PRELIMINARY COMMUNICATION

Severe vitamin D deficiency in patients with Type 2 diabetes in north India

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Practice Points

- Vitamin D deficiency is increasingly recognized as a global problem and it has been estimated that nearly 1 billion people have either vitamin D deficiency or insufficiency. Possible explanations include lack of adequate sun exposure in urban areas, lack of intake of fortified foods and obesity.
- Vitamin D deficiency could be a potential risk factor for the metabolic syndrome, Type 2 diabetes mellitus (T2DM), and coronary heart disease.
- In this study, we report concentration of serum 25-hydroxy vitamin D3 in T2DM for the first time among Asian Indians living in north India.
- This study found a greater level of severe vitamin D deficiency among Asian Indians living with T2DM in a metropolitan city of north India than those without T2DM and this difference was statistically significant.
- Men with T2DM were statistically more likely to be observed with vitamin D deficiency than women with T2DM.
- The most important limitation of this study is the lack of availability of seasonal data for serum 25-hydroxy vitamin D3 sampling and information regarding the health of the nondiabetic patients.
- Future research could include intervention studies which would help to clarify if supplementation of vitamin D leads to improvement in insulin sensitivity or glycemia in Asian Indians.

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SUMMARY **Aim:** In this study, we aimed to determine the prevalence and correlates of vitamin D deficiency in Asian Indians with Type 2 diabetes mellitus (T2DM) living in north India. **Materials & methods:** A total of 92 patients with T2DM were compared with nondiabetic patients (n = 92) matched for age, gender, BMI, waist circumference and total body fat. Demographic and clinical parameters, anthropometry (i.e., BMI, waist circumference, waist-to-hip ratio, total body fat and trunk fat), fasting blood glucose, glycosylated hemoglobin and concentration (ng/ml) of serum 25-hydroxy vitamin D3 (25(OH)D3) were assessed. **Results:** The average concentration of serum 25(OH)D3 (ng/ml; mean ± standard deviation) was significantly lower for T2DM patients as compared with nondiabetic patients (11.0 ± 7.5 vs 15.5 ± 9.8, p = 0.00). Severe vitamin D deficiency (%) was significantly more prevalent among T2DM patients than the nondiabetic patients (57.6 vs 33.3, p = 0.001). The average concentration of serum 25(OH)D3 (ng/ml; mean ± standard deviation) was significantly lower for diabetic males than diabetic females (9.07 ± 6.7 vs 12.6 ± 7.6, p = 0.02). No significant correlation was seen on simple correlation analysis between concentration of serum 25(OH)D3 and BMI, waist circumference, total body fat, truncal fat, fasting blood glucose, glycosylated hemoglobin, systolic blood pressure, diastolic blood pressure, triglycerides and high-density lipoprotein cholesterol among T2DM patients. On logistic regression analysis low concentrations of serum 25(OH) D3 did not emerge as a predictor of T2DM. **Conclusion:** Severe vitamin D deficiency is more prevalent in T2DM patients than in nondiabetic patients. Men with T2DM have greater deficiency of vitamin D than diabetic women.

Incidence and prevalence of Type 2 diabetes mellitus (T2DM) is increasing rapidly; there were greater than 285 million patients worldwide with diabetes in 2010, increasing to approximately 438 million by 2030 [101]. Asian Indians are at a high risk for developing insulin resistance, the metabolic syndrome, T2DM and coronary heart disease [1]. The prevalence of diabetes between the age groups of 20–79 years was around 7.1% in India in 2010 (50.7 million) and these figures were estimated to rise to 8.6% by 2030 (87.0 million) [2,101].

Vitamin D deficiency is increasingly recognized as a global problem and it has been estimated that nearly 1 billion people have either vitamin D deficiency or insufficiency [3]. Possible explanations include lack of adequate sun exposure in urban areas, lack of intake of fortified foods and obesity [4–6].

Vitamin D deficiency is significant among individuals living in countries receiving large amounts of sunshine such as Italy, Spain, Greece and parts of the USA (i.e., South Florida) [6]. Living further from the equator (high latitudes) also poses an equally high risk for deficiency, if not greater. Further those with dark skin and women who cover large parts of the body with clothes (e.g., burqas or veils) are at a greater risk for developing vitamin D deficiency [7]. In particular, individuals with dark skin require greater than 5–10-times more sun exposure than a white person to obtain the required amount of vitamin D [8,9].

Increasing global prevalence of obesity could also contribute to vitamin D deficiency [5]. The relation between obesity and vitamin D deficiency is poorly understood. However, it is found that vitamin D is fat soluble and if excessive amounts of it are stored in the fat tissue then it could decrease the bioavailabity of endogenously produced vitamin D [5,10].

Conventional risk factors for T2DM include genetic predisposition, increasing age, poor dietary practices, obesity and sedentary lifestyle [2]. Recent research has also shown that vitamin D deficiency could be a potential risk factor for the metabolic syndrome [11], T2DM [12] and coronary heart disease [13].

Vitamin D deficiency has been reported to be more prevalent among T2DM patients (63.5%, mean value 17.1 ng/ml, $p < 0.05$) than patients with Type 1 diabetes mellitus (36%, mean value 23.6 ng/ml, $p < 0.05$) [14]. Vitamin D deficiency has also been reported to be more common among south Asians with T2DM living in the UK compared with the control group, which consisted of subjects without T2DM (83 vs 70%, p = 0.07, respectively) [15]. However, it has been reported that treatment with lower doses of vitamin D (400 vs 1200 IU for 4 months) did not show any improvement in glycemia, insulin sensitivity or lipid profile among T2DM patients [16]. Conversely, larger doses of vitamin D (4000 IU per day, which consists of four capsules of 1000 IU each vs four capsules of placebo per

day for 6 months) showed reduction in insulin resistance and improvement in insulin sensitivity at earlier stages of abnormal glucose homeostasis among south Asian women who were insulin resistant and deficient in vitamin D [17].

The concentration of serum 25-hydroxy vitamin D3 (25(OH)D3) levels in Asian Indians with T2DM has not been previously researched. We hypothesized that vitamin D deficiency is widely prevalent and severe in Asian Indians with T2DM living in north India, and low concentration may correlate with the metabolic syndrome and poor glycemic control. To test this hypothesis we studied clinical, anthropometric and metabolic profiles, and concentration of serum 25(OH)D3 in T2DM patients and nondiabetic patients matched for age, gender, BMI, waist circumference (WC) and total body fat.

Methods

This study was carried out in the Department of Diabetes and Metabolic Diseases at Fortis Hospital, New Delhi, India. Consecutive patients with T2DM, alongside age-, gender-, BMI-, WC- and body fat-matched nondiabetic patients, attending the outpatient department of the hospital were recruited. The adult patients attending the hospital outpatient department were selected irrespective of their glycemic status. We roughly estimated the number of patients to be taken in the study with the help of the statistician. We did not perform a sample size calculation. Out of 184 consecutive patients, 92 had T2DM and 92 were nondiabetic patients. Demographic, clinical, anthropometric and metabolic parameters were assessed in all patients.

For measurement of weight, subjects were instructed to stand still in the platform, with the body weight evenly distributed between both the feet. After removing heavy clothing, weight was measured to the nearest 0.1 kg. Height was measured using a stadiometer with head held in Frankfurt plane to the nearest 0.1 cm. BMI was calculated by the following formula; weight (kg)/height (m^2). WC was measured midway between anterior superior iliac spine and lowermost margin of the ribs, during quiet breathing. Hip circumference was measured at the maximum protruding part of buttocks at the level of the greater trochanter with the patient wearing minimal clothing and feet together. Total body fat (%), and trunk (chest and abdomen) fat (%) were measured using the segmental leg-to-leg bioelectrical impedance method (Tanita BC-418MA, Tanita Corporation, Tokyo, Japan) as previously described [18]. Blood pressure was recorded after at least 5 min of rest in a chair, with feet on the floor, and arm supported at heart level, using a mercury sphygmomanometer. An appropriate-sized cuff (cuff bladder encircling at least 80% of the arm) was used to ensure accuracy. Systolic blood pressure was measured at the point where the first of two or more sounds was heard (Phase 1), and diastolic blood pressure was measured before the disappearance of sounds (Phase 5).

Biochemical analysis

The biochemical tests were done at International Organization for Standardization certified laboratory (SRL Ranbaxy, New Delhi, India). Estimations for fasting blood glucose (FBG) and lipids were performed using spectrometry (Perkin Elmer, MA, USA). Glycosylated hemoglobin was measured by the high performance liquid chromatography method (Bio-Rad Laboratories, Waters, MA, USA). The assay has been accredited by National Glycohemoglobin Standardization Program. Concentration of serum 25(OH)D3 was measured by radioimmunoassay (ImmunoDiagnostic Systems, Boldon, UK) and the inter- and intra-assay variation for vitamin D test was less than 30%.

Definitions

Overweight was defined as BMI ≥23–24.9 kg/m^2 and obesity as BMI ≥25 kg/m^2 [19]. A WC of ≥80 cm for females and ≥90 cm for males was diagnostic of abdominal obesity [19]. Serum 25(OH)D3 levels (ng/ml) were defined as: severe deficiency: <10; deficiency: 10–20; insufficiency: 21–29 and sufficiency: ≥30 [20]. The metabolic syndrome was defined using the criteria laid out by the International Diabetes Federation: WC ≥90 cm for males and ≥80 cm for females, serum triglycerides ≥150 mg/dl, FBG ≥100–125 mg/dl, high-density lipoprotein cholesterol <40 mg/dl for males and <50 mg/dl for females and blood pressure ≥130/85 mmHg [21].

Statistical analysis

Data were presented as mean ± standard deviation (SD). The differences in mean values of the variables between cases and controls were tested using student t-test and t-test with adjustment for variables with unequal variances (Welch's test). Differences between proportions were tested using the Chi-square test. Logistic regression analysis was carried out to identify the independent

predictors of T2DM considering BMI, WC, blood pressure, serum triglycerides, FBG and concentration of serum 25(OH)D3 as risk factors and to estimate odds ratio and 95% CI. Stata 9.0 (Stata Corporation, College Station, TX, USA) was used for the statistical analysis. For this analysis, $p < 0.05$ was considered as statistically significant.

Ethical approval

This study was approved by the Ethics Committee of Diabetes Foundation of India and a written informed consent was obtained from all the subjects.

Results

The data for anthropometric and biochemical parameters for T2DM patients and nondiabetic patients are given in **Table 1**. Age (years) range among T2DM patients (30–79) and nondiabetic patients (30–80), mean age, BMI (kg/m^2), WC (cm), hip circumference (cm), waist-to-hip ratio, body fat (%) and truncal fat (%) were similar **(Table 1)**. Mean duration (mean ± SD) of T2DM was 10.5 ± 7.2 years and 41 males and 51 female patients had T2DM.

The results for concentration (ng/ml) of serum 25(OH)D3 (mean ± SD) were significantly lower for the T2DM patients than the nondiabetic patients (11.0 ± 7.5 vs 15.5 ± 9.8, p = 0.00). Severe vitamin D deficiency (%) was significantly more prevalent among the T2DM patients than the nondiabetic patients (57.6 vs 33.3, p = 0.001) **(Figure 1)**. Vitamin D deficiency and insufficiency (%) was more prevalent among nondiabetic patients than T2DM patients (44.4 vs 28.6 and 14.4 vs 11.9, respectively) **(Figure 1)**. The concentration (ng/ml) of serum 25(OH) D3 (mean ± SD) was significantly lower for diabetic males than diabetic females (9.07 ± 6.7 vs 12.6 ± 7.6, p = 0.02, respectively).

On logistic regression analysis low concentrations of serum 25(OH)D3 did not emerge as a predictor of T2DM (data not presented). No significant correlation was seen on simple correlation analysis between concentration of serum 25(OH)D3 and BMI (R^2 = 0.004), WC (R^2 = 0.0000007), total body fat (R^2 = 0.0029), truncal body fat (R^2 = 0.0077), FBG (R^2 = 0.0238), glycosylated hemoglobin (R^2 = 0.0692), systolic blood pressure (R^2 = 0.0003), diastolic blood pressure (R^2 = 0.0005), triglycerides (R^2 = 0.0007) and high-density lipoprotein (R^2 = 0.0156) among T2DM patients.

Table 1. Anthropometric and biochemical parameters.

Variable	T2DM, n = 92 (mean ± SD)	Nondiabetic, n = 92 (mean ± SD)	p-value
Age (years)	52.7 ± 11.1	52.7 ± 11.1	1.00
BMI (kg/m^2)	28.6 ± 5.3	28.3 ± 5.96	0.73
Waist circumference (cm)	97.7 ± 12.5	94.9 ± 14.1	0.18
Hip circumference (cm)	101.6 ± 11.7	102.0 ± 9.9	0.80
Waist-to-hip ratio	0.96 ± 0.08	0.92 ± 0.08	0.006
Total body fat (%)	33.9 ± 10.1	32.0 ± 10.2	0.42
Trunk fat (%)	35.9 ± 9.64	34.3 ± 7.71	0.41
Fat mass (kg)	27.1 ± 12.3	26.2 ± 8.5	0.71
Systolic blood pressure (mmHg)	135.8 ± 17.8	129.7 ± 18.7	0.02
Diastolic blood pressure (mmHg)	74.9 ± 9.06	75.0 ± 9.30	0.94
Fasting blood glucose (mg/dl)	169.7 ± 63.6	101.8 ± 25.2	0.00
HbA1c (%)	8.3 ± 1.9	6.1 ± 0.68	0.00
Total cholesterol (mg/dl)	165.2 ± 49.2	193.6 ± 40.6	0.00
Triglycerides (mg/dl)	162.6 ± 78.0	136.4 ± 68.4	0.02
Low-density lipoprotein cholesterol (mg/dl)	91.9 ± 40.6	113.7 ± 33.4	0.00
High-density lipoprotein cholesterol (mg/dl)	40.3 ± 10.9	46.4 ± 14.7	0.00
Microalbuminuria (mg/ml)	152.3 ± 598.1	19.4 ± 53.0	0.18
High-sensitivity C-reactive protein (mg/l)	17.4 ± 48.3	3.5 ± 4.0	0.07
Calcium (mg/dl)	9.27 ± 0.72	9.14 ± 0.90	0.34
Phosphorous (mg/dl)	3.74 ± 0.77	3.68 ± 0.65	0.69
Serum 25-hydroxy vitamin D3 (ng/ml)	11.0 ± 7.5	15.5 ± 9.8	0.00

SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

Discussion

In this study, we report concentration of serum 25(OH)D3 for the first time in Asian Indians with T2DM living in north India. This study population only represents the urban adult population of Delhi located in north India as opposed to the whole Indian population. This study found a greater level of severe vitamin D deficiency among Asian Indians living with T2DM in a metropolitan city of north India than those without T2DM and this difference was statistically significant. Men with T2DM have greater deficiency of vitamin D than diabetic women.

The mechanisms for increased insulin resistance in vitamin D insufficiency have not been fully elucidated. Many tissues and cells including the β cells of the pancreas express 1-OHase and can produce 1,25-dihydroxy vitamin D. The β cells have a vitamin D receptor, which may improve insulin secretion and production and an increase in serum 25(OH)D3 levels leads to reduction in β-cell glucose insensitivity and increases Phase 1 and 2 of insulin secretion after a glucose challenge [9,22]. Vitamin D can also affect insulin secretion by increasing the intracellular calcium concentration via the nonselective voltage-dependent calcium channels [23].

In clinical studies, vitamin D deficiency has been shown to cause impairment of insulin secretion and an increase in insulin resistance among patients with T2DM [3]. Furthermore, when the concentration of serum 25-hydroxy vitamin D levels increased from 12.5 to 30 ng/ml, insulin secretion was shown to increase by almost 60% in patients with T2DM [9]. In a large prospective study conducted among women, an intake of ≥1200 mg of calcium and ≥800 IU of vitamin D reduces the risk of developing T2DM by 33% compared with those who had a calcium intake of <600 mg and vitamin D of <400 IU per day [24]. Interestingly, in a preliminary study in 100 centrally obese but nondiabetic Asian Indian men, vitamin D3 supplementation (three doses of 120,000 IU each of vitamin D3 fortnightly and assessed after 42 days) has been suggested to improve postprandial insulin sensitivity [25]. Further, vitamin D supplementation (4000 IU D3 [n = 42] or placebo [n = 39] daily for 6 months) improved insulin resistance and insulin sensitivity in south Asian women living in New Zealand who were insulin resistant and suffered from vitamin D deficiency [17]. However, we could not find any association of measures of glycemia and vitamin D in our small study.

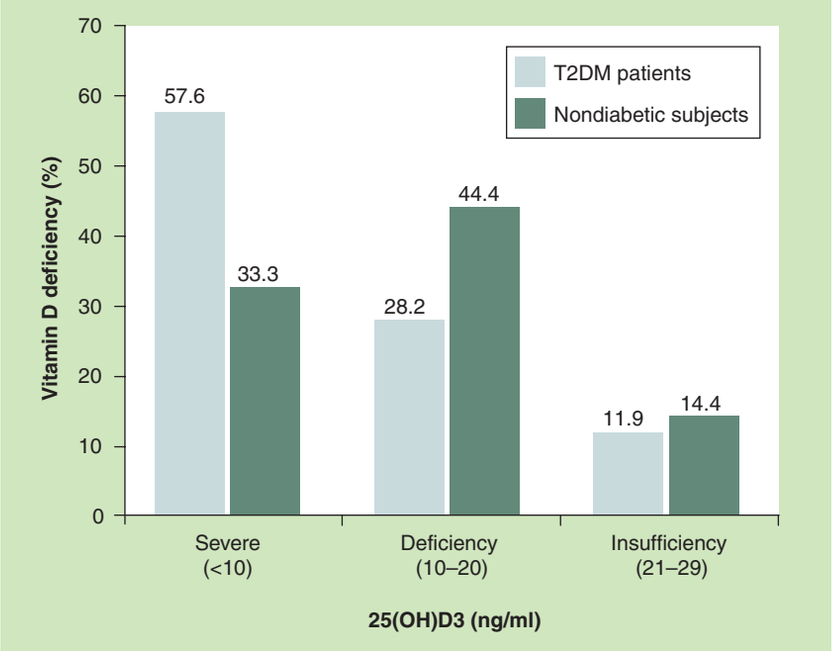

Figure 1. Presence of 25-hydroxy vitamin D3 deficiency among Type 2 diabetes mellitus patients and nondiabetic subjects.
25(OH)D3: 25-hydroxy vitamin D3; T2DM: Type 2 diabetes mellitus.

Causes of widespread vitamin D deficiency in Asian Indians remain poorly researched. However, less exposure to sunlight in urban settings and consumption of predominantly vegetarian foods (59–65% of the population) low in vitamin D content may be the likely explanations [102]. Furthermore, only a small proportion of urban-based populations in India consume foods fortified with vitamin D (e.g., fortified milk or cereals). Vitamin D deficiency in urban Asian Indians could also be due to increasing obesity because serum 25(OH)D3 levels decrease when the BMI is greater than 30 [26]. In our study 32.6% of the patients had a BMI greater than 30 and our observations do not suggest any correlation between the BMI of the two groups (BMI >30 vs BMI <30) with vitamin D deficiency.

There could be a possible link between low concentrations of serum vitamin D and the risk of developing the metabolic syndrome. In US adults, risk of metabolic syndrome decreases with increasing concentration of vitamin D in the blood [11]; however, in the study by McGill and colleagues, 250 adults living in New Zealand did not show any correlation [27]. In our study, though the entire study cohort was analyzed no relationship was found between vitamin D deficiency and metabolic syndrome and poor glycemic control.

A possible explanation for this might be the comparatively small population size and the results vary with an increase in sample size.

There are some limitations of this study. The most important being the lack of availability of seasonal data for serum 25(OH)D3 sampling and information regarding the health of the nondiabetic patients. The study involves a comparatively small number of subjects, which could affect the absence of differences in some characteristics between the two groups analyzed. This study also does not represent the whole Indian population and includes only a small population of urban adults living in Delhi in north India. Information about duration of sun exposure per week, whole or partial body exposure, season, time of the day and dress code could not be accurately obtained. Data regarding parathyroid hormone, betel chewing, alcohol intake and smoking was not available. If the study was extended further, a higher number of subjects could be analyzed along with seasonal data for serum 25(OH)D3 sampling. Genetic studies should also be included because research indicates that there is an association between vitamin D receptor gene polymorphism and a combination of genotypes and this is associated with a risk of developing T2DM [28].

In conclusion, we report severe vitamin D deficiency in Asian Indians with T2DM compared with the nondiabetic patients and that more men with T2DM are affected with vitamin D deficiency than women. Intervention studies are needed to clarify if supplementation of vitamin D leads to improvement in insulin sensitivity or glycemia in Asian Indians.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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