www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i10.189

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Vitamin D Status and Glycemic Control in Type 2 Diabetes Mellitus

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Abstract
India has widespread prevalence of diabetes and hypovitaminosis D. This study was conducted to evaluate the relationship between serum 25-hydroxyvitamin D [25(OH)D] and glycemic control in patients with type 2 Diabetes Mellitus [T2DM]. 157 subjects (100 T2DM; 57 controls) were sampled and their 25(OH)D, FBG, PPBG and HbA1c were measured. Additionally, T2DM patients were classified into controlled diabetic and uncontrolled diabetic group based on glycemic control (HbA1c level <7% or ≥ 7%). Data analysis was done by t-test for continuous measures and chi-square test for categorical measures. Mean vitamin D level was significantly lower in the diabetic compared to Control group (15.1 ± 5.18 v/s 22.66 ± 5.49 ng/ml, P<0.01). 82% diabetics and 33.4% controls were Vitamin D "deficient" (<20ng/ml). 18% diabetics and 56.1% Controls were Vitamin D "insufficient" (20-29 ng/ml). FBS (96.8±16.3 v/s 146.5±55.2, P<0.01), PPBS (125.3±22.9 v/s 210.5±76.6, P<0.01), HbA1c (8.1 ± 2.2 % v/s 5.6 ± 0.2 %, P<0.01) and calcium (9.21±.89 v/s 7.89±.70, P =0.04) were also found to be statistically different between controls and diabetics. Mean vitamin D level in the controlled diabetic v/s uncontrolled diabetic group was (14.95±4.77 v/s 15.15±5.59 ng/ml, P =1.00). Thus, Vitamin D deficiency may be an etiological factor for the development of T2DM, but may not have a role in the glycemic control in T2DM.
Keywords: *Type 2 diabetes mellitus; Vitamin D; Glycemic control; Glycated haemoglobin*

Introduction

The prevalence of diabetes is rapidly rising at an alarming rate all over the globe. According to recent estimates, by 2030, 552 million people of the adult population, is expected to have diabetes. It is estimated that the total number of people with diabetes in India will rise to a staggering 101.2 million by 2030[1].

Vitamin D, the sunshine vitamin, has been lauded for a myriad of health benefits including reduction in the risk of cancer, autoimmune, cardiovascular and other chronic diseases apart from its importance in bone health of children and adults

[2]. Vitamin D, being an essential nutrition component with unique metabolism and physiological effects compared to other vitamins, has also been conferred to be more suitably classified as a hormone[3].

Studies carried across different countries in South and South-East Asia, with a few exceptions, has shown widespread prevalence of hypovitaminosis D regardless of age or gender[4]. Animal experiments and in vitro experiments utilizing pancreatic islet cells have demonstrated that 1,25-dihydroxyvitamin D increases insulin secretion, improves glucose tolerance and is essential for the normal insulin release[5,6]. Vitamin D receptors and Vitamin D dependent calcium binding protein have been identified in pancreatic islets and tissues respectively, thus clearly suggesting that Vitamin D may be essential for normal insulin secretion and hence glucose homeostasis[7,8].

Considering the increasing prevalence of diabetes mellitus and the high occurrence of vitamin D deficiency in the Indian population, this study was conducted to evaluate the relationship between serum 25-hydroxyvitamin D [25(OH)D] and glycemic control in patients with type 2 Diabetes Mellitus [T2DM]. Furthermore, in Indian population the association of vitamin D status with HbA1c, a global measure of glucose homeostasis has not been studied.

Methods

This study included patients with T2DM in the age group 30-50 years who were attending the diabetic outpatient clinic of a tertiary-care teaching hospital in northern Kerala, South India. This study was planned with the following aims: (1) to compare serum Vitamin D level in patients with type 2 Diabetes with non-diabetic controls, (2) to compare serum vitamin D level in patients with controlled diabetes with that of uncontrolled diabetes, and (3) to assess the relationship between serum vitamin D and HbA1c in the study group. Two groups were selected. Group *I* included diabetic patients (n=100) on medication and group *II* included control subjects (n=57) without history of diabetes with HbA1c ≤ 5.9% or FPG ≤ 110 mg/dl (6.1 mmol/L) and PPG ≤ 140mg/dl (7.8 mmol/L). Diabetic patients were further grouped into two. Controlled diabetes (n=50) with HbA1c < 7% or FPG < 130mg/dl (7.2 mmol/L) and PPG <180mg/dl (10 mmol/L); and uncontrolled diabetes (n=50) with HbA1c ≥ 7% or FPG ≥ 130mg/dl (7.2 mmol/L) and PPG ≥ 180mg/dl (10 mmol/L). The exclusion criteria were: (1) Subjects not giving written consent to participate in the study, (2) pregnant, lactating and peri-menopausal women, (3) chronic renal, hepatic, malignant or intestinal disease (self-reported or any suggestive medical documents) or renal stones, (4) patients with acute diabetes mellitus complications, and (5) subjects taking calcium, vitamin D or steroid medications.

This was a comparative study. Informed consent was obtained from each of the participants and the study was approved by the Institutional Review Board. Detailed history was taken (age, gender, education level, duration of illness, history of family illness, frequency of outdoor activity, duration of direct sun exposure in their outdoor activities, and history of using sun protector). Blood pressure, weight, Height and BMI were recorded.

A venous blood sample was collected after a 12 hour overnight fasting for estimation of FBS, 25(OH) D, HbA1c and calcium and a 2-hour post prandial blood collected for PPBS estimation. 25(OH) D level was measured by electro chemiluminescence immunoassay and HbA1c measured by turbidimetric immunoassay.

Statistical analysis

Data are reported as mean ± SD for continuous variables and as proportions for categorical variables. Data analysis was done by t-test for continuous variables and chi-square test for categorical variables. A *P* value < 0.05 was considered to indicate statistical significance. All data analysis was done using Microsoft Excel and the Statistical package for the Social Sciences (SPSS, Version: 16.0) software for Windows.

Results

A total of 157 subjects satisfying the inclusion criteria were included in the study. The mean age was 42.6 ± 5.3 years with females comprising 52.9% and males 47.1%. The clinical and biochemical parameters in the diabetic group (n=100) and healthy controls are given in table 1. The mean HbA1c level in this group was 8.1 ± 2.2 % and the mean Vitamin D level in this group was 15.05 ± 5.18 ng/ml.

Clinical and biochemical parameters in people with controlled diabetes (HbA1C<7) and uncontrolled diabetes (HbA1C>7) is described in table 2. The mean HbA1c level in the controlled diabetic group was 6.4 ± 0.4 % and the mean Vitamin D (25-Hydroxy vitamin D) level in this group was 14.92 ± 4.75 ng/ml.In the uncontrolled diabetic group, mean HbA1c level was 9.7 ± 2.1 % and the mean Vitamin D level in this group was 15.12 ± 5.58 ng/ml.

The serum Vitamin D level in the diabetic group was less than that of the controls (figure 1) and was found to be statistically significant (p=.000).

Whereas, the serum Vitamin D level between controlled diabetic group and uncontrolled diabetic group was not statistically significant (p=1.00).

Pearson correlation between serum Vitamin D and HbA1c in the study group was -0.305(p<0.01)) which means as HbA1c level increases serum Vitamin D level decreases. Other parameters like FBS (96.8±16.3 *v/s* 146.5±55.2), PPBS (125.3±22.9 *v/s* 210.5±76.6), HbA1c (5.66±.26 *v/s* 8.07± 2.23) and calcium (9.21±.89 *v/s* 7.89±.70) were found to be statistically significant between control and diabetic patients.

Table 1: Clinical and biochemical parameters in people with diabetes and healthy controls

Parameter	T2DM (n = 100)	Controls (n=57)	p-value
Age (years)	43.1±5.1	41.7±5.5	0.108
Sex (M/F)	41/59	32/25	-
BMI	25.8±4.9	24.7±2.4	0.104
FBG(mg/dl)	146.5±55.2	96.8±16.3	<0.01
PPBG(mg/dl)	210.5±76.6	125.3±22.9	<0.01
HbA1C (%)	8.1±2.2	5.6±0.3	<0.01
Vitamin D (ng/ml)	15.05±5.18	22.66±5.49	<0.01

Table 2: Clinical and biochemical parameters in people with Controlled diabetes(HbA1C<7) and Uncontrolled diabetes(HbA1C≥7)

Parameter	Uncontrolled diabetes (n = 50)	Controlled diabetes (n=50)	p-value
Age (years)	43.8±5.1	42.4±5.1	0.123
Sex (M/F)	25/25	16/34	-
BMI	24.8±3.3	26.8±6.1	0.014
FBG(mg/dl)	176.1±59.9	116.9±27.8	<0.01
PPBG(mg/dl)	246.6±89.3	174.5±35.3	<0.01
HbA1C (%)	9.7±2.1	6.4±0.4	<0.01
Vitamin D (ng/ml)	15.15±5.59	14.95±4.77	<0.01

Figure 1. Vitamin D status in the diabetic and control group

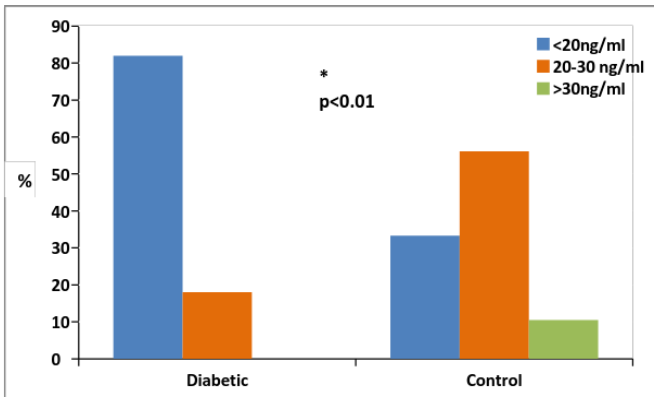
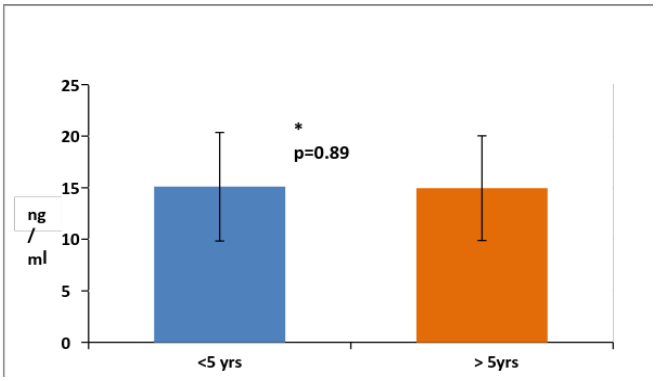


Figure 2. Vitamin D level in relation to duration of diabetes in diabetes group



Discussion

Three important observations were found in this study. First observation was that, serum 25(OH) vitamin D in T2DM patients (15.05 ± 5.18ng/ml) were lower when compared to non-diabetic control (22.66 ± 5.49 ng/ml) of the same age group and was statistically significant(p<0.01).

Based on available clinical and epidemiological data, the positive effects of vitamin D seem to be

primarily related to its action on insulin secretion and sensitivity and secondary to its action on inflammation. Previous cross-sectional and case-control studies found an inverse association between serum 25(OH)D and type 2 diabetes as well as markers of adverse glucose homeostasis in many, although not all, studies. In 2011, a Caucasian study[9] with 2465 subjects found that the diabetes was significantly associated with lower 25(OH)D and 1,25(OH)2 D levels, after adjustment for confounding by sex, geographical location, BMI, physical activity, vitamin D and calcium intake.

In 2007, Pittas et al[10] conducted a systematic review and meta-analysis of observational studies and clinical trials in adults with outcomes related to glucose homeostasis in type 2 diabetes mellitus and found that observational studies showed a relatively consistent association between low vitamin D status and prevalence of type 2 diabetes. Though few studies have shown there is no significant association between 25(OH) vitamin D and type 2 Diabetes[11,12] in other parts of the world, Indian studies have not been reported with similar findings.

Second important observation from this study was that there was no statistically significant difference in serum 25(OH) vitamin D between controlled diabetic subjects (14.92 ± 4.75 ng/ml) and uncontrolled diabetic subjects(15.12 ± 5.58 ng/ml) of the same age group (p=1.00). We also observed that there was no significant association between 25(OH) vitamin D and duration of diabetes in the diabetic group (figure 2). We have no data that might explain the similar vitamin D level in controlled diabetic patients and uncontrolled diabetic patients. This results show that the vitamin D deficiency may be an etiological factor for the development of type 2 diabetes and not the reverse. It also shows that the diabetes status, whether controlled or uncontr-olled, does not influence the serum 25 (OH) vitamin D level. This suggests a mechanistic link among serum vitamin D concentrations, glucose homeostasis, and the evolution of diabetes.

Progressive insulin resistance and insulinopenia is the hallmark of T2DM. Experimentally, vitamin D deficiency progressively reduces insulin secretion, and this reduction soon becomes irreversible[13]. There are many reports on the association of vitamin D with insulin secretion and insulin resistance. In 1995 Boucher et al[14] reported a significant positive association between 25(OH)D and oral glucose tolerance test induced insulin secretion in East London Asians at risk for T2DM. With regard to insulin resistance, significant inverse associations were reported between 25(OH)D and HOMA-IR by Scragg et al[15] in 2004, and Lu et al[16] in 2009.

Third important observation in this study was the inverse association between 25(OH) vitamin D and HbA1c levels (r = -.305; p- value < 0.01). Plausible biological mechanisms may involve insulin secretion and sensitivity which was discussed earlier. Our findings are consistent with similar studies done in other countries.[16,17,18] Our findings also cohere with investigations relating vitamin D status to diabetes from the Third NHANES[15] and the Medical Research Council Ely Prospective Study 1990–2000[36]. These findings highlight the need to consider screening for vitamin D insufficiency in individuals with an elevated HbA1c level and vice versa.

The result of this cross sectional study showed an inverse relation between serum 25(OH) vitamin D and fasting blood sugar (r-value = -.303, p value < 0.01) as well as post prandial blood sugar(r-value = -.311, p < 0.01). The inverse association between vitamin D and blood sugar had been proven by a lot of studies. [20,16]

In the present study it was found that the serum 25(OH) Vitamin D was more in males than females. In the whole cohort, the mean vitamin D in males was 20.1±7.32 ng/ml and females was 15.76±4.67 ng/ml and statistically significant (p<0.01). In the diabetic group, vitamin D in males and females were 16.33±6.10 ng/ml and 14.16±4.25 ng/ml respectively(p=0.04). In the control group Vitamin D was 25.01±5.87 ng/ml for men and 19.65±3.03 ng/ml for women

($p<0.01$). Reason for the low level of vitamin D in females may be due to the difference in their activities, i.e. male subjects generally had more frequent and longer duration in doing outdoor activities and therefore most of them had more exposure to direct sun light.

Another important observation from the present study was the high prevalence of hypovitaminosis D in our population. If we follow the currently proposed cut-off to define vitamin D sufficiency, 64.4% subjects in the study group were vitamin D deficient (<20 ng/ml), 31.8% had insufficient vitamin D (20-30ng/ml) and only 3.8% subjects had sufficient vitamin D (>30ng/ml). In the diabetic group, 82% were deficient in vitamin D, 18% insufficient and none of the diabetic patient in the study had sufficient vitamin D. In the control group 33.4% were vitamin D deficient, 56.1% insufficient and only 10.5 % had sufficient vitamin D.

Lack of exposure to the sun is a leading cause of vitamin D deficiency in our population. With modernization, the number of hours spent indoor have increased thereby preventing adequate sun exposure. Another reason for the hypovitaminosis D is the relatively dark skin complexion.

Studies from different parts of our country have drawn attention towards wide prevalence of vitamin D deficiency. [20,21,22] These reports thus scientifically establish evidence for prevalence of vitamin D deficiency in India, despite abundant sunlight.

A major strength of our study is the use of serum 25hydroxy vitamin D (Total D) as a measure of vitamin D status because 'Total D' measures both D2 and D3. Many of the previous studies used only Vitamin D3 and so may not represent the true vitamin D status. We collected and measured all the study samples in the month of March, so that we could avoid seasonal variation in Vitamin D level between subjects. The low level of Vitamin D in diabetic patients and inverse relationship between Vitamin D level and HbA1c in this sample supports an active role of Vitamin D in the pathogenesis of Type 2 diabetes mellitus. There is a possibility that the widespread prevalence of type 2 diabetes mellitus observed in our population could be partially related to vitamin D deficiency. We believe our results will lead to additional studies on the hypothetical circular relationship among diabetes and vitamin D.

Acknowledgement

The authors acknowledge that abstract of this article has been published in Diabetes, July 2013 62: A640-A685 (ADA 2013).

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