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Research Article

INVERSE RELATION OF 25-OH VITAMIN D LEVEL WITH SEVERITY OF DIABETIC RETINOPATHY AND HBA1C IN TYPE 2 DIABETES PATIENTS: SUPPLEMENTATION MAY HALT SEVERITY

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ABSTRACT

Objective: Our aim was to analyze the relationship of 25-OH Vitamin D level with severity of diabetic retinopathy (DR) and HbA1c in Type 2 diabetes patients.

Methods: In the present observational study, we enrolled 140 cases of type 2 diabetic patients (98 with DR and 42 without DR). A complete ophthalmological evaluation was done. 25-OH vitamin D levels were compared with the severity of DR and HbA1c levels. The serum concentration of 25-hydroxyl vitamin D was measured by the radioimmunoassay method. Vitamin D deficiency was considered when the 25-hydroxyl vitamin D level was <20 ng/mL.

Results: There was no significant difference in age, sex, calcium, parathyroid hormone, and phosphate levels between groups. Sixty-nine out of 98 patients with retinopathy and 15 out of 42 without retinopathy had a 25-hydroxyl vitamin D level <20 ng/mL. DR patients have a higher proportion of subjects with vitamin D deficiency as compared to those without DR (p=0.045). We also found a significant inverse correlation between serum 25-OH vitamin D and severity of DR on ANOVA and HbA1c levels (p<0.001) on Pearson's correlation.

Conclusion: 25-OH vitamin D deficiency is associated with DR and increased HbA1c levels. Vitamin D supplementation with good blood sugar control may decrease the severity of DR in type 2 diabetes. All patients with type 2 diabetes mellitus, besides undergoing fundoscopic examinations, must be assessed for their vitamin D status.

Keywords: Diabetic retinopathy, HbA1c, 25-OH vitamin D, NPDR, PDR, PTH.

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INTRODUCTION

Diabetic retinopathy (DR) stands as a predominant cause of vision impairment among adults, particularly in the age group spanning from 20 to 74 years old [1]. The global burden of DR is projected to escalate substantially, with estimates indicating a potential rise from 126.6 million cases in 2010 to a staggering 191 million cases by the year 2030. Within India, the prevalence of DR varies between 17.6% and 28.2%, underlining its significant impact on the population [2].

Research suggests that 25-OH vitamin D plays a pivotal role in mitigating inflammation by reducing the proliferation of immune cells like lymphocytes and natural killer cells, as well as suppressing various pro-inflammatory cytokines. This underscores the potential involvement of vitamin D in the development of DR through its modulation of the immune system and angiogenic processes [3]. Furthermore, studies have demonstrated the efficacy of calcitriol, the active form of vitamin D, as a potent inhibitor of retinal neovascularization in experimental models of ischemic retinopathy in mice [4].

Despite advancements in the treatment of DR, effectively managing its progressive manifestations remains a significant challenge. Establishing a correlation between 25-OH vitamin D deficiency and the severity of DR, along with glycated hemoglobin (HbA1c) levels, could pave the way for preventive and corrective measures that could substantially improve the prognosis of DR and enhance the overall quality of life for affected individuals. While it's well established that elevated HbA1c levels and prolonged diabetes duration correlate with DR severity in type 2 diabetes, the relationship between DR severity and vitamin D levels remains relatively understudied [5].

Therefore, the current study was conceived to elucidate the connection between serum 25-OH vitamin D levels, severity of DR, and HbA1c in patients diagnosed with type 2 diabetes mellitus. By shedding light on this intricate interplay, we aim to contribute to a better understanding of the pathophysiology of DR and potentially uncover novel avenues for its management and prevention.

METHODS

Study population

A cohort of 140 diabetic individuals was meticulously assembled for this investigation, comprising 98 subjects diagnosed with DR and 42 without such ocular manifestations. Carefully selected from a pool of 643 type 2 diabetic patients attending the outpatient department of the esteemed Department of Ophthalmology at BRD Medical College in Gorakhpur, India, these participants, spanning ages 20 to 60 and encompassing both genders, were enrolled only after obtaining explicit consent. Furthermore, ethical clearance was diligently secured from the Ethical Committee at BRD Medical College. Exclusion criteria encompassed a spectrum of conditions, including type 1 diabetes, macroangiopathy, substantial proteinuria (>300 mg/24 h), pregnancy, recent acute illness, hepatic or renal dysfunction, cardiovascular maladies, lactation, oncological history, malnutrition, hyperparathyroidism or hypoparathyroidism, and individuals on pharmacotherapy known to influence 25-hydroxy vitamin D levels, such as anticonvulsants, steroids, and Rifampicin.

Ophthalmic examinations

Each participant underwent an exhaustive ocular evaluation, meticulously conducted by skilled professionals, including refraction,

tonometry, slit lamp examination, and thorough dilated fundoscopy, all preceded by obtaining informed consent. Moreover, both direct and indirect ophthalmoscopies were diligently performed. The assessment of retinopathy was meticulously executed through a combination of meticulous ophthalmoscopic examination and sophisticated fundus photography techniques. Standardized 45° field, 35-mm-colored fundus photographs were meticulously captured for each eye, meticulously centered on both the macular area and the optic disc. DR was meticulously graded in concordance with the International Clinical DR Guidelines, meticulously delineating non-proliferative and proliferative stages based on a meticulous evaluation of specific clinical features.

Biochemical parameters

On meticulous enrollment, participants were subjected to a comprehensive medical history questionnaire, meticulously followed by an array of blood tests, including HbA1c, serum creatinine, 25-hydroxy vitamin D, a complete blood count, liver function tests, parathyroid hormone (PTH), fasting and postprandial blood glucose levels, phosphate, and serum calcium levels. In addition, meticulous urine microscopy and 24-h urinary protein quantification were meticulously executed. Serum 25-hydroxy vitamin D concentrations were meticulously assayed utilizing the radioimmunoassay method, with vitamin D deficiency meticulously defined as levels below 20 ng/mL [6].

Statistical considerations

Continuous variables were meticulously expressed as mean±standard deviation. Between-group comparisons were meticulously carried out using the Chi-square test or independent t-test as deemed appropriate. The ANOVA meticulously served to facilitate comparisons among multiple groups, while Pearson's correlation analysis meticulously enabled the assessment of relationships between variables. All statistical analyses were meticulously conducted using SPSS (SPSS, Chicago, IL, USA), with meticulous significance set at $p<0.05$.

RESULTS

The mean age of patients was 57.6±10.4 and 56.1±9.4 years with DR (n=98) and without DR (n=42), respectively, which was not significant. There were 52 males in the DR group and 26 males in the DR group. The maximum number of patients belongs to the age group of 51–60 years in both groups. The mean vitamin D levels were higher in males (29.62±11.38) as compared to females (27.22±11.33; p=0.217). There was a significant difference in the duration of diabetes between those with DR and those without DR (p=0.043). However, there was no significant difference in homocysteine, HDL, LDL, FBG, calcium, phosphate, and PTH levels. HbA1c level was higher in DR with compared to without DR patients significantly ($p<0.001$). The mean 25-hydroxyl vitamin D level in DR is significantly less than that in people without retinopathy ($p<0.001$) (Table 1).

Sixty-nine out of 98 patients with retinopathy and 15 out of 42 without retinopathy had a 25-hydroxyl vitamin D level <20 ng/mL. DR patients had a higher proportion of subjects with vitamin D deficiency as compared to those without DR (p=0.045) Table 2.

We meticulously categorized patients with DR based on the severity of their ocular condition, adhering closely to the stringent guidelines set forth by the International Clinical DR Consortium. Our classification included stratifications such as mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, low-risk proliferative diabetic retinopathy (PDR), and high-risk PDR.

Upon meticulous analysis, we observed a substantial and consistent decline in the levels of 25-hydroxy vitamin D across various stages of retinopathy severity. Specifically, we noted a statistically significant decrease in 25-hydroxy vitamin D levels among patients with moderate NPDR (p=0.025), severe NPDR (p=0.006), low-risk PDR ($p<0.001$), and high-risk PDR (p=0.001) compared to diabetic individuals without any retinal pathology. These findings underscore a compelling trend: as the severity of retinopathy escalates, there is a marked reduction in 25-hydroxy vitamin D levels. This correlation, depicted vividly in Fig. 1, suggests a potential association between vitamin D status and the progression of DR, shedding new light on the intricate interplay between retinal health and systemic factors.

Table 1: Clinical and biochemical characteristics of patients with type 2 diabetes with and without retinopathy

Patients	Retinopathy (98)	Without Retinopathy (42)	p-value
Age (years)	57.6±10.4	56.1±9.4	NS
Male (n)	52	26	NS
Duration (years)	11.15±5.6	4.5±3.1	0.043
HbA1c (%)	8.84±2.37	7.12±2.00	<0.001
25-OH vitamin D (ng/mL)	25.91±7.83	34.74±15.43	<0.001
HDL (mg/dL)	41.84±9.87	44.84±9.87	NS
Homocysteine (μM/L)	12.249±4.89	11.89±4.31	NS
Calcium (mg/dL)	8.98±0.49	9.01±50	NS
LDL (mg/dL)	120.66±36.53	116.66±36.53	NS
FBG (mg/dL)	192.50±66.86	170.77±58.63	NS
PTH (pg/ml)	51.9±14.23	52.6±16.18	NS
Phosphate (mg/dL)	3.4±0.51	3.3±0.48	NS

Correlation between 25-hydroxyl vitamin D and HbA1c levels among diabetic patients

We observed that 25-hydroxyl vitamin D levels decreased as there was a rise in HbA1c levels. On applying Pearson's correlation, we found a significant negative correlation between 25-hydroxyl vitamin D and HbA1c ($r=-0.701$, $p<0.001$) in our study population (Fig. 2).

DISCUSSION

Our research affirms the correlation between vitamin D deficiency and DR in individuals with type 2 diabetes. Notably, we found no discernible relationship between age and sex and vitamin D levels within our study.

Importantly, diabetic patients with retinopathy exhibited a significantly higher prevalence of vitamin D deficiency compared to those without retinopathy (p=0.045). Additionally, the mean vitamin D level among individuals with retinopathy was significantly lower than in those without retinopathy. These findings align with previous studies indicating that type 2 diabetic patients with retinopathy tend to have lower serum 25(OH)D concentrations [7,8].

Furthermore, our study revealed a higher prevalence of vitamin D deficiency among individuals afflicted with this microvascular complication, highlighting a consistent decline in mean serum vitamin D levels with the advancement of DR grades.

Interestingly, we observed that mean vitamin D levels were significantly higher in subjects with lower HbA1c levels compared to those with higher HbA1c levels. While it is well established that retinopathy severity correlates with elevated HbA1c levels [5]. Few studies mention an inverse relation between vitamin D level and HbA1c [9]. The relationship between HbA1c and vitamin D levels in type 2 diabetes patients, with or without retinopathy, remains relatively unexplored. This aspect of our study adds a novel dimension to existing literature.

A large-scale population-based cross-sectional study conducted in Korea corroborates our findings, demonstrating an inverse correlation between 25(OH)D concentrations and the presence of retinopathy, including proliferative forms. Notably, this study did not provide detailed information regarding the type of diabetes among its subjects, underscoring the unique contribution of our study in focusing specifically on type 2 diabetes patients [10].

Table 2: Frequency of vitamin D deficiency (25-hydroxyl vitamin D level <20 ng/mL) in patients with and without diabetic retinopathy

25-hydroxyl vitamin D Level	Patients without DR (n=42)	Patients with DR (n=98)	Odds ratio/CI	p-value
≥20 ng/mL	27	29	0.5072/(0.26–0.98)	0.045
<20 ng/mL	15	69		

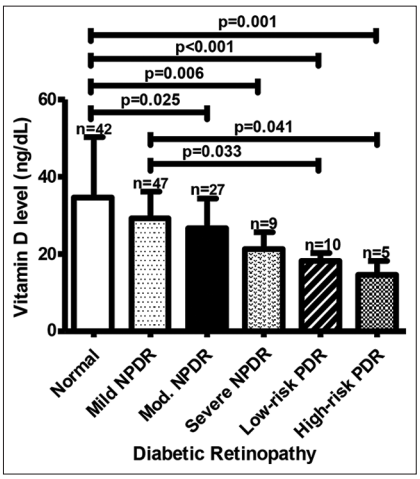

Fig. 1: 25 hydroxyvitamin D level in non-proliferative DR and proliferative DR

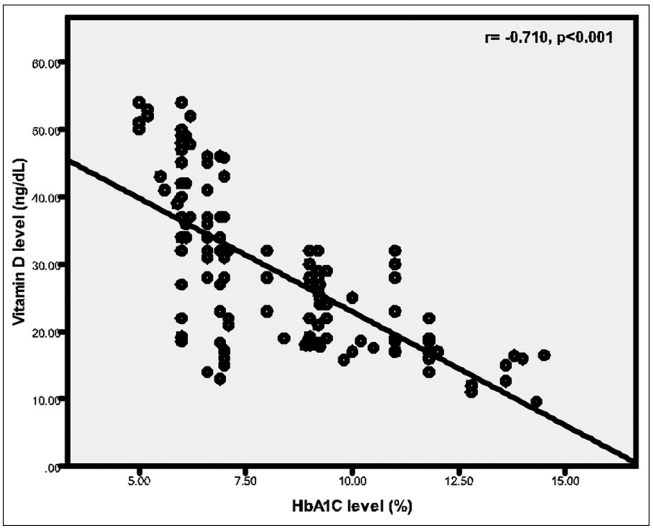

Fig. 2: Graph showing correlation between 25 hydroxyvitamin D and HbA1c level in diabetic patients

Vitamin D is theorized to play a pivotal role in maintaining ocular health due to its anti-angiogenic and anti-inflammatory properties. Emerging evidence suggests that supplementation with vitamin D could potentially ameliorate insulin resistance, a prevalent concern among individuals grappling with diabetes [11].

The presence of the vitamin D receptor in the retina and in human-cultured retinal endothelial cells lends credence to this hypothesis. Furthermore, the expression of the enzyme 1-α-hydroxylase, responsible for synthesizing the active form of vitamin D, hints at a possible localized action of calcitriol (1,25(OH)2D) within the eye, acting as a potent inhibitor of neovascularization [12,13].

While vitamin D serves as a straightforward marker associated with the severity of retinopathy in cases of DR, it's essential to acknowledge the constraints of our study, such as its modest sample size and the absence of post-supplementation follow-up. Consequently, further investigations with larger cohorts and longitudinal assessments are warranted to provide a more comprehensive understanding.

There's a potential avenue for intervention in addressing vitamin D insufficiency alongside managing blood sugar and blood pressure levels, which could potentially attenuate the progression of retinopathy. This insight paves the way for future research endeavors and clinical strategies aimed at enhancing outcomes for individuals affected by DR.

CONCLUSION

The most significant and outstanding finding of the study is that serum vitamin D levels significantly decreased as the severity of DR increased. Also, there is an inverse relationship between vitamin D and HbA1c.

We therefore conclude that all patients with type 2 diabetes mellitus, besides undergoing fundoscopic examination, must be assessed for their vitamin D status at the point of diagnosis and supplemented appropriately to possibly prevent or even retard the progression.

Limitations

Single-center study with a small sample size.

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AUTHOR CONTRIBUTION

Data, Writing, concept DR Chhaya Verma

CONFLICT OF INTEREST STATEMENT

None.

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