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Assessing association of serum vitamin D levels and diabetic retinopathy in Asian Indians with type 2 diabetes

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Abstract

Assessing association of serum vitamin D levels and diabetic retinopathy
in Asian Indians with type 2 diabetes
By Beteal Ashinne

Background: Vitamin D deficiency (VDD) is a condition that has been associated with diabetic retinopathy (DR) in various populations, but has not been studied in Asian Indians.

Aim: To evaluate the association of serum 25-hydroxyvitamin D (25(OH)D) levels with presence and severity of DR among Asian Indians with type 2 diabetes.

Methods: We collected information on individuals with type 2 diabetes that received care at a tertiary diabetes centre in southern India, between 2012 and 2015. Patients were 18 years of age or older, underwent retinal examinations with DR grading, had serum 25(OH)D measurements, and were not taking vitamin D supplements. Relevant clinical and biochemical parameters were included in the assessment and VDD was diagnosed if 25(OH)D levels were <20ng/ml.

Results: Serum 25(OH)D levels were lower in patients with retinopathy compared to those without (11.9 ± 2.2ng/ml vs. 13.7 ± 2.1ng/ml, $p<0.001$). Stratifying patients by DR grade, reduced geometric means of 25(OH)D levels were associated with increased retinopathy severity: no DR (13.7 ± 2.1ng/ml), non-sight threatening DR (12.8 ± 2.1ng/ml), and sight threatening DR (11.1 ± 2.2ng/ml) ($p<0.0001$). After adjusting for six key covariates, VDD increased the odds of developing proliferative DR (OR 2.05; 95% CI 1.35-3.11; $p=0.001$).

Conclusion: In Asian Indians with type 2 diabetes, (1) lower serum 25(OH)D was associated with increased severity of DR and (2) the presence of VDD was associated with a two-fold increased risk for proliferative DR.

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Table of Contents

Introduction

Diabetic retinopathy (DR), an important microvascular complication of diabetes mellitus (DM), is a prominent cause of blindness globally and the number of afflicted are only expected to increase [1]. DR results from longstanding or poorly controlled diabetes, and improved glycemic control reduces likelihood of retinopathy onset and progression [2, 3]. According to International Diabetes Federation (IDF) estimate, the prevalence of DR in Asian Indians is 8.7% [4]. However, in population based studies the prevalence has been reported to be as high as 18% [5, 6]. Strategies to prevent complications of DM and DR are of public health importance and identification of additional key modifiable risk factors will therefore have immense value.

One target of great interest is vitamin D which is primarily known for involvement in calcium regulation. However, its role in DM and DR are becoming increasingly well-established [7-19]. Vitamin D deficiency (VDD) is defined as serum 25-hydroxyvitamin D (25(OH)D) levels <20ng/ml, and is associated with skeletal malformation and fractures [20]. Analysis from the United States of nearly 4,500 adults in the National Health and Nutrition Examination Survey (NHANES) demonstrated the overall prevalence of VDD to be 41% [21]. In India, despite its tropical location, the prevalence of VDD is 69.3%, with urban populations and women disproportionately more affected [22]. Among Asian Indians with type 2 DM (T2DM), the prevalence of VDD is reported to be 71.4% [23], but the cause-effect relationship between these entities is not fully understood.

Prior studies have reported an inverse relationship between VDD and DR [7, 9-14, 16, 17, 19], but little evidence exists in Asian Indians. A small cross-sectional study in Asians Indians demonstrated differences in plasma 25(OH)D levels between participants with diabetes and

healthy controls. However, among those with DM, no difference was noted in comparing those with DR to those who without DR [24]. The purpose of the current study was to further examine the relationship between vitamin D deficiency and diabetic retinopathy in Asian Indians.

Methods

This study analyzed the medical records of 3,226 patients from a tertiary diabetes care center in southern India. Eligible participants included all known people with T2DM above the age of 18 years from 2012 to 2015, and who had undergone a detailed retinal examination with DR grading. Additionally, each study participant had a recorded measurement of serum 25(OH)D level within 30 days of retinal evaluation. 172 individuals were excluded due to being misclassified as having T2DM and/or taking vitamin D supplementation.

Ethical approval for this study was obtained from the Madras Diabetes Research Foundation Ethics Committee, the Emory University Institutional Review Board, and the Duke University Institutional Review Board.

Clinical information of the final 3,054 individuals included age, gender, height, weight, age at onset of diabetes, duration of diabetes, diabetes management regimen (usage of oral hypoglycemic agents and/or insulin), and presence of hypertension. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Blood pressure was recorded by mercury sphygmomanometer (LED Diamond Deluxe Industrial Electronic and Products, Pune, India), Serum 25(OH)D was assessed by electrochemiluminescence immunoassay using a Roche e601Cobas immunoassay analyzer (Roche Diagnostics, Indianapolis, Indiana, USA) and the coefficient of variation was 6.38%. Glycated hemoglobin (HbA1c) was measured by high-pressure liquid chromatography via the Variant II Turbo machine (Bio-Rad Laboratories, Hercules, CA, USA) and the coefficient of variation was 1.36%. Serum creatinine (Jaffe Kinetic method), serum urea (GLDH UV kinetic method), and urine albumin levels (immunoturbidimetry assay) were

determined using Beckman AU 2700 (Fullerton, CA, US). Study participants with serum 25(OH)D recordings <20ng/ml were labeled as having VDD.

Ophthalmologists examined the fundus through dilated pupils and graded the presence and severity of DR according to a modified Early Treatment of Diabetic Retinopathy Study (ETDRS) scale [25]. DR status was categorized as no DR, mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR, or proliferative DR (PDR) [11, 26]. Hard exudates within one disc diameter of the macular center was categorized as diabetic macular edema (DME) [27]. By convention, individuals with mild to moderate NPDR were labeled as having non-sight threatening DR (NSTDR) and those with severe NPDR, PDR, and/or DME were labeled as having sight threatening DR (STDR) [28].

Statistical Analysis

Analysis of quantitative data were conducted in SAS, version 9.4 (SAS Institute, Cary, NC, USA). Two-sample *t*-test was used for comparing mean values between groups and one-way analysis of variance (ANOVA) for comparing mean values among groups. Chi square test was used to compare proportions between groups. Multivariable logistic regression analysis was conducted to examine the association of serum 25(OH)D with DR. A score test was run to determine whether an ordinal logistic regression could be used to evaluate the relationship of 25(OH)D with severity of DR as well as VDD with different DR stages. However, the score test was statistically significant ($p < 0.001$); therefore, a multinomial logistic regression was selected.

Four models examined the relationship between vitamin D deficiency and the severity of diabetic retinopathy. Model 1 examined DR as binary data classified as disease absence or presence. Model 2 examined DR severity by the modified ETDRS stages. Model 3 classified DR as categorically

non-proliferative versus proliferative. Model 4 grouped DR as sight threatening versus non-sight threatening. Multivariate analysis was conducted to control for the effects of age, gender, BMI, HbA1c, presence of albuminuria, and duration of diabetes.

Results

Of the 3,054 subjects with T2DM examined, 62% were male and the mean age was 55.3 ± 10.2 years (Table 1). Duration of T2DM was 11.8 ± 7.9 years and the mean HbA1c was 8.6 ± 2.1%. 58.0% of subjects were on insulin. Distribution of DR demonstrated 46% with DR (38.4% with NPDR, 7.6% with PDR, 6.5% with DME and 22% with STDR).

Overall, 69.4% of participants had 25(OH)D levels less than 20ng/ml. Serum 25(OH)D was lower (11.9 ± 2.2ng/ml vs. 13.7 ± 2.1ng/ml, $p < 0.001$) in people with DR than people without DR (Table 1). Men had a higher vitamin D concentration (13.2 ± 2.1ng/ml) compared to women (12.2 ± 2.2ng/ml, $p=0.006$).

In Model 1, the nominal presence of VDD was not significantly associated with presence of DR (Table 2). Models 2 and 3 explored the presence of VDD by categorical DR severity levels, demonstrating that the presence of VDD doubles the risk of PDR (OR 2.05; 95% CI 1.35-3.11; $p=0.001$). Other multivariate analyses from Models 3 and 4 did not demonstrate a significant association between VDD and the remaining DR subtypes.

Figure 1 plots the results from ANOVA comparison of serum 25(OH)D levels against STDR status. It demonstrates a statistically significant difference in the serum vitamin D in those with STDR categorizations: no DR (13.7 ± 2.1ng/ml), non-sight threatening DR (12.8 ± 2.1ng/ml), sight threatening DR (11.1 ± 2.2ng/ml), ($p < 0.001$).

Discussion

In this analysis of over 3,000 Asian Indians with type 2 diabetes, people with diabetic retinopathy had lower serum 25(OH)D concentrations than individuals without retinopathy. These findings are consistent with prior studies [7, 9-11, 13, 14, 16, 17, 19]. Our data was examined in multiple models to establish if the effect was dose-response related (serum 25(OH)D and stage of retinopathy) and explore if VDD was associated with greater risk of onset of DR and/or advancing stages of DR. A stepwise dose-response effect was not found (Model 2) except in dichotomizing NPDR and PDR (Model 3). No significant difference was noted in distinguishing sight threatening DR from non-sight threatening DR (Model 4).

Many studies examining this topic have resulted in similar conclusions, but not all data concurs. Contradiction in the published data likely derives from variations in population sampling, adjustments for covariates, and quality in the assessment of retinopathy. Nationally representative survey studies [11, 13] report an increased risk of DR in people with VDD. One study reported a dose-response relationship but could not evaluate for PDR due to a low number of subjects with PDR [18], whereas another examining type 1 DM did not find a relationship with vitamin D and DR [29]. Case-control and cross-sectional studies have fairly consistently supported a protective benefit of higher serum 25(OH)D levels [7-10, 12, 13, 15, 16, 19, 24, 30], but several are discordant [31-35]. In particular, the retinopathy outcome in the Veterans Affair Diabetes Trial (VADT) is important to consider given the prospective nature, large number (n=936), and robust assessment of 7-field photography at a five-year interval [32]. The analysis in this study separated 25(OH)D levels into quartiles, bounded in the lowest from 1-15.9ng/ml, and the highest ranging from 29.9-77.2ng/ml. The comparison from lowest to highest quartile did not find differences in rates of DR.

However, the margin of difference between these quartiles is quite small, and it is possible that a different outcome may have been concluded if absolute numbers were used, rather than quartiles.

The pathophysiology of VDD on DM and associated complications has been studied extensively. In animal model studies, rats with VDD were found to have decreased beta cell insulin secretion and vitamin D was shown to mediate increased insulin receptor creation in promonocytic cells [36-38]. The active metabolite of vitamin D, calcitriol, reduced retinal neovascularization in a dose-dependent fashion on a mouse model of DR [39]. Additionally, this metabolite has been shown to decrease expression of vascular endothelial growth factor in tumor cells, both *in vivo* and *in vitro* [40, 41]. Furthermore, calcitriol exhibits anti-inflammatory properties through vitamin D receptors on T cells, blocking nuclear transcription factors that promote cytokine production [42, 43].

This study is limited by the cross-sectional design, from which causation cannot be established. Grading of the retinopathy was obtained from clinical examination as written in the participant's chart, with the potential for misclassification, particularly for macular edema. Vitamin D metabolism is complex and affected by season, sun exposure, medical co-morbidities such as liver and kidney damage, and dietary intake [20]. Although this study controlled for the impact of adiposity, liver function, and exogenous vitamin D intake, it is possible other confounding variables influence the data in unanticipated ways.

The strengths of this study include a large number of participants which allowed for adjustments for potential confounding covariates and multiple models used to explore the relationships. This study contributes to the body of evidence supporting a protective role of vitamin D on diabetic retinopathy, particularly at the most advanced end of the spectrum.

Prior studies have demonstrated an inverse association between VDD and DR in various populations [7, 9-11, 13, 14, 16, 17, 19], but there is little data on Asian Indians, a population with high susceptibility to T2DM. Despite optimizing glycemic level, blood pressure control, and stabilizing serum lipid concentration, people still develop sight threatening DR and the associated visual impairment. Further studies are warranted to assess if vitamin D supplementation could be useful for prevention of development or progression of diabetic retinopathy.

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Tables and Figures

Table 1 – Characteristics of study population

Parameters	Total Sample (n= 3054)	No DR (n= 1647)	DR (n= 1407)	p value
Age (years)	55.3 ± 10.2	54.1 ± 11.0	56.7 ± 9.0	**<0.001**
Gender (% male)	61.8	56.7	67.8	**<0.001**
DM diagnosis age (years)	43.5 ± 9.5	45.6 ± 9.9	41.0 ± 8.4	**<0.001**
DM duration (years)	11.8 ± 7.9	8.4 ± 6.7	15.7 ± 7.5	**<0.001**
BMI (kg/m^2)	27.5 ± 4.7	27.7 ± 4.7	27.2 ± 4.8	**0.002**
HTN (%)	60.0	54.6	66.3	**<0.001**
VDD prevalence (%)	69.4	67.5	71.6	**0.014**
Serum 25(OH) D (ng/ml) *	12.8 ± 2.1	13.7 ± 2.1	11.9 ± 2.2	**<0.001**
Insulin usage (%)	58.0	39.9	79.9	**<0.001**
HbA1c (%)	8.6 ± 2.1	8.3 ± 2.0	9.1 ± 2.0	**<0.001**
Serum urea (mg/dl)	27.9 ± 14.9	24.4 ± 9.7	31.9 ± 18.4	**<0.001**
Serum creatinine (mg/dl)	0.9 ± 0.6	0.8 ± 0.3	1.1 ± 0.9	**<0.001**
Albuminuria (%)	62.4	24.5	53.2	**<0.001**

DM – diabetes mellitus, BMI – body mass index, HTN – hypertension, HbA1c – glycated hemoglobin.

VDD – vitamin D deficiency status for 25(OH)D levels < 20ng/ml.

Urine albumin values of ≥30 mg/dl reported as albuminuria.

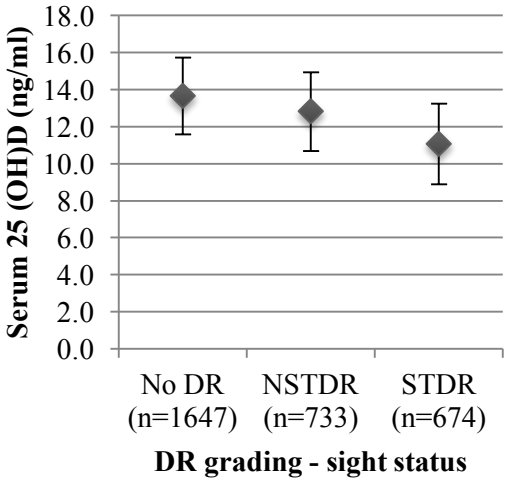
Mean ± standard deviation (sd) reported for continuous variables, with exception of those labeled (*) which are reported in geometric mean ± sd of the geometric mean. Percentages are stated for categorical variables. P value reported for comparison between those without versus with DR.

Table 2 – Logistic regression models assessing relationship between vitamin D deficiency and diabetic retinopathy presence and severity

	Multivariate		
	OR	CI	p value
Model 1			
DR	1.10	(0.91, 1.33)	0.31
Model 2			
Mild NPDR	1.14	(0.90, 1.43)	0.28
Moderate NPDR	0.77	(0.59, 1.02)	0.07
Severe NPDR	1.28	(0.90, 1.82)	0.17
PDR	2.05	(1.35, 3.11)	**0.001**
Model 3			
NPDR	1.03	(0.85, 1.25)	0.74
PDR	2.08	(1.37, 3.14)	**0.001**
Model 4			
NSTDR	1.03	(0.83, 1.27)	0.82
STDR	1.24	(0.96, 1.59)	0.10

OR - odds ratio; CI - 95% confidence interval; All four models based on a sample size of 2,909.
Multivariate models for DR status as predicted by VDD, adjusted for age, gender, DM duration, HbA1c, BMI, and albuminuria.
DR – Diabetic retinopathy presence, NPDR – Non-proliferative diabetic retinopathy, PDR – Proliferative diabetic retinopathy
NSTDR – Non-sight threatening diabetic retinopathy, STDR – Sight threatening diabetic retinopathy

Figure 1 – Serum 25(OH)D levels in non-sight threatening and sight threatening retinopathy



Geometric mean values with corresponding sd of geometric mean reported.
ANOVA comparison of 'No DR', 'NSTDR' and 'STDR' with p value <0.001.
NSTDR – Non-sight threatening diabetic retinopathy, STDR – Sight threatening diabetic retinopathy