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Lower vitamin D levels are associated with higher blood glucose levels in Asian Indian women with pre-diabetes: a population-based cross-sectional study in North India

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ABSTRACT

Background Asian Indian women are predisposed to develop obesity, metabolic syndrome and vitamin D deficiency. Relationship of vitamin D deficiency with blood glucose levels has not been explored in Asian Indian women with pre-diabetes.

Objective We evaluated the associations of serum 25-hydroxy vitamin D (25(OH)D) concentrations among adult women with the pre-diabetes residing in North India (Delhi).

Methods This cross-sectional population-based study involved 797 women with pre-diabetes aged 20–60 years. Blood pressure, body mass index (BMI), fasting blood glucose (FBG), extent of sun exposure and serum 25(OH) D levels were assessed. For purpose of analysis, serum 25(OH)D levels (nmol/L) were categorized in quintiles as follows: 0–21.5 (first quintile), 21.51–35.60 (second quintile), 35.61–46.50 (third quintile), 46.51–62.30 (fourth quintile) and >62.31 (fifth quintile).

Result The prevalence (%) of vitamin D deficiency, insufficiency and sufficiency was 68.6, 25.9 and 5.5, respectively. Mean age (p=0.004), systolic (p=0.05) and diastolic (p=0.04) blood pressure, weight (p=0.03), BMI (p=0.04) and FBG (p=0.02) were significantly higher in subjects with vitamin D deficiency as compared with those with vitamin D insufficiency and sufficiency. Unadjusted mean values of FBG were significantly decreased in fourth (p=0.02) and fifth quintiles (p=0.030) of 25(OH) D levels as compared with second quintile. Furthermore, after adjusting for age and family income FBG levels were significantly increased in first quintile (compared with fourth (p=0.012) and fifth (p=0.018) quintiles) and second quintile (compared with fourth (p=0.003) and fifth (p=0.004) quintiles) of 25(OH)D levels, respectively.

Conclusion Lower vitamin D levels are associated with higher blood glucose values in Asian Indian women with pre-diabetes. These findings need confirmation in case–control and prospective studies.

Significance of this study

What is already known about this subject?

- Previous research has shown that subjects with pre-diabetes and low circulating 25(OH)D levels are insulin resistant and have impaired β cell function.

What are the new findings?

- This is first study (in context of pre-diabetes and vitamin D) on carefully selected large sample of Asian Indian women, showing significant relationship of lower vitamin D levels with higher fasting blood glucose levels.

How might these results change the focus of research or clinical practice?

- In view of above association, intervention trials with vitamin D are needed in Asian Indian women with pre-diabetes to evaluate if diabetes could be prevented.

INTRODUCTION

Vitamin D deficiency is a major public health problem worldwide. The Indian subcontinent, situated between 8.4^0 -N and 37.6^0 N latitude, is exposed to adequate sunshine and ultraviolet B rays throughout the year. Because of such abundant exposure to sunlight, it has been presumed that Indians have adequate levels of vitamin D. Several studies in India show high prevalence of vitamin D deficiency in different populations[1] and related to abdominal obesity.[2] Previously, we had shown that patients with type 2 diabetes mellitus (T2DM) have lower levels of vitamin D as compared with non-diabetic individuals.[3]

Specifically, women in India are more likely to have vitamin D deficiency because many of them are confined to households and have high coverage of body part with clothes, thus they may not be exposed to sufficient sunlight. In a study in North India (Delhi), the prevalence of vitamin

D deficiency was high in women, particularly those belonging to low socioeconomic status.[4] Similar results have been reported for postmenopausal women in South India.[5] It is important to note that low vitamin D levels and inadequate intake of calcium may predispose postmenopausal Indian women to bone fractures.[6]

Pre-diabetes is associated with abdominal obesity, insulin resistance, non-alcoholic fatty liver disease and metabolic syndrome, and such individuals are at an increased risk for developing T2DM and cardiovascular disease.[7] A recent study in 15 states of India showed that the prevalence of pre-diabetes and T2DM was 10.3% (95% CI 10.0 to 10.6) and 7.3% (95% CI 7.0 to 7.5), respectively.[8] Specifically, pre-diabetes was more prevalent than T2DM in all states in India excluding north (Punjab) and in the northeast. Importantly, Asian Indians with pre-diabetes are at a heightened risk for conversion to T2DM as compared with British Caucasians.[9] In a previous study in North India (Delhi), we showed that the women and men had similar prevalence of diabetes (13.8% and 13.3%, respectively) but average blood glucose levels (mg/dL) were higher in women as compared with men (147.3±46.3 vs 141+46.8, respectively).[10]

The relationship between vitamin D and development of pre-diabetes has not been well understood. Cross-sectional and longitudinal studies have shown inverse association between vitamin D levels and incident diabetes.[11] In Nurses' Health Study (age, 30–55 years), living in USA, after multivariate adjustments, women who consumed more than 800 IU/day of vitamin D had a 23% lower risk for developing incident T2DM compared with women who consumed less than 200 IU/day (RR 0.77, 95% CI 0.63 to 0.94; p<0.01).[12]

Only a few studies have been done in India regarding insulin resistance, hyperglycemia and vitamin D deficiency. No association has been reported between vitamin D levels, body mass index (BMI), T2DM and hemoglobin A1C across the spectrum of glucose intolerance in Asian Indians residing in Western India.[13] In a cross-sectional study in East India, individuals with pre-diabetes (n, 157) were investigated for vitamin D deficiency and insulin resistance. In this study, individuals with vitamin D deficiency showed significant inverse correlation to insulin resistance and positive correlation with insulin sensitivity.[14] Further, same authors showed significantly lower levels of serum adiponectin and serum 25-hydroxy vitamin D (25(OH)D) and higher serum insulin levels in persons with pre-diabetes or T2DM as compared with controls.[15] Of note, all above studies in India involved limited number of subjects and have included individuals from both genders. In view of propensity of Indian women to have obesity, metabolic syndrome and consequent hyperglycemia and low serum 25(OH)D levels, an investigation on larger number of women at high risk for development of diabetes is required.

METHODS

Subjects

We conducted a cross-sectional population-based study approved by the institutional ethics committee. Subjects were randomly selected to have approximate representation from each income group (high-income group ~10%, middle-income group ~65%–70%, and low-income group ~15%–20%) from 35 residential locations according to the approximate proportion of individuals living in Delhi. After informed consent, fasting blood glucose (FBG) levels were done in 1361 women (20–60 years of age) from June 2012 to June 2017. Among this group, 797 women were categorized as having pre-diabetes (figure 1). Subjects who received vitamin D or calcium supplementation in the previous 6 months, any medication which could affect insulin sensitivity, vitamin D or calcium metabolism (eg, metformin, thiazolidinediones, steroids, and so on) within the last 1 month, those with pregnancy, severe end-organ damage or chronic diseases, malignancy, and known diabetes mellitus and other endocrine disorders were excluded from the study.

Demographic, clinical and anthropometric measurements

Demographic and clinical profiles, medical history (personal and family), socioeconomic characteristics, skin exposure to sun and overall duration of sunlight exposure were determined with the use of prevalidated questionnaire. Skin exposure was recorded by per cent of body surface area (face/hands, face/hands and arms, and face/hands and legs) exposed to sunlight. The duration of sunlight exposure (min/day) was assessed in the following manner: <5 min, 5–15 min, 15–30 min and >30 min. Blood pressure was measured by a standard mercury sphygmomanometer, over the right arm in sitting position. Weight and height were recorded, and BMI was calculated.

Biochemical analysis

FBG was analyzed as previously described.[16] Serum 25(OH)D levels were measured by chemiluminescence method (DiaSorin LIAISON 25-OH D, Stillwater, Minnesota, USA). The LIAISON 25(OH)D assay is a direct competitive chemiluminescence immunoassay for quantitative determination of total 25(OH)D in serum sample.[17] The intra-assay coefficient of variation was 1.61% and the interassay coefficient was 2.06%.

Definitions

Overweight and obesity were defined as BMI 22–24.9 kg/m^2 and >25 kg/m^2, respectively.[18] Blood pressure ≥130/85 mm Hg (or on antihypertensive therapy) was defined as abnormal. Pre-diabetes was defined as FBG levels >100 and 125.9 mg/dL.[19] Serum 25(OH)D levels were categorized as follows: deficiency <49.9 nmol/L, insufficiency 50–75 nmol/L, and normal more than 75 nmol/L.[20] Serum 25(OH)D levels (nmol/L) were categorized in quintiles as follows: 0–21.5 (first quintile), 21.51–35.60 (second quintile), 35.61–46.50 (third quintile),

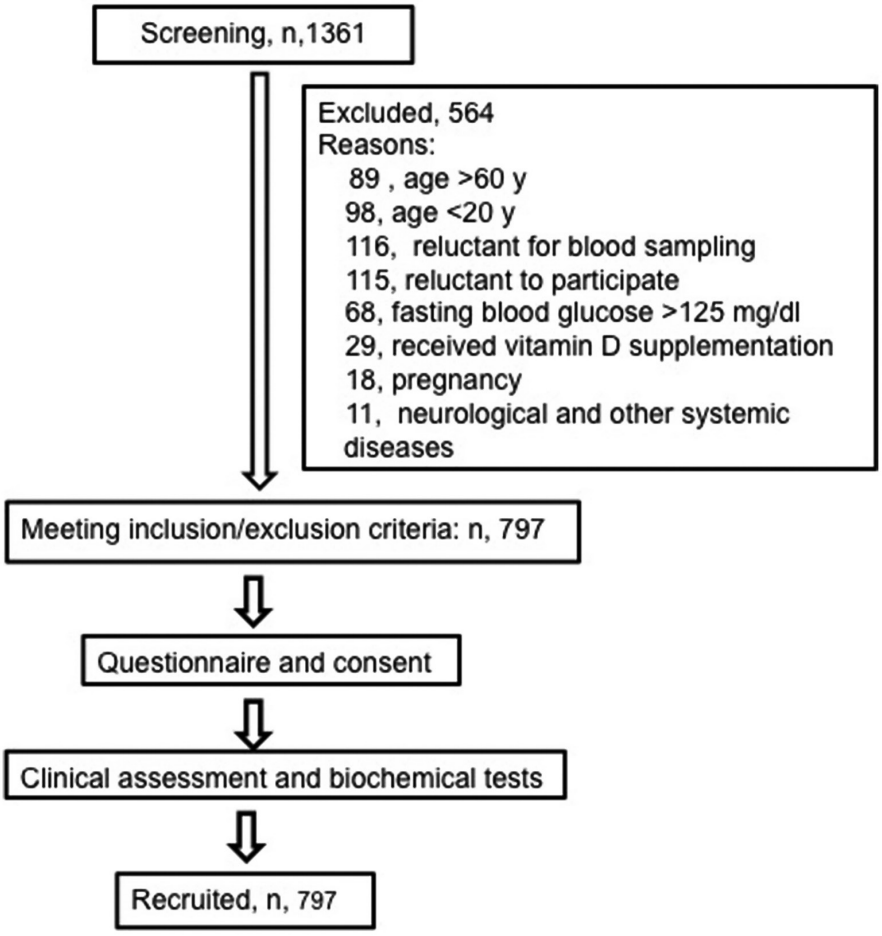

Figure 1 Study design and workflow.

46.51–62.30 (fourth quintile) and >62.31 (fifth quintile). Because many values of 25(OH)D were clustered around cut-off values of quintiles, slightly different numbers of subjects were segregated in each quintile.

Statistical analysis

Data were entered in an Excel spreadsheet (Microsoft, Washington, USA). The distribution of demographic, clinical, medical history (personal and family), socioeconomic and behavioral characteristics, sun and skin exposure and biochemical parameters was confirmed for approximate normality. We used mean and SD and number (%) to summarize the variables. Comparison of general characteristics, mean of variables and proportion of risk factors by serum 25(OH)D status groups including mean of serum 25(OH)D levels were performed using Fisher's exact test and non-parametric statistics such as Kruskal-Wallis tests (post hoc by Bonferroni's method). The correlation regression was calculated using Spearman's test. After adjusting for age and family income (surrogate of socioeconomic status of the family), one-way analysis of variance (ANOVA) and analysis of covariance were carried out. All statistical analyses were performed using SPSS (V.21.0, SPSS). For all above, p value of<0.05 was considered as statistically significant.

RESULTS

Demographical, socioeconomic, and clinical profiles

Educational status (p=0.004), employment status (p=0.003), family income (p=0.05), skin exposure (face and hands) (p=0.05) and sun exposure (5–15 min/day) (p=0.04) were significantly higher in subjects with vitamin D sufficiency as compared with those with vitamin D deficiency and insufficiency (p=0.030). We did not find any significant association of 25(OH)D with demographic, personal and family medical history, and tobacco and alcohol consumption (p>0.05) (table 1).

Body composition and biochemical profile

Among the total subjects:

A. BMI less than 22.9 kg/m^2 (normal BMI): 193 (24.2%).
B. BMI between 22.9 and 24.9 kg/m^2 (overweight): 112 (14.1%).
C. BMI equal to or more than 25 kg/m^2 (obese): 492 (61.7%).

Hence, total number who are non-obese (A plus B): 305 (38.3%).

The mean±SD for age was 42.02±11.4 years. Mean age (p=0.003), systolic (p=0.05) and diastolic (p=0.04) blood pressure, weight (p=0.003), BMI (p=0.04) and

Table 1 Demographic profile, family history and duration of sun exposure

Variables		Deficiency (0–49.998 nmol/L)	Insufficiency (50–74.99 nmol/L)	Sufficiency (>75 nmol/L)	P values
Religion	Hindu	544 (99.4)	206 (100)	44 (100)	0.8
	Others	3 (0.6)	0	0	
Marital status	Married	500 (91.4)	182 (88.3)	42 (95.4)	0.51
	Unmarried	47 (8.6)	24 (11.7)	2 (4.6)	
Education	Never attended school	102 (18.6)	30 (14.5)	15 (34)	0.004
	Grades 1–8	112 (20.5)	42 (20.5)	10 (22.7)	
	Grades 9 and 10	72 (13.2)	38 (18.4)	0	
	Higher secondary	77 (14)	25 (12.1)	4 (9)	
	College/diploma	9 (1.6)	12 (5.8)	2 (4.6)	
	Graduate	117 (21.5)	33 (16.1)	7 (16)	
	Postgraduate	58 (10.6)	26 (12.6)	6 (13.7)	
Employment status	Employed	158 (28.8)	58 (28.1)	13 (29.5)	0.05
	Self-employed	34 (6.2)	19 (9.2)	5 (11.5)	
	Housewife	355 (65)	129 (62.7)	26 (59)	
Family income (in Indian National Rupee)	Less than 10 000	51 (9.3)	24 (11.7)	8 (18.1)	0.003
	10 001–30 000	275 (50.2)	129 (62.6)	24 (54.5)	
	More than 30 000	221 (40.5)	53 (25.7)	12 (27.4)	
Tobacco consumption		4 (0.7)	0	0	0.399
Alcohol consumption		2 (0.3)	0	0	0.732
Personal medical history	Hypertension	66 (12)	20 (9.7)	6 (13.6)	0.65
	Thyroid	62 (11.3)	12 (5.8)	7 (16)	0.3
	Tuberculosis/ asthma	4 (0.7)	2 (0.9)	2 (4.5)	0.598
Family medical history	Obesity	6 (1)	4 (1.9)	0	0.44
	Diabetes	102 (18.6)	42 (20.4)	4 (9)	0.09
	Hypertension	56 (10.2)	28 (13.6)	6 (1.36)	0.113
	Heart disease	21 (3.8)	12 (5.8)	4 (9.0)	0.746
	Thyroid disease	7 (1.3)	2 (0.9)	2 (4.5)	0.2
	Tuberculosis	4 (0.7)	4 (1.9)	2 (4.5)	0.6
Skin exposure	Face/hands	209 (38.2)	62 (30)	15 (34)	0.05
	Face/hands/arms/ leg	338 (61.8)	144 (70)	29 (66)	
Duration of sun exposure (min/day)	<5	320 (58.5)	110 (53.4)	20 (45.4)	0.04
	5–15	183 (33.4)	80 (38.8)	15 (34.6)	
	15–30	44 (8.1)	16 (7.8)	9 (20)	

Values are given as the number, %. P<0.05 is statistically significant.

FBG levels (p=0.013) were significantly higher in subjects with vitamin D deficiency as compared with those with vitamin D insufficiency and sufficiency (table 2).

25(OH)D levels

The prevalence (%) of vitamin D deficiency, insufficiency and sufficiency was 68.6, 25.9 and 5.5, respectively. After stratifying the sample according to serum 25(OH) D quintiles, we observed age (p=0.002) was significantly increased in the first quintile as compared with other quintiles. Further, family history of diabetes (p=0.03) was significantly higher in the second quintile as compared with other quintiles (tables 2 and 3).

We did not find any significant difference of FBG values (mg/dL) between three categories of individuals

Table 2 Demographic, clinical and biochemical profiles by vitamin D category

Variables	Deficiency (0–49.99 nmol/L)	Insufficiency (50–74.99 nmol/L)	Sufficiency (>75 nmol/L)	P values
n (%)	547 (68.6)	206 (25.8)	44 (5.5)	0.003
Age (years)	42.9±11.2	40.0±12.07	40±8.8	0.004
Pulse rate (per minute)	83.6±5.30	84.0±4.6	84.0±5.7	0.4
Blood pressure (mm Hg)				
Systolic	124.1±14.9	122.5±13.4	122.6±12.3	0.05
Diastolic	80.8±7.7	79.8±8.2	78.4±8.0	0.04
Body weight and BMI				
Weight (kg)	65.0±9.1	62.1±12.1	60.3±12.0	0.03
Height (cm)	153.3±5.8	153.7±6.0	154.0±6.1	0.6
BMI (kg/m^2)	27.5±4.5	26.5±5.3	25.5±4.9	0.01
Biochemical profile				
Fasting blood glucose (mg/dL)	111.9±8.6	109±8.4	108.6±6.7	0.002
25(OH) vitamin D (nmol/L)	30.3±12.5	63.7±7.8	91.0±8.7	0.0001

Values are given as the mean±SD. P<0.05 is statistically significant.
BMI, body mass index.

as determined by BMI: (A) 110.5±7.8, (B) 109.9±7.7 and (C) 110.6±7.4 (p=0.69). Further, we did not find any significant difference vitamin D (nmol/L) levels between three categories of BMI: (A) 43.6±20.9, (B) 41.7±21.6 and (C) 41.9±22.1 (p=0.62).

One-way ANOVA and analysis of covariance

Unadjusted mean values of FBG were statistically significantly decreased in fourth (p=0.02) and fifth quintiles (p=0.030) as compared with second quintile. Furthermore, after adjusting for age and family income, we observed FBG levels were significantly increased in the lowest 25(OH)D quintile (compared with fourth (p=0.012) and fifth (p=0.018)) and second quintiles (compared with fourth (p=0.003) and fifth (p=0.004) quintiles), respectively (table 4 and figure 2).

DISCUSSION

This study shows that higher FBG levels are associated with lower vitamin D levels in Asian Indian women living in North India with pre-diabetes. Blood glucose and 25(OH)D levels in this cohort were not influenced by BMI category, or in other words, by overweight and obesity status. Such findings in a large cohort of Asian Indian women have been reported the first time. While the strength of this study was large number of subjects and careful selection criteria, limitations included cross-sectional of nature of the study, absence of a control group of normoglycemic individuals, and non-availability of calcium, phosphorus, parathyroid hormone and calcitriol levels. A more robust statement regarding relationship between 25(OH)D and FBG could be made if serum calcitriol levels were available.

The role of vitamin D in insulin pathway has been debated. Based on preclinical studies, vitamin D appears to play a regulatory role in calcium flux within β cells, insulin secretion, and β cell survival. Vitamin D deficiency impairs glucose-mediated insulin secretion in rat pancreatic beta cells, while vitamin D supplementation seems to restore such glucose-stimulated insulin secretion.[21 22] Overall, these and several other studies have indicated that vitamin D may have a direct effect on β cell function mediated by binding of the circulating active form, 1,25(OH)2D, to vitamin D receptor, which is expressed in pancreatic β cells.[23] Further, activation of vitamin D occurred within the β cells by the 25(OH)D1α hydroxylase enzyme (CYP27B1), which is expressed in β cells, thereby allowing for a paracrine effect of circulating 25(OH)D.[24]

Having stated that, association of low vitamin D levels with hyperglycemia in human beings continues to be researched and debated. Specifically, individuals with pre-diabetes have been less investigated in the context of vitamin D deficiency (table 5). These data highlight some important information; first except a few, most studies have been done in limited number of subjects. Second, no investigator has specifically focused on women with pre-diabetes.

Abbasi *et al*[25] showed that subjects with pre-diabetes and low circulating 25(OH)D levels were most insulin resistant and had impaired β cell function as compared with normal fasting glucose-vitamin deficient and normal fasting glucose-vitamin D sufficient subgroups. In National Health and Nutrition Examination Survey (2001–2006), average vitamin D levels decreased steadily across range of FBG levels in Caucasian men and women; with mean concentrations (nmol/L) of 66.2, 62.3 and 54.2, respectively. In this study, mean concentration of vitamin D was significantly lower in individuals with pre-diabetes and diabetes as compared with those with normoglycemia.[26]

Table 3 Demographic and anthropometry profiles according to serum 25(OH)D quintiles

Variables	First quintile (3.0–21.5, n, 160)	Second quintile (21.51–35.60, n, 178)	Third quintile (35.61–46.50, n, 172)	Fourth quintile (46.51–62.30, n, 130)	Fifth quintile (>62.31, n, 157)	P values
Age (years)	44.3±10.7	42.8±11.3	41.9±11.4	39.2±12.3	41.2±10.7	0.0027
Pulse rate (per minute)	84.2±5.0	83.4±5.2	82.9±5.5	84.2±4.6	84.0±5.1	0.11
Family medical history (n, %)						
Obesity	0	2 (1.12)	4 (2.33)	2 (1.54)	2 (1.27)	0.44
Diabetes	32 (21.6)	39 (26.3)	23 (15.5)	26 (17.5)	28 (18.9)	0.03
Blood pressure (mm Hg)						
Systolic	123.6±12.6	123.2±14.0	120.9±10.4	122.8±12.3	122.8±13.8	0.33
Diastolic	80.7±7.4	81.4±8.2	80.2±7.8	80.1±7.9	80±8.1	0.47
Weight and BMI						
Weight (kg)	65.2±19.0	62.3±13.0	63.1±14.2	64.1±12.6	63.5±14.5	0.23
Height (cm)	152.3±6.2	153.2±6.4	154.2±5.2	152.6±5.4	153.8±5.1	0.45
BMI (kg/m^2)	26.7±5.9	26.1±5.1	26.4±4.9	26.1±4.8	26.2±5.1	0.86

Results are shown as mean±SD and n, %. Analysis of covariance (ANCOVA) test was applied. Serum 25(OH)D levels were categorized in quintiles as described in text. P<0.05 is statistically significant.
25(OH)D, 25-hydroxy vitamin D; BMI, body mass index.

Table 4 Unadjusted* and adjusted§ fasting blood glucose values according to quintiles of serum 25(OH)D

Variables	First quintile (3.0–21.5, n, 160)	Second quintile (21.51–35.60, n, 178)	Third quintile (35.61–46.50, n, 172)	Fourth quintile (46.51–62.30, n, 130)	Fifth quintile (>62.31, n, 157)	P values
FBG (mg/dL)* Mean±SD	111.3±7.9	111.7±8.1	110.1±9.9	109.7±7.1‡	109.2±7.3‡	0.009
FBG (mg/dL)§ Mean±SD	111.3±7.0	111.7±7.6	110.7±7.4	109.0±7.5†,‡	109.3±7.5†,‡	0.012

Serum 25(OH)D levels were categorized in quintiles. Results are shown as mean+SD. P<0.05 is statistically significant.
*Unadjusted mean value (for age and family income). §Adjusted mean value (for age and family income). †Significantly different from the first quintile.‡ Significantly different from the second quintile, adjusted p<0.005.
25(OH)D, 25-hydroxy vitamin D; FBG, fasting blood glucose.

In a longitudinal cohort study, Deleskog *et al*[27] showed that high serum 25(OH)D levels predicted a reduced risk of converting to diabetes from pre-diabetes, but this was not seen in those with normal glucose tolerance.

Despite data showing widespread deficiency of vitamin D in India, its relationship with the metabolic syndrome and T2DM has not been adequately researched; some of these have been discussed in the introduction of this paper. In 2010, a 4-week pilot study showed that short-term improvement in vitamin D levels was not associated with improvement in glucose tolerance, insulin secretion, or insulin sensitivity in 28 Asian Indian patients with moderately controlled T2DM.[28] In 2013, Dutta *et al*[14] showed that individuals with the lowest 25(OH)D levels (<10 ng/mL) had the highest level of insulin resistance. Intervention trials with vitamin D in Asian Indians are fewer. In a double-blind randomized placebo controlled trial (35 in supplementation group and 36 in control group), Nagpal *et al*[29] showed that oral supplementation with cholecalciferol for 6 weeks improved insulin sensitivity and β cell function. In a longer open-label randomized prospective study, Dutta *et al*[30] showed that vitamin D supplementation in subjects with pre-diabetes led to decreased progression to diabetes and promoted reversal to normoglycemia. In a smaller (n, 36) trial in North India, vitamin D supplementation (4000 IU/day) for 6 months in vitamin D-deficient women (aged 18–35 years) with polycystic ovary syndrome did not show any significant effects on parameters of insulin sensitivity/resistance and insulin secretion despite normalization of serum 25(OH)D levels.[31]

Internationally, there have been several trials on vitamin D supplementation in individuals with pre-diabetes and diabetes. In a meta-analysis (10 randomized controlled trials) of effects of vitamin D supplementation on insulin resistance and pre-diabetes, homeostatic model assessment of insulin resistance did not show any change. However, vitamin D supplementation reduced FBG and HbA1c levels.[32] A systematic review and meta-analysis of 23 randomized controlled trials (n, 1797) showed no significant effect in change of HbA1c after vitamin D intervention as compared with placebo. However, a significant effect of vitamin D supplementation was seen on FBG in four studies with a mean baseline HbA1c ≥8%.[33] Overall, it appears that further trials are warranted with vitamin D supplementation in individuals with pre-diabetes. The

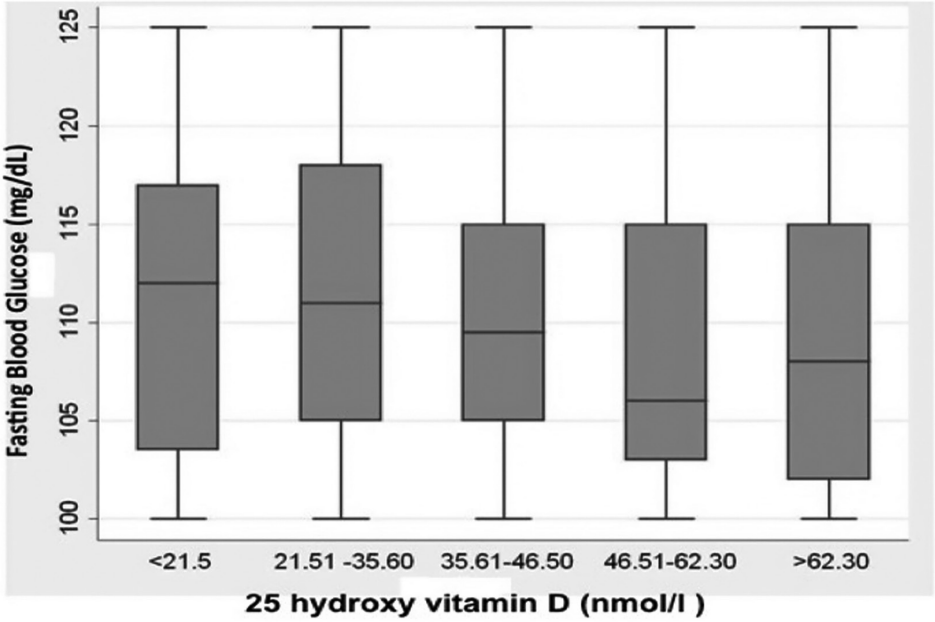

Figure 2 Box plot showing distribution of fasting blood glucose levels according to 24(OH)D quintiles.

Table 5 Summary of the major cross-sectional and longitudinal studies evaluating the relationship between vitamin D and pre-diabetes

Author	Study	Type of population	Number and type of subjects	Remarks
Kwon and Lim[34]	Cross-sectional	South Korean	60 subjects with pre-diabetes, aged 20–65 years	Subjects with pre-diabetes were more likely to have low serum 25(OH)D levels.
Karras *et al*[35]	Case–control	Greek	144 individuals with pre-diabetes and 81 healthy age-matched control subjects, aged >65 years	Vitamin D deficiency with high parathyroid hormone levels was significantly associated with glycemic dysregulation in patients with pre-diabetes.
Zagami *et al*[36]	Cross-sectional	Italians	286 subjects including those with pre-diabetes (n, 83)	Subjects with pre-diabetes had significantly reduced 25(OH)D levels.
Ekbom and Marcus[37]	Cross-sectional	Swedish	202 obese children, aged 4.5–17.9 years	Low serum 25(OH)D levels were strongly associated with higher risk of impaired fasting glucose.
Abbasi *et al*[25]	Cross-sectional	North Americans	488 non-diabetic subjects including individuals with pre-diabetes	Subjects with pre-diabetes and low circulating 25(OH)D concentrations were the most insulin resistant and had impaired β cell function.
Deleskog *et al*[27]	Longitudinal case–control study	Swedish	Normal glucose tolerance at baseline and progressed to either pre-diabetes (304 women, 428 men) or type 2 diabetes (47 women, 87 men)	High serum 25(OH)D concentrations predicted a reduced risk of T2DM in individuals with pre-diabetes, but not in those with normal glucose tolerance.
Gupta *et al*[26]	National Health and Nutrition Examination Survey, 2001–2006	North American Caucasians	Pre-diabetic and prehypertensive subjects (men, n, 898 and women, n, 813)	Individuals with low 25(OH)D levels had elevated the risk for pre-diabetes.
Dutta *et al*[14]	Cross-sectional	Asian Indians residing in India (West)	157 individuals with pre-diabetes	Vitamin D deficiency/insufficiency was associated with worsened insulin resistance in individuals with pre-diabetes.
Banerjee *et al*[15]	Cross-sectional	Asian Indians residing in India (West)	73 individuals with pre-diabetes, 77 individuals with T2DM and 52 healthy control subjects.	Serum 25(OH)D in subjects with pre-diabetes and T2DM was found to be inversely correlated with the serum levels of insulin.

T2DM, type 2 diabetes mellitus.

relationship of FBG with vitamin D deficiency necessitates further research (case–control studies including individuals with normoglycemia, cross-sectional and prospective cohort studies) in Asian Indians.

CONCLUSION

This study shows that low serum 25(OH)D levels are associated with higher blood glucose values in Asian Indian women with pre-diabetes.

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Contributors AM conceived the study and contributed to the discussion and reviewed the manuscript. SPB conducted the study and wrote the manuscript. SPB, SG and NS performed laboratory analysis of samples. RMP analyzed and interpreted the data. AM is the guarantor for this manuscript.

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REFERENCES

1. Akhtar S, Sofi NY, Jain M. Vitamin D status in South Asian populations - risks and opportunities. *Crit Rev Food Sci Nutr* 2016;56:1925–40.
2. Bhatt SP, Misra A, Sharma M, *et al*. Vitamin D insufficiency is associated with abdominal obesity in urban Asian Indians without diabetes in North India. *Diabetes Technol Ther* 2014;16:392–7.
3. Nigam P, Nigam P, Misra A, *et al*. Severe vitamin D deficiency in patients with type 2 diabetes in north India. *Diabetes Manag* 2011;1: :477–83.
4. Sofi NY, Jain M, Kapil U, *et al*. Status of serum vitamin D and calcium levels in women of reproductive age in national capital territory of India. *Indian J Endocrinol Metab* 2017;21:731–3.
5. Harinarayan CV. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. *Osteoporos Int* 2005;16:397–402.
6. Harinarayan CV, Sachan A, Reddy PA, *et al*. Vitamin D status and bone mineral density in women of reproductive and postmenopausal age groups: a cross-sectional study from south India. *J Assoc Physicians India* 2011;59: :698–704.
7. Shrivastava U, Misra A, Mohan V, *et al*. Obesity, diabetes and cardiovascular diseases in India: public health challenges. *Curr Diabetes Rev* 2017;13:65–80.
8. Anjana RM, Deepa M, Pradeepa R, *et al*. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol* 2017;5): :585–96.
9. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. *Lancet Diabetes Endocrinol* 2015;3:1004–16.
10. Misra R, Misra A, Kamalamma N, *et al*. Difference in prevalence of diabetes, obesity, metabolic syndrome and associated cardiovascular risk factors in a rural area of Tamil Nadu and an urban area of Delhi. *Int J Diabetes Dev Ctries* 2011;31:82–90.
11. Mitri J, Pittas AG. Vitamin D and diabetes. *Endocrinol Metab Clin North Am* 2014;43:205–32.
12. Pittas AG, Dawson-Hughes B, Li T, *et al*. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006;29:650–6.
13. Modi KD, Ahmed MI, Chandwani R, *et al*. Prevalence of vitamin D deficiency across the spectrum of glucose intolerance. *J Diabetes Metab Disord* 2015;14:54.
14. Dutta D, Maisnam I, Shrivastava A, *et al*. Serum vitamin-D predicts insulin resistance in individuals with prediabetes. *Indian J Med Res* 2013;138:853–60.
15. Banerjee A, Khemka VK, Roy D, *et al*. Role of serum adiponectin and vitamin D in prediabetes and diabetes mellitus. *Can J Diabetes* 2017;41:259–65.
16. Bajaj S, Nigam P, Luthra A, *et al*. A case-control study on insulin resistance, metabolic co-variates & prediction score in non-alcoholic fatty liver disease. *Indian J Med Res* 2009;129:285–92.
17. Meyer M. LIASION 25 hydroxy vitamin D Total premarket notification. Available at https://www.accessdata.fda.gov/cdrh_docs/pdf11/K112725.pdf (accessed October, 2017).
18. Misra A, Chowbey P, Makkar BM, *et al*. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *J Assoc Physicians India* 2009;57: :163–70.
19. Association. AD. Standards of medical care in diabetes. *Diabetes Care* 2017;40:S11–24.
20. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
21. Bourlon PM, Billaudel B, Faure-Dussert A. Influence of vitamin D3 deficiency and 1,25 dihydroxyvitamin D3 on de novo insulin biosynthesis in the islets of the rat endocrine pancreas. *J Endocrinol* 1999;160:87–95.
22. Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. *Endocrinology* 1986;119:84–90.
23. Johnson JA, Grande JP, Roche PC, *et al*. Immunohistochemical localization of the 1,25(OH)2D3 receptor and calbindin D28k in human and rat pancreas. *Am J Physiol* 1994;267:E356–E360.
24. Bland R, Markovic D, Hills CE, *et al*. Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in pancreatic islets. *J Steroid Biochem Mol Biol* 2004;89-90:121–5.
25. Abbasi F, Blasey C, Feldman D, *et al*. Low circulating 25-hydroxyvitamin D concentrations are associated with defects in insulin action and insulin secretion in persons with prediabetes. *J Nutr* 2015;145:714–9.
26. Gupta AK, Brashear MM, Johnson WD. Prediabetes and prehypertension in healthy adults are associated with low vitamin D levels. *Diabetes Care* 2011;34:658–60.
27. Deleskog A, Hilding A, Brismar K, *et al*. Low serum 25-hydroxyvitamin D level predicts progression to type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. *Diabetologia* 2012;55:1668–78.
28. Parekh D, Sarathi V, Shivane VK, *et al*. Pilot study to evaluate the effect of short-term improvement in vitamin D status on glucose tolerance in patients with type 2 diabetes mellitus. *Endocr Pract* 2010;16:600–8.
29. Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. *Diabet Med* 2009;26): :19–27.
30. Dutta D, Mondal SA, Choudhuri S, *et al*. Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: an open label randomized prospective study from Eastern India. *Diabetes Res Clin Pract* 2014;103:e18–e23.
31. Garg G, Kachhawa G, Ramot R, *et al*. Effect of vitamin D supplementation on insulin kinetics and cardiovascular risk factors in polycystic ovarian syndrome: a pilot study. *Endocr Connect* 2015;4:108–16.
32. Poolsup N, Suksomboon N, Plordplong N. Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis. *Diabet Med* 2016;33): :290–9.
33. Krul-Poel YH, Ter Wee MM, Lips P, *et al*. Management of endocrine disease: The effect of vitamin D supplementation on glycaemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Eur J Endocrinol* 2017;176:R1–R14.
34. Kwon HN, Lim H. Relationship between serum vitamin D status and metabolic risk factors among korean adults with prediabetes. *PLoS One* 2016;11:e0165324.
35. Karras SN, Anagnostis P, Antonopoulou V, *et al*. The combined effect of vitamin D and parathyroid hormone concentrations on glucose homeostasis in older patients with prediabetes: A cross-sectional study. *Diab Vasc Dis Res* 2018;15:150–3.
36. Zagami RM, Di Pino A, Urbano F, *et al*. Low circulating vitamin D levels are associated with increased arterial stiffness in prediabetic subjects identified according to HbA1c. *Atherosclerosis* 2015;243:395–401.
37. Ekbom K, Marcus C. Vitamin D deficiency is associated with prediabetes in obese Swedish children. *Acta Paediatr* 2016;105:1192–7.