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CORRELATION OF VITAMIN D DEFICIENCY AND TYPE- 2 DIABETES IN HIGH-RISK INDIAN POPULATION-A PROSPECTIVE STUDY AT TERTIARY CARE HOSPITAL FROM CENTRAL INDIA

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ABSTRACT

Type 2 diabetes is a major public health problem, accounting for significant premature mortality and morbidity. Over the last 5 years, a number of large observational studies have suggested an association between the onset of type 2 diabetes and Vitamin D deficiency. Vitamin D has important effects on insulin action and may impact on a number of pathways which may be of importance in the development of type 2 diabetes. Present study has been done to find out role of Vitamin D deficiency in the pathogenesis of type 2 diabetes and suggests areas for further research to determine whether Vitamin D replacement has a role in the prevention of type 2 diabetes. We evaluated the fact that 25(OH)D deficiency is associated with the high incidence of Type2-DM We recruited 540 non-diabetic Indian subjects [mean ± SD age: 48.90± 10] based on the presence of one or more risk factors for Type2-DM including obesity, hypertension, dyslipidemia and/or family history of Type2-DM. We measured anthropometric and biochemical indicators, HOMA2-IR and insulinogenic index (IGI; calculated as change in insulin at 30 min/change in glucose at 30 min) from a 75-g oral-glucose-tolerance test. Of the participants, 10.8% had a serum 25(OH)D deficiency (<10 ng/mL), 50.98.% had an insufficiency (10.0–19.9 ng/mL), and 37.90 0% had a sufficiency (≥20 ng/mL) and the incidence of Type2-DM declined accordingly: 15.7%, 10.00%, and 5.38% respectively (P < 0.001). After adjustment for age, sex, blood pressure, lifestyles, family history and high-sensitivity C-reactive protein, the participants with 25(OH)D deficiency had an increased risk of Type2-DM independently of BMI, HOMA2-I and IGI; the HRs were 2.06 (95% CI: 1.22, 3.49) for 25(OH)D 10–19.9 ng/mL compared with ≥20 ng/mL and 3.23 (95% CI: 1.66, 6.30) for 25(OH)D <10 ng/mL compared with ≥20 ng/mL. The present prospective study suggests that vitamin D metabolism may play a role in Type2-DM pathogenesis independently of known risk factors.

KEYWORDS:

INRTODUCTION

Cross-sectional studies have shown that 25-hydroxyvitamin D [25(OH)D]1,2,5 concentration, a commonly used marker for vitamin D status, is lower in individuals with type 2 diabetes (T2D) and impaired glucose tolerance than in those with normal glucose tolerance2,3.4 Prospective studies have shown a significant association between baseline serum 25(OH)D and type2-DM.[3,11] In some studies, the association persisted after adjustment for T2D risk factors such as obesity, fasting glucose and hypertension.[6,7,8,9,10] Prevention or at least delay in onset of type 2 diabetes is possible by intensive lifestyle intervention. This is costly and labour intensive and alternative methods of preventing diabetes have been sought. Vitamin D has important physiological effects aside from its effects on bone metabolism including an important role in glucose homeostasis, insulin release and response. Observational data strongly support the role of vitamin D deficiency in the pathogenesis of type 2 diabetes. The time is ripe for a well conducted randomised controlled trial of vitamin D in high risk individuals to test the hypothesis that vitamin D delays the onset of type 2 diabetes The mechanisms whereby low 25(OH)D concentrations increase Type2-DM risk are not well understood. Cross-sectional studies have reported associations of 25(OH)D with insulin resistance[12,13] and β cell function[14,15], whereas others have not found an association.[17,18] The aforementioned prospective studies did not adjust for specific glycemic measures of insulin secretion or insulin sensitivity. A few

prospective studies to date have shown an association between baseline 25(OH)D and future insulin resistance as measured on the basis of the HOMA-IR[4,11,18] and fasting insulin concentration.[4,16] A most recent study by Kayaniyil1 etal, Insulinogenic index (IGI) adjusted for insulin resistance found that higher baseline 25(OH)D predicted better β cell function and decreased progression to Type2-DM; however, this association was not significant after adjustment for BMI. Thus, the influence of vitamin D on diabetes risk after the effects of insulin secretion, insulin sensitivity, and overall adiposity are accounted for is not clearly understood.

Few studies have examined the association in high-risk populations, in whom preventive interventions are most likely to be targeted.[7,18] Asian populations are of special interest because vitamin D deficiency is common and the diabetes burden is increasing.[19,20] In this prospective study, we aimed to investigate the association between 25(OH)D status and Type2-DM incidence, independent of obesity and specific baseline measures of insulin resistance and β cell function in 540 non-diabetic Indian subjects at high risk of diabetes development.

MATERIAL AND METHOD

Study population

More than 5000 people underwent through comprehensive health check up in 2017. Of them, we consecutively included 540 (both men and women aged 30–69 year) who had cardiometabolic risk factors and gave their informed consent for the biomarkers on Glucose Metabolism and Cardiovascular Risk study. The goal of the Biomarkers on Glucose Metabolism and Cardiovascular Risk Study was to investigate associations between biomarkers and incidence rates of T2D in subjects at high risk of Type2-DM.

After 128 participants with Type2-DM diagnosed on the basis of glycated hemoglobin (Hb A_{1c}) ≥6.5% were excluded, nondiabetic participants with one or more risk factors for diabetes—including overweight [defined as a BMI (in kg/m^2) ≥ 25; 55.0% of all recruited participants], hypertension [defined on the basis of the Joint National Committee 7th report.[18,20] as ≥140 (systolic blood pressure)/90 (diastolic blood pressure) mm Hg or the use of antihypertensive medications; 18.9% of all recruited participants], dyslipidemia [defined by high triglycerides (>150 mg/dL) or low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women) or lipid-lowering-medication use; 21.1% of all recruited participants], a family history of diabetes (7 % of all recruited participants), and/or prediabetes (defined as Hb A_{1c} ranging from 5.7 to 6.4%; 2.1% of all recruited participants)—were included. At baseline and follow-up, we used Hb A_{1c} instead of fasting plasma glucose or postprandial 2-h glucose to diagnosis diabetes, because the variability of Hb A_{1c} is less than that of fasting plasma glucose or 2-h plasma glucose.[21,22]

In this cohort, 14% of participants were taking antihypertensive medications: 90 (8.%) were taking calcium channel blockers, 29 (5.4%) angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 15 (2.98%) β-blockers, 13 (2.6%) diuretics, and 3(0.6%) other drugs. For lipid control, 10.8% of participants were taking lipid-lowering medications: 90 (9.2%) were taking statins, 9 (1.98%) fibrates, 3 (0.3%) niacin, 4 (0.4%) omega-3 (n-3) fatty acids and 2 (0.2%) other medications. Totals of 4.9% and 0.7% of participants were taking more than one antihypertensive medication (n = 53) or lipid-lowering medication (n = 8), respectively; 8.4% of participants (n = 91) were taking both antihypertensive and lipid-lowering medications.

In addition, 80 participants were excluded because they were taking vitamin D supplements. Finally, 540 participants were enrolled at baseline. Participants were assessed at 6-month intervals for up to 3 year (from Apr 2017 to March 2020) to collect data on development of Type2-DM including fasting plasma glucose, Hb A_{1C} and lipid concentrations. Use of vitamin D supplements was also checked at every 6-month.

The primary endpoint was the development of Type2-DM, which was defined as Hb A_{1c} ≥6.5% based on one of diagnosis criteria for diabetes[22] and symptoms including extreme thirst, increased hunger, frequent urination, unexplained weight loss and fatigue with sudden onset.

25(OH)D Concentration as a primary exposure

To assess vitamin D status[23], serum 25(OH)D was measured by using Diels-Alder derivatization and ultraperformance liquid chromatography–tandem mass spectrometry (Waters)—a gold standard for evaluating 25(OH)D concentration[24] Total 25(OH)D was summed from $25(OH)D_2$ and $25(OH)D_3$. Calibration with standard reference material 972 from the National Institute of Standards and Technology was done and the intraassay and interassay CVs were 4.0% and 7.7% at 29.0 ng/mL, respectively. We also recorded dates of 25(OH)D measurement and categorized them into 4 seasons: spring (March≈May), summer (June≈August), fall (September≈November), and winter (December ≈February). In the current study, 20 ng/mL 25(OH)D was used as a cutoff for vitamin D sufficiency according to the recommendation from the WHO and more recently the Institute of Medicine.[25,26]

Confounding clinical and biochemical exposure

Height, body weight, waist circumference and BMI were measured by using standard methods. Blood pressure measurements were made after participants were seated for 20 minute. Measurements were done twice, with a 10 minutes rest period between measurements and the mean value of measurements was used.

Smoking status was divided into 3 categories: current smokers (if the subjects smoked currently for ≥1 y),

nonsmokers (if the subjects never smoked), and ex-smokers (if the subjects had quit). Alcohol intake was assessed by questioning patients about how often they usually drank beer, whisky,rum or wine during the most recent 12 month and quantified according to the following categories: *1*) almost every day, *2*) 3–4 d/wk, *3*) once or twice a week, *4*) once or twice a month, or *5*) never in the past year. Patients were also asked how much they usually drank on a drinking day (reported in mL). Alcohol intake (in gm alcohol/wk) was determined by multiplying the weekly intake of each alcoholic beverage by its ethanol content (beer 5%, whisky 40%, rum 45%, and wine 12%), which was categorized into 3 categories: abstinent (<20.0 g/wk), mild to moderate (20.0–199.9 g/wk) or heavy (≥200 g/wk) drinker.

Participants' involvement in leisure and sport activities (eg, walking, jogging, running, aerobics, dancing, yoga, cycling, hiking, climbing, skating, swimming, table tennis, badminton, tennis, basketball, soccer, and golf) were surveyed for physical activity, which was classified into 3 categories: none, irregular (1–2 times/wk), and regular (≥3 times/wk) exercise or used as a continuous variable. One bout of exercise was defined as exercising for ≥30 min.

In a 12-h fasting state, a 75-g oral-glucose-tolerance test (OGTT) was done at baseline. Fasting and postglucose load at 30 min and 2-h glucose and fasting and postglucose load at 30 min insulin concentrations were measured. Plasma glucose concentrations were measured with a Hitachi 747 chemistry analyzer, and plasma insulin concentrations were measured by radioimmunoassay (Linco). The fasting concentrations of triglycerides and HDL were measured by using the Hitachi 747 chemistry analyzer. High-sensitivity C-reactive protein (hsCRP) concentrations were measured by immunonephelometry (Dade Behring). Circulating concentrations of intact parathyroid hormone (iPTH) were measured by using an electrochemiluminescence immunoassay on the Modular Analytics E170 platform (Roche).

Mediating physiologic exposure

To evaluate insulin resistance, HOMA2-IR was calculated from fasting glucose and insulin concentrations as reported previously.[27] Pancreatic β cell function was evaluated by taking the IGI, which was calculated by the ratio of 30-min insulin minus fasting insulin to 30-min glucose minus fasting glucose (Δinsulin30/Δglucose30)[28,29] and has been validated against the gold standard measures of insulin secretion (first-phase insulin secretion on intravenous glucose tolerance testing).[29]

Statistical analysis

All data are presented as means ± SDs and were analyzed by using SPSS Windows version 17.0 (SPSS Inc). Triglyceride and hsCRP concentrations were normalized by logarithmic transformation. The differences in continuous variables between 25(OH)D classifications were tested by using ANOVA followed by Tukey's multiple-comparison test. Categorical variables were compared by the linear-by-linear association analysis. Correlations between variables were analyzed by using Pearson correlation. The HRs of 25(OH)D on Type2-DM risk were determined by using the Cox proportional hazard models, with Type2-DM incidence as the dependent variable. The following variables were included as independent variables in model 1: age, sex, systolic blood pressure, physical activity, family history of Typ2-DM, smoking status, alcohol consumption, antihypertensive medication use, lipid-lowering-medication use, season at 25(OH)D measurement, Hb A_{1c}, log-transformed triglycerides, HDL cholesterol, iPTH, and log-transformed hsCRP. In model 2, BMI was additionally adjusted for. In model 3, HOMA2-IR and IGI were additionally adjusted to the model 2. Significance was defined as 2-sided $P < 0.05$.

RESULT

Comparison of variables at baseline according to 25(OH)D categories

The current study participants were aged 49.5 ± 11.4 year including 46.2% % men and 53.80 women. The concentration of 25(OH)D was 19.6 ± 9.3 ng/mL. The 25(OH)D concentrations measured in winter were similar to those measured in other seasons: 19.1 ± 8.4 ng/mL in winter, 19.4 ± 9.1 ng/mL in spring, 20.0 ± 9.9 ng/mL in summer and 20.1 ± 9.9 ng/mL in fall.

In Table-1, the clinical characteristics and biochemical variables are compared according to 25(OH)D categories: ≥20.0 ng/mL (50 nmol/L; sufficient) compared with 10.0–19.9 ng/mL (25≈50 nmol/L; insufficient) compared with <10.0 ng/mL (25 nmol/L; deficient). These cutoff values were suggested by the WHO and Institute of Medicine.[25,26] No significant differences in Hb A_{1c} and fasting glucose and insulin concentrations obtained during the OGTT were found between the 3 groups. Postglucose load 30-min insulin concentrations were higher in participants with 25(OH)D sufficiency than in those with 25(OH)D insufficiency or deficiency. The participants in the 25(OH)D sufficient group had a higher IGI and a lower HOMA2-IR than did those in the 25(OH)D-insufficient or -deficient groups.

Table 1: Comparison of anthropometric and biochemical variables according to sufficient, insufficient, or deficient 25(OH)D concentrations.[1]

	25(OH)D status		
	Sufficient (*n* = 205)	**Insufficient (*n* = 279)**	**Deficient (*n* = 56)**
25(OH)D (ng/mL)	29.2 ± 7.9[2]	14.9 ± 2.7	8.2 ± 1.3
Age (y)	49.5 ± 10.9	49.5 ± 11.5	49.2 ± 13.0
Men (%)[3]	56.6	43.3	23.0
BMI (kg/m^2)	25.0 ± 3.4	25.3 ± 3.5	25.0 ± 3.7
Waist circumference (cm)	88.1 ± 9.3	88.5 ± 9.5	88.8 ± 9.8
SBP (mm Hg)	127.2 ± 14.1	128.0 ± 15.5	128.8 ± 16.8
DBP (mm Hg)	78.7 ± 10.5	78.7 ± 11.2	78.4 ± 12.5
Calcium (mg/dL)	9.1 ± 0.6	9.1 ± 0.5	9.0 ± 0.5
Fasting glucose (mg/dL)	104.8 ± 15.3	105.0 ± 15.3	105.9 ± 16.2
Postload 30-min glucose (mg/dL)	208.5 ± 57.8	214.1 ± 49.3	242.7 ± 70.1
Postload 2-h glucose (mg/dL)	149.1 ± 26.5	152.1 ± 28.2	152.2 ± 28.7
Fasting insulin (μIU/mL)	9.8 ± 3.6	10.6 ± 4.6	11.2 ± 4.6
Postload 30-min insulin (μIU/mL)	37.4 ± 14.0*,†	32.4 ± 15.1	30.3 ± 15.2
Hb A_{1c} (%)	5.8 ± 0.4	5.8 ± 0.4	5.9 ± 0.4
Insulinogenic index[4]	0.29 ± 0.18*,†	0.26 ± 0.20†	0.20 ± 0.15
HOMA2-IR[5]	1.3 ± 0.5*,†	1.4 ± 0.6†	1.5 ± 0.6
Triglycerides (mg/dL)[5]	154.8 ± 105.1	148.3 ± 104.2	146.4 ± 96.5
HDL cholesterol (mg/dL)	55.6 ± 13.3	55.3 ± 13.9	54.3 ± 12.6
hsCRP (mg/dL)[5]	0.19 ± 0.85*,†	0.46 ± 1.16	0.52 ± 1.42
iPTH (pg/mL)	28.7 ± 13.6*,†	35.4 ± 14.2†	44.2 ± 25.0
Physical activity (bouts/wk)	3.6 ± 1.9*,†	2.6 ± 2.1	1.9 ± 1.5
Family history of diabetes (%)[3]	27.8	28.2	25.7
Current smoker (%)[3]	13.4	14.9	14.2
Heavy drinker (%)[3]	9.5	12.6	9.7
Regular exercise (%)[3]	25.1	19.4	18.6

Sufficient, insufficient, and deficient 25(OH)D concentrations were defined as ≥20.0, 10–19.9, and <10 ng/mL, respectively. *Significantly different from insufficient, $P < 0.05$ (ANOVA followed by Tukey's multiple-comparison test). †Significantly different from deficient, $P < 0.05$ (ANOVA followed by Tukey's multiple-comparison test). DBP, diastolic blood pressure; Hb A_{1c}, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; SBP, systolic blood pressure; 25(OH)D, 25-hydroxyvitamin D. Mean ± SD (all such values).

Comparison between 25(OH)D groups was performed by linear-by-linear association.
Calculated as change in insulin at 30 min/change in glucose at 30 min.
Log-transformed values were used for comparison.
The correlation analysis showed that the serum 25(OH)D concentration correlated negatively with fasting and postload 30-min insulin concentrations, HOMA2-IR, iPTH, and hsCRP and positively with serum calcium and IGI (all $P < 0.05$) (*see* Supplementary Table 1 under "Supplemental data" in the online issue).

Primary outcome: incidence of Type2-DM

Of the 540 participants, 49 (9.0%) developed Type2-DM over 32.3 ± 15.6 month of observation. The incidence rates of Type2-DM defined as Hb $A_{1c} \geq 6.5\%$, were 15.9%, 10.2%, and 5.4% in the 25(OH)D-deficient, -insufficient, and -sufficient groups, respectively ($P < 0.01$). Kaplan-Meier analysis showed a higher probability of developing Type2-DM in participants in the 25(OH)D-deficient group than in those in the 25(OH)D-insufficient or 25(OH)D-sufficient group ($P < 0.01$).

Kaplan-Meier plot for incident type 2 diabetes according to 25(OH)D status: <10, 10–19.9, and ≥20.0 ng/mL. 25(OH)D, 25-hydroxyvitamin D.Using the Cox proportional hazard model, we further investigated the independent role of 25(OH)D concentration in Type2-DM development during the 5-year follow-up period (Table-2 No subject died before Type2-DM development. In model 1, participants with 25(OH)D insufficiency and deficiency had a higher incidence of Type2-DM than did those with 25(OH)D sufficiency: the HRs were 1.85 and 3.40, respectively. In model 2, in which BMI was additionally adjusted for, the significant associations between 25(OH)D concentration and incidence of Type2-DM were maintained: HRs for the 25(OH)D-insufficient and -deficient groups were 1.81 and 3.42, respectively. When waist circumference was adjusted instead of BMI because waist circumference is known to better reflect visceral obesity, the significant associations between 25(OH)D concentration and incidence of Type2-DM, the association between

25(OH)D concentration and incidence of Type2-DM independently of these 2 important risk factors for Type2-DM. In model 3, we further adjusted for HOMA2-IR and IGI and found that there was the strongest significant predictor for incidence of Type2-DM. Current smoking status, high BMI, HOMA2-IR, and IGI were also significantly associated with the incidence of Type2-DM (*P* = 0.001–0.033).

Table 2: Independent Role Of 25(Oh)D For Incidence Of Type2-Dm.[1]

	25(OH)D groups			
Model	**Sufficient(*n* = 205)**	**Insufficient(*n* = 279)**	**Deficient(*n* = 56)**	***P***
Model 1: MV	1.00	1.84 (1.11, 3.05)	3.22 (1.66, 6.26)	0.0012
Model 2: MV + BMI	1.00	1.80 (1.08, 2.99)	3.25 (1.67, 6.31)	0.002
Model 3: MV + BMI + HOMA2-IR + IGI	1.00	2.06 (1.22, 3.49)	3.23 (1.66, 6.30)	0.002

All values are RRs (95% CIs). A Cox proportional hazards model was used for incidence of type 2 diabetes after adjustment for age, sex, systolic blood pressure, physical activity, family history of type 2 diabetes, smoking status, alcohol consumption, antihypertensive medication use, lipid-lowering medication use, season at 25(OH)D measurement, glycated hemoglobin, log-transformed triglycerides, HDL cholesterol, intact parathyroid hormone, and log-transformed high-sensitivity C-reactive protein. Sufficient, insufficient, and deficient 25(OH)D concentrations were defined as ≥20.0, 10–19.9, and <10 ng/mL, respectively. IGI, insulinogenic index; MV, multivariate; 25(OH)D, 25-hydroxyvitamin D.

Calculated as change in insulin at 30 min/change in glucose at 30 min.

The 75-g OGTT result at baseline revealed 48.7% and 20.5% of participants in this study were classified as IFG (fasting glucose concentration = 100–125 mg/dL) and IGT (postload 2-h glucose concentration = 140–199 mg/dL), respectively. When the interaction term IFG/IGT × 25(OH)D category was included in the final Cox proportional hazards model, this interaction term had no statistically significant role in the development of Type2-DM. When hazard models were performed separately in men and women, the HRs were slightly increased except in men in the 25(OH)D insufficient group.

When 25(OH)D ≥30.0 ng/mL (75 nmol/L), 15.0–29.9 ng/mL (37.5≈75 nmol/L), and <15.0 ng/mL (37.5 nmol/L) were used for vitamin D sufficiency, insufficiency, and deficiency, respectively, on the basis of previous studies[30,31], the HRs for the 25(OH)D-insufficient and -deficient groups compared with the 25(OH)D-sufficient group were 2.17 and 3.02, respectively.

When quartiles of 25(OH)D concentrations were used instead of current 25(OH)D categories, a similar but attenuated trend was found between 25(OH)D status and incidence of Type2-DM (HR of lowest quartile compared with highest quartile: 2.41; 95% CI: 1.21, 5.75). The fact that the highest-quartile 25(OH)D group (24.5–60.4 ng/mL) overlapped with our defined 25(OH)D-insufficient group may explain the slightly attenuated findings. When 28 participants who had taken vitamin D supplements for >3 month during the follow-up period were excluded in the hazard models, similar results were obtained.

DISCUSSION

In this study of an indian population at high risk of Type2-DM, we found that the participants with 25(OH)D deficiency had an incidence of Type2-DM development 3.4 times that in those with sufficient levels, even after adjustment for obesity, dynamic measure of insulin resistance and pancreatic β cell function and other known risk factors for Type2-DM.

Vitamin D is a multifunctional hormone that can affect many essential biological functions, ranging from immune regulation to mineral ion metabolism. Although the major function of vitamin D is to maintain calcium and phosphate homeostasis and to promote bone mineralization, many extraskeletal roles for vitamin D have been identified.[1,32] We recently found that vitamin D inadequacy is associated with significant coronary artery stenosis in a community-based elderly cohort.[1,2,3,4,33] Other investigators have shown that low vitamin D status is associated with an increased risk of various disease, such as cancer, hypertension and cardiovascular disease[1,32] Many longitudinal studies.[3,4,11,12,18] have shown significant correlation between vitamin D3 deficiency and high incidence of Type2-DM These studies have found that BMI is the key confounding factor because obesity is correlated with low vitamin D and high Type2-DM risk[1,2,6,7,10] In our study, obesity was accounted for explicitly by adjusting for BMI or waist circumference in the regression models which did not attenuate the association between vitamin D and Type2-DM risk. Most recently, a meta-analysis provided evidence of a strong association between circulating 25(OH)D concentrations and risk of incident Type2-DM[5,7,16,17,18] This association remained in a new analysis of the European Prospective Investigation into Cancer and Nutrition–Norfolk study after adjustment for relevant confounding factors.[4,6,9,14,15]

Of note, the previous studies that investigated the association between vitamin D and Type2-DM did not

adjust for dynamic baseline glycemic measures of insulin secretory function or insulin sensitivity[3,4,11,12,13] In contrast, our study highlights the influence of 25(OH)D concentration on Type2-DM incidence, independent of baseline measures of insulin secretion and sensitivity—potential risk factor for Type2-DM -development. We examined the independent contribution of 25(OH)D concentration to Type2-DM risk after adjusting for HOMA2-IR, IGI and obesity. These data suggest that 25(OH)D is an independent predictor of Type2-DM risk beyond BMI, body weight and specific measures of insulin resistance and β cell function—measures for which abnormalities may predispose to Type2-DM.

There is ample evidence in vitro and in vivo studies showing that vitamin D activity is essential for pancreatic β cell function.[34,35,36] In our study, the circulating concentration of 25(OH)D was positively associated with IGI which reflects acute phase insulin secretion; however, the correlation was weak (r = 0.077, $P <$ 0.05). Insulin resistance has also been reported to be associated with vitamin D insufficiency[4,12,37] Vitamin D may have a direct effect on insulin sensitivity through stimulation of insulin receptor expression.[38] The 25(OH)D concentration in this study was negatively correlated with HOMA2-IR but the correlation between these 2 was also modest (r = −0.107, $P <$ 0.05). Thus, although vitamin D may be involved in pancreatic β cell function and insulin sensitivity, the association with IR or β cell function cannot fully explain how vitamin D affects the development of Type2D.

Several putative mechanisms whereby vitamin D status influences Type2-DM risk can be postulated.[30,31,32,37.38] A modest but significant correlation between 25(OH)D and serum calcium concentrations was shown in our study. Recent in vivo and in vitro studies reported that *VDR* gene suppression resulted in a decrease in intracellular Ca^{2+} concentrations.[39,40,41] and 1,25-dihydroxyvitamin D_3 and calcium regulated transcription of calcium transporter genes. Thus, vitamin D deficiency might be associated with T2D development by calcium balance, which is essential for insulin secretion in pancreatic β cells.[37]

The concentration of 25(OH)D was negatively correlated with hsCRP in the current study. A study in humans showed that the serum 25(OH)D status was inversely related to the tumor necrosis factor-α concentration.[42] Another experimental study suggested that a low 25(OH)D concentration influences the activity or expression of macrophages and lymphocytes.[42,43] These data suggest a close link between 25(OH)D concentration and inflammatory process and could suggest a potential mechanism by which vitamin D may be involved in Type2-DM development.

In the current study, we used 20 ng/mL 25(OH)D as a cutoff for vitamin D sufficiency because the WHO and, more recently, the Institute of Medicine have suggested the use of 20 ng/mL as an adequate cutoff value[25,26,42] Recent studies have adopted this value more[43,44] Indeed, a recent study found that 20 ng/mL 25(OH)D was associated with an increased risk of relevant clinical diseases, including hip fracture, myocardial infarction and death.[45,46,47]

This study had several strengths. First, we assessed IGI, a dynamic estimate of first-phase insulin secretion, which has been validated from healthy subjects to diverse phenotypes Second, the serum 25(OH)D concentration was measured by ultraperformance liquid chromatography–tandem mass spectrometry. Third, the iPTH concentration, which is important but not commonly measured, was adjusted. Inadequate vitamin D usually leads to increased iPTH which in turn is inversely associated with insulin sensitivity.[46,47,48] Last, this study was performed in high-risk subjects of Asian ethnicity. Most previous studies were done in healthy subjects[6,8,11], and the study subjects consisted of predominantly white populations. Indeed, vitamin D insufficiency was 62% (85% when 30 ng/mL was used as the cutoff) in the current study, similar to that in other Asian countries, which indicated that up to 70% of the general population had vitamin D insufficiency, defined as 30 ng/mL 25(OH)D[19]This may represent a public health problem, considering the numerous complications and diseases associated with vitamin D deficiency.[49,50]

Our study also had limitations. Although a sophisticated function to assess β cell function, such as IGI, was used, the gold standard technique (ie, a clamp study) was not used. We had no data on β cell function or insulin resistance at follow-up. Data on sun exposure time, use of sunscreen, and dietary habits were not captured. Last, there was a possibility of unmeasured confounding underlying the association between vitamin D and diabetes, which precluded conclusions about causality.

CONCLUSION

Our study illustrate an independent association between 25(OH)D and Type2-DM incidence in the prospective study of the relation between vitamin D status, Type2-DM and dynamic glycemic traits. Evaluation of vitamin D deficiency and its potential health effects is particularly important because 25(OH)D concentrations are lower than recommended in many countries whose diabetes burden is also highly prevalent.[20,25]

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