diabetes and 41.2% and 21.6% of controls had VDD and insufficiency respectively. The mean serum level of 25OHD was significantly lower in T2DM group compared to controls (20.55 ± 12.27 vs 27.62 ± 5.32 ng/mL; P = 0.001). Fasting plasma insulin and HOMA-IR values were significantly higher in T2DM cases compared to control group (12.18 ± 10.28 vs 7.93 ± 4.74 mIU/L; P = 0.006) and (5.62 ± 6.42 mg/dl vs 1.61 ± 0.82 mg/dl; P = 0.000). However, HOMA-B was significantly higher in control group compared to T2DM patients (30.65 ± 24.48 vs 22.88 ± 24.16; P = 0.000). On sub analysis of diabetest group (Table 2), comparison of patients with good glycemic control (HbA1c < 7%) with those of poor glycemic control (HbA1c ≥ 7) revealed fasting insulin levels and HOMA-B were significantly higher (14.99 ± 12.54 mg/dl vs 10.23 ± 7.94 mg/dl; P = 0.032) and (32.33 ± 31.80 vs 16.34 ± 13.98; P = 0.002) in good glycemic group compared to those in poor glycemic group. Similarly 25OHD level was significantly higher in patients with good glycemic control (24.69 ± 12.17 ng/mL vs 17.68 ± 11.60 ng/mL; P = 0.008). The prevalence of hypovitaminosis D was significantly higher in patients with poor glycemic control (88.4% vs 66.7%; P = 0.013), with patients having significantly higher VDD (61.5% vs 36.1%; P = 0.019).

There was a significant inverse relationship between vitamin D and serum fasting blood glucose in control group (r = -0.402; P = 0.003) (Table 3). While it was inversely related but not statistically significant
We found a significant positive association between serum fasting insulin level and vitamin D in both cases \((r = 0.250; P = 0.019)\) and controls \((r = 0.319; P = 0.022)\). Similarly there was a significant positive association between vitamin D and HOMA-B in both cases \((r = 0.237; P = 0.026)\) and controls \((r = 0.370; P = 0.008)\), however, there was no correlation between vitamin D status and HOMA-IR in diabetes patients \((r = 0.172; P = 0.109)\) as well as in healthy control \((r = 0.280; P = 0.056)\). We found a significant inverse correlation between serum 25OHD level and HbA1c in both cases \(r = -0.225; P = 0.035\) and controls \(r = -0.373; P = 0.007\) (Figure 1, 2).

### Discussion

Vitamin D deficiency is a global health problem affecting almost all the countries of the world including India, with studies estimating the community prevalence of 50% to 94% [12]. Similarly a very high prevalence of vitamin D inadequacy was demonstrated in apparently healthy, young, and non-pregnant adults of Kashmir region in northern India [13] aged 18–40 years. Of the 92 healthy natives including 64 men and 28 non-pregnant/non-lactating women, aged 18–40 years, 83% had VDD with 25%, 33%, and 25% having mild, moderate, and severe deficiency, respectively. The presence of high prevalence of both VDD and T2DM in the Kashmir valley and evidence linking VDD with variety of chronic diseases including T2DM prompted us to take up this study to find the link between the two major health problems.

Insulin resistance and or action and impaired insulin secretion are the main significant factors involved in the pathogenesis of T2DM though other distinct pathophysiological abnormalities commonly referred as...
"Ominous Octet" have been associated with T2DM. Vitamin D has been found to influence these mechanisms and has been suggested to play an important role in modulating impaired pancreatic beta cell function, insulin resistance and systemic inflammation, seen in patients with T2DM [14]. Vitamin D has been implicated to have beneficial effect on insulin sensitivity through various mechanisms including, directly acting on insulin receptors [15], thus improving glucose transport across the cells in the target tissues and by activating peroxisome proliferator activator receptor-δ thereby regulating fatty acid metabolism [16] in addition to affecting the calcium homeostasis [17] Similarly vitamin D has been found to have beneficial effects on insulin release by acting directly on vitamin D receptor in β-cells and vitamin D-dependent calcium-binding proteins [18] and indirectly via regulation of calcium transport through β-cells [19].

The present study is the first study on the relationship between type 2 DM and 25OHD in the Kashmir valley of Northern India. In the current study, mean age of patients with T2DM and controls was 48.28 ± 9.535, and 48.12 ± 9.354 years respectively.

The prevalence of VDD and insufficiency in T2DM patients in the current study was 51.1% and 28.4% respectively, whereas the prevalence of VDD and vitamin D insufficiency in healthy controls was 41.2% and 19.6% respectively. Despite the high prevalence of hypovitaminosis D (< 30 ng/mL) in the studied population it was significantly pronounced in patients with T2DM (79.5%) compared to healthy controls (60.8%). On further analysis it was found that VDD was more prevalent in diabetic patients with poor glycemic control compared to those with good glycemic control. The presence of comparatively higher prevalence of hypovitaminosis D in diabetic patients in general and in patients with poor glycemic control in particular is in agreement with the results documented in previous studies from Asian countries [20–22].

The main source of Vitamin D is skin exposure to ultraviolet B radiation (UVB) from the sun however, dietary and supplemental intake, lifestyle and underlying health conditions also influence the vitamin D status of the body [23]. The higher levels of VDD in patients of T2DM could be because of relatively limited sun exposure on account of limited physical activity and presence of obesity in diabetes in addition to impaired conversion of precursors of vitamin D in liver and kidneys in the presence of liver disease and nephropathy. Large number of observational studies across the world have demonstrated an inverse association of serum levels of 25OHD and HbA1c supporting a possible active role of VDD in pathogenesis of T2DM. NHANES analysis of 9,773 adults who participated in the 2003–2006 NHANES, found that serum 25OHD concentration was inversely associated with HbA1c level in individuals 35–74 years old, but not among the younger or older adults [24]. Our study like other observational studies also demonstrated a significant inverse correlation between Vitamin D levels and HbA1c levels which is in agreement with results documented in the literature [20, 22, 24, 25]. Patients with VDD have been found to have higher HbA1c, a marker of prolonged glycemic control, however, some authors suggest that vitamin D may be a marker of general health and its association with T2DM may be a coincidence [26]. Observational nature of these studies did not provide a conclusive evidence for any possible cause and effect relationship between VDD and type 2 diabetes mellitus. Despite sufficient evidence for possible association in observational studies, Interventional studies have been inconclusive.
to address the nature of relationship between the two. Lack of conclusive evidence of association between the two have given credence to the observation that a low serum 25OHD level might be the result of poorer health or even worse metabolic control of diabetes.

One of the observations of our study was the inverse association of serum vitamin D levels with fasting plasma glucose in patients of T2DM; however the relation was not statistically significant. The reason for statistically insignificant relation for the cases could be the adequate treatment by oral anti-diabetic medications. This observation was consistent with results from a study by Kumar et al. who observed that vitamin D level was inversely related to fasting blood sugar in patients with T2DM [22]. We also found that the fasting plasma glucose levels of healthy controls had significant inverse relation with serum vitamin D levels. This is similar to the conclusion drawn from a meta-analysis which showed that there was an overall inverse association of vitamin D status and fasting plasma glucose in the non-diabetic population [22, 27]. This relationship of vitamin D with plasma glucose level suggested that hypovitaminosis D is associated with increased risk of hyperglycemia both in diabetic and non-diabetic subjects. We found a significant positive association between serum fasting insulin level and vitamin D in both cases and controls, which is similar to results demonstrated in an earlier study where authors concluded that vitamin D is positively associated with insulin levels [28]. HOMA-B represents insulin secretory capacity of pancreatic beta cells and thus the higher the value the more the beta-cells have to secrete insulin to handle existing blood glucose level. VDD has been found to inhibit insulin secretion by modulating VDR on pancreatic beta cells. Our study demonstrated a significant positive association between vitamin D levels and HOMA-B in both cases and controls thus highlighting the importance of vitamin D in insulin secretion. In the current study we did not found any significant correlation between serum vitamin D levels and HOMA-IR levels in both the control group and the diabetic patients. The lack of association between the vitamin D levels and HOMA-IR is consistent with the results demonstrated in earlier studies [25, 29, 30].

Limitations of the study

The present study has several limitations. Observational nature of present study prevents us from making any conclusive observation as far as any cause and effect relationship between VDD and T2DM is concerned. The study sample was relatively too small to project the results to whole population to draw any conclusive inference.

Summary and conclusion

We conclude that the prevalence of hypovitaminosis D is very common; however, in patients with T2DM, it is relatively more common compared to non-diabetics. We also found that there is an inverse relation between vitamin D and HbA1c, which is marker of prolonged glycemic status, thus highlighting the possible role of vitamin D in glycemic control (HbA1c). On the basis of the findings in our study, we suggested, there should be a routine screening for vitamin D levels in patients with diabetes and patients with diabetes should supplement vitamin D in their diet; a plausible way to mitigate the impact of VDD in the pathogeneses of T2DM. However, long term studies with a larger cohort, investigating the effect of supplementation of vitamin D on the incidence and glycemic control of T2DM can significantly help to drive a conclusive evidence linking those two.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Conflict of interest

None declared.

REFERENCES


