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Study on the association between total vitamin D levels and diabetic retinopathy in type 2 diabetic mellitus

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ABSTRACT

Background: This study aims to recognize the interrelation among total vitamin D levels and diabetic retinopathy in diabetic mellitus particular type 2 variant.
Materials and Methods: That was a cross-sectional look on 276 patients with diabetes mellitus. Cases were grouped similarly into with and without DR.
Screening tactics like unique records, best-corrected visual acuity, fundoscopic examination, and blood investigations like fasting blood sugar, post prandial blood sugar, HbA1C vitamin-D were carried out. Diabetic retinopathy is graded the use of ETDRS.
Results: The relation of the period of diabetes to the severity of retinopathy showed an advantageous correlation, with a p-value <0.001. It has confirmed an inverse relationship among the severity of diabetic retinopathy and Vitamin D values. Sufferers with mild NPDR and moderate NPDR had Vitamin D insufficiency, which decreased to Vitamin D deficiency stages in severe NPDR and PDR.
Conclusion: A relation change is observed among diabetic retinopathy and total Vitamin D levels. Henceforth, it is important to examine the affiliation of Vitamin D with the extent of DR, its use to forecast of the severity of DR, and as a device to restrict or prevent the development of retinopathy modifications.

1. Introduction

Diabetes is the increasing status of an epidemic in India, with more than or same to sixty-two million diabetic individuals.[1]

In line with Wild et al., diabetes is thought to incline from 171 million to 366 million in 30 years from 2000- 2030, marking the highest in India. In 2000, India had a significant number of patients with diabetes mellitus.[2]

Diabetes mellitus is classified into two classes, relying upon the pathogenesis of Type 1 and Type 2 Diabetes Mellitus. Type 1 Diabetes Mellitus which is likewise referred to as insulin-dependent diabetes mellitus [IDDM]) is caused by autoimmune-mediated destruction of the beta cells of the pancreas and the cells in which insulin manufacturing takes place. Type 2 Diabetes Mellitus is characterized by 3 major mechanisms: insulin resistance, reduced insulin manufacturing, and elevated glucose production. Although it has been properly tested that strictly controlling blood glucose can lower the hazard of microvascular issues from diabetes, the pathophysiology of retinopathy development continues to be yet to be established.[3]

Studies have proven that poor glycemic control and longer diabetes durations are threat elements for DR.[4] Diabetes desires to be detected at the earliest as it has a devastating impact at the satisfactory of life. Detecting the sufferers earliest at danger for developing diabetic retinopathy is important to lessen preventable blindness from this disorder. Vitamin D is essential for many

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physiologic processes such as musculoskeletal and immune, however, numerous studies have proven its role in diabetes mellitus. Vitamin D deficiency has come to be a health problem. Studies have shown sizeable Vitamin D deficiency, and insufficiency is seen in over 1/2 of the world's population.

Accelerated threat of cardiovascular disease, cancer, and mortality is established with vitamin D insufficiency.[5,6] Vitamin D deficiency has proven to be normal in individuals with diabetes mellitus (84.2%). Its outcomes on the immune system, angiogenesis, and anti inflammatory effects, plays a role in diabetic retinopathy pathology. Additionally, it has been shown that in a mouse oxygen-prompted ischemic retinopathy model, calcitriol is an active nutrition D metabolite and inhibits retinal neovascularization.[7,8]

The affiliation of vitamin D deficiency in type 2 diabetic mellitus sufferers with diabetic retinopathy has not yet been well established. In contrast, there are studies that states there is an armed affiliation and correlation between vitamin D deficiency and diabetic retinopathy. Furthermore, the studies in this problem within the Indian populace are quite very few. As the superiority of diabetes mellitus is high in our vicinity, this examine is undertaken to determine the ubiquity of vitamin D deficiency in type 2 diabetic mellitus sufferers with diabetic retinopathy and to correlate the vitamin D levels with retinopathy changes.

2. Materials and Methods

The study was initiated after the necessary approvals from the Institute Ethics Committee. Study design and period: The hospital-based cross-sectional Study was conducted in India during October 2019-April 2021. The total 276 patients with diabetic mellitus Type 2 were enrolled and they were grouped into two with those having diabetic retinopathy and those without diabetic retinopathy (138 patients per group). The patients were explained about the study, institutional clearance, and patients' willful consent was taken. Details of the patients, including history, clinical examination, and investigations, were recorded.

All patients aged 30 years and above with Type 2 Diabetes Mellitus are included in the study. Followings were excluded from the study: (i) all patient with a history of supplementation of Vitamin D, (ii) patients with low haemoglobin, (iii) patients are on drugs that affect the retina, such as quinolines, thiazide, latanoprost, tamoxifen, and interferon. (iv) subjects with diseases such as tuberculosis, liver cirrhosis and hypertension., (v) those having pregnancy and (vi) unwilling patients.

The sample size was calculated as follows:

$n = f(\alpha/2, \beta) \times [p1 \times (100 - p1) + p2 \times (100 - p2)] / (p2 - p1)2$

Where p2 and p1 are the per cent 'success' in the experimental group and control, respectively.

All patients were screened with a detailed history, including the duration of symptoms, their nature, duration of exposure to sunlight, dietary habits, and history of tobacco chewing or alcohol consumption. Treatment history with oral hypoglycaemic medications, insulin injection, vitamin D supplements, and past ophthalmological surgery or other laser treatment was also taken.

Ocular examination includes visual acuity by Snellen's chart, anterior segment assessment, Goldmann applanation tonometer used for intraocular pressure examination, fundoscopy with indirect ophthalmoscop and fundus photography.

Applicable blood investigations like fasting blood glucose (FBS), postprandial blood glucose (PPBS), random blood sugar (RBS), glycolsated haemoglobin (HBA1c), and serum total vitamin D were measured.

The patients were explained approximately, institutional clearance, and participants willful consent were taken. Information of the patients, together with history, clinical examination, and investigations were recorded.

Biochemical estimation of vitamin D by Vitros immunodiagnostic device.

In our study at, a competitive immunoassay technique is used, which entails the release of 25-OH.

Vitamin D from the binding protein using a low Ph denaturant and the subsequent competition of the free 25-OH Vitamin D with horseradish peroxidase (HRP) labelled 25-OH Vitamin D reagent for monoclonal anti-Vitamin D bound too well. Unbound materials are removed by washing.

2.1. Statistical analysis

Data analysis by Spss version 16 statistical package. Statistical tools used for data analysis and results tables are evolved through data analysis tools in ms-excel as an add-on tool.

3. Results

Two hundred seventy-six patients have been enrolled in this study. A hundred thirty-eight of them had diabetic retinopathy modifications in the fundus, serving as the case group, while 138 had normal fundus findings (without diabetic retinopathy), serving as the case group.

In this study, patients aged 30 years and above had been included with male predominance. The age group of 60 – 70 years became maximally affected (45%) among the case group (with retinopathy changes) and control group (without retinopathy modifications). The least affected group in the study are above eighty years in both groups.

The length of diabetes was taken as the interval between the initial diagnosis of diabetes mellitus and the existing study length. When thinking about the controls, maximum patients (n=104) had a period of diabetes less than 5 years,

followed by period between 5-10 and 15-20 years. On the other hand considering the case group, most patients had a period among five to ten years (n=58), and approximately 11 sufferers had a period of 20 to 25 years.

On reviewing the length of diabetes according to the severity of retinopathy, many of the patients with moderate NPDR, the majority had a period of much less than five years(n=16), patient with moderate NPDR showed a length of five to ten years, even as among the severe NPDR maximum were in the duration of 10 to 15 years. Then again, among the PDR cases, the majority have been covered in five to ten years but had been among irregular treatment.

The relation between HBA1c and severity of retinopathy is proven in Figure 1. The levels show a proportional relation between improved serum HbA1c and the severity of retinopathy.

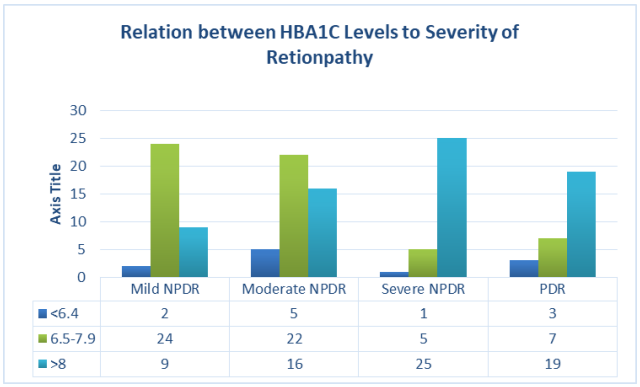

Figure 1: Relation between HBA1C levels to severity of retionpathy

The distribution of Vitamin D values among the case and manage organizations is shown in Figure 2.

A complete of 276 participants enrolled, when considering the control group, the majority had been discovered to have vitamin D sufficiently (overall vitamin D >30 ng/ml), (1.5%) patients were observed to have vitamin D insufficiency and deficiency, respectively.

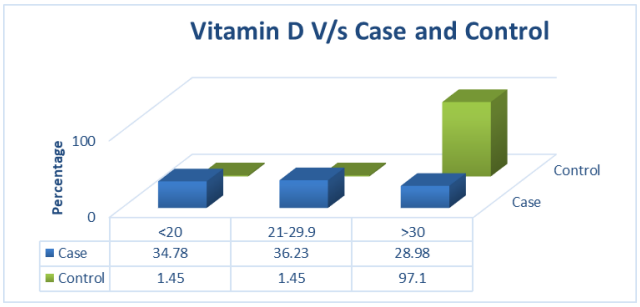

Figure 2: Graph showing a relation between vitamin D and groups

Alternatively, thinking about the case group, it suggests nearly same distribution of the patients with Vitamin D deficiency (overall vitamin D< 20 ng/ml) and vitamin D insufficiency (Vitamin D among 21 - 29.9 ng/ml).

Figure 3 displays the distribution of vitamin D levels in accordance to retinopathy, where a significant relation is present between the vitamin D levels and the retinopathy grade. The majority of patients with mild NPDR and moderate NPDR had vitamin insufficiency.

A p-value of 0.000 shows significance, suggesting a relation between the grade of retinopathy and vitamin D levels.

High-risk PDR cases had the lowest value of total vitamin D. 55.5% were included in the deficiency group. None of the patients of post-PDR and PDR with RD had Vitamin D sufficiency (total vitamin D> 30 ng/ml).

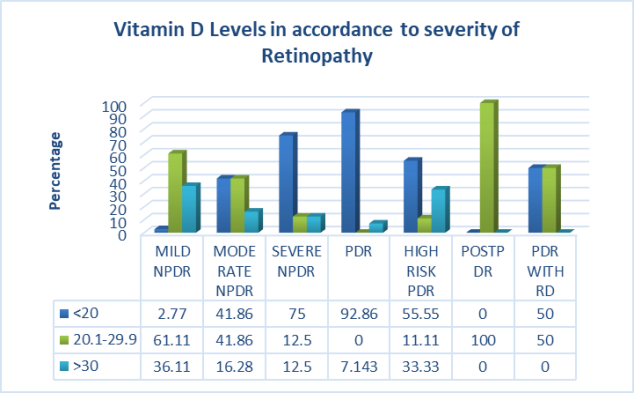

Figure 3: Graph showing vitamin D Levels in accordance to the severity of retinopathy

As per the statistical testing part by Assumption Checks by, Shapiro-Wilk test shows a positive correlation in vitamin D levels. (Table 1)

Table 1: Shapiro-Wilk test

		W	P
Age	Abnormal	0.98	0.044
	Normal	0.987	0.232
Duration	Abnormal	0.869	< .001
	Normal	0.8	< .001
RBS	Abnormal	0.92	< .001
	Normal	0.841	< .001
FBS	Abnormal	0.934	< .001
	Normal	0.764	< .001
PPBS	Abnormal	0.961	< .001
	Normal	0.86	< .001
HBA1C	Abnormal	0.929	< .001
	Normal	0.815	< .001
Vitamin D	Abnormal	0.953	<.001
	Normal	0.774	<.001

Note. Significant results suggest a deviation from normality

As per test of normality (Shapiro Walk test) parameters such as duration, fasting blood sugar, post prandial blood sugar, HbA1C vitamin-D in both case and control groups shows deviation from normality.

Vitamin D shows significant deviation from normality on considering the values in both normal (control group) and abnormal (case group). While on the other hand age doesn't show any significance among case and control groups.

Test of equality of Variances were used to further check for the significance of age among the case and control group as shown (Table 2).

Table 2: Levene's test

	F	df	p
Age	11.616	1	< .001
Duration	23.178	1	< .001
RBS	10.64	1	0.001
FBS	35.196	1	< .001
PPBS	25.151	1	< .001
HBA1C	9.656	1	0.002
Vitamin D	1516.000	1	<.001

Kruskal Wallis test shows that there is significance between the type of treatment and the parameters such as duration, fasting blood sugar, post prandial blood sugar, HbA1C vitamin-D. (Table 3)

4. Discussion

Vitamin D deficiency (VDD) has been implicated in growing diabetic complications, in particular diabetic retinopathy (DR). It has numerous metabolites, the two most essential of that are 1, 25-dihydroxyvitamin D3 (1,25 (OH)2D3) and 25 vitamin hydroxyapatites 25(OH)D.

This cross-sectional study is aimed to take a look at the affiliation among vitamin D values and diabetic retinopathy in 276 person patients within the age institution above 30 years.

In our study, about 45% of patients belonged from the sixth to seventh many years of life. This will be due to the superiority of systemic diseases which includes diabetes of the same age population, ensuing in microvascular issues.

Wong et al. recommended that early age onset of much less than 45 years changed into an independent hazard element for DR; but disorder duration is known as an important hazard factor for DR.[9] Helping the previous studies, we have observed that a majority of the patient (n= 104) without retinopathy had a duration of diabetes between much less than five years, observed via 5 – 10 years. Even as considering the sufferers with retinopathy, most had a duration of 5 – 10 years and 10 -15 years, of which majority had been taking treatment irregularly. Accordingly, these values show that a multiplied severity of retinopathy changed into found, with a more length of diabetes.

In our examine, thinking about the regularity and pattern of treatment, maximum patients have been under everyday treatment. On in addition studying the remedy pattern, maximum patients were taking oral hyperglycemic drugs in each regular and irregular groups, 79.9% and 93.3%, respectively, with a p-value of 0.197.

Further to our findings, the advance trial suggested a major interplay between the age at diagnosis of diabetes and its period at the threat of microvascular occasions. The highest risk of microvascular activities become found in groups with the longest diabetes period and the youngest age.[10]

Majority of sufferers enrolled in the control group had serum HbA1c degrees of beneath 6.4% and inside the case group, serum HbA1c ranges was between 6.4 and 7.9%. On similarly reading the relation between HbA1c and severity of diabetic retinopathy the stages of serum HbA1c had been highest in patients with both severe NPDR and PDR (serum HbA1c = 8.0%- 10.0%), and lowest in patients with moderate NPDR. For that reason, it signifies that serum HbA1c tiers had been discovered to be statically significant in case and control group. The baseline imply serum HbA1c stages had been 8.383 +/- 0.158% in cases and 6.575 +/- 0.132% in controls. On performing the statistical assessments with Shapiro -Wilk test, outcomes advocates a deviation from normality with p value <0.001.

Pragati et al. and Manaviat et al. have provided insights that patients having exact glycemic manage (HbA1c < 7%) had a lower prevalence of diabetic retinopathy as compared to those having poor control (HbA1c > 7%). To feature to the previous research, we have studied that 1 (0.4%) patient having HbA1c degrees < 7% had proliferative diabetic retinopathy as compared to (3.4%) of those having HbA1c level between 7.1-8.5% and (36%) of those having HbA1c level > 8.5%.[11,12]

In our observe 97% of patients have been found to have vitamin D sufficiency (total vitamin D: > 30 ng/ml), whereas in the case group (patients with retinopathy changes) 36.23% were found to have diet D insufficiency (total diet D: 20-30 ng/ml), 34.7% were vitamin D deficiency (overall Vitamin D <20 ng/ml) and 28.9% were found to have normal vitamin D levels.

The levels of total vitamin D measured in the 276 patients were found significantly at lower levels as the severity of retinopathy increased from moderate NPDR to PDR. Of the patients with mild NPDR, 36% had total vitamin D of >30 ng/ml, even as in patients of moderate NPDR 41.86% had total vitamin D:20-30 ng/ml, severe NPDR and PDR cases proven vitamin D of < 20 ng/ml. Therefore, our examine demonstrates an inverse relation between the grades of diabetic retinopathy and overall vitamin D values, which different studies also supported.

Hence, this anticorrelation among serum vitamin D tiers and severity of grades of diabetic retinopathy proposes that

Table 3: Kruskal wallis test

	Type of Treatment	N	Mean Rank	Chi-Square Value	P-value
	Insulin	49	148.87		
Age	Oral	226	136.81	3.395	0.183
	Newly diagnosed	1	13.5		
	Insulin	49	181.5		
Duration	Oral	226	129.02	17.7777	0.000
	Newly diagnosed	1	174		
	Insulin	49	178.58		
RBS	Oral	226	130.19	15.985	0.000
	Newly diagnosed	1	52		
	Insulin	49	179.82		
FBS	Oral	226	130.11	18.239	0.000
	Newly diagnosed	1	10		
	Insulin	49	188.82		
PPBS	Oral	226	128	24.719	0.000
	Newly diagnosed	1	47		
	Insulin	49	171.23		
HBA1C	Oral	226	128.48	14.028	0.001
	Newly diagnosed	1	15.5		
	Insulin	49	83.28		
Vitamin D (MG/DL	Oral	226	151.08	32.075	0.000
	Newly diagnosed	1	1.00		

the neovascularization in the retina is liable for the lower in vitamin D ranges in sufferers with diabetic retinopathy, which is likewise studied via Mehrdad et al. on 30 patients and John F. Payne et al., in their observe, the sufferers with Type 2 Diabetes, PDR in precise, had decrease vitamin D levels than people with non-diabetes. Similarly, there may be an increase in subjects with vitamin D insufficiency a few of the diabetic retinopathy groups. [13,14]

In addition, study by Dinesh R et al., in their study on 412 diabetic patients, studied the correlation of vitamin D and diabetic retinopathy. In his study, it was observed that a large correlation is seen between the severity of diabetic retinopathy and vitamin D deficiency, truly establishing the role of vitamin D within the pathology and severity of diabetic retinopathy. [15]

Suzuki et al. studied hypovitaminosis D in type 2 diabetic mellitus affiliation with microvascular complications in 581 Japanese patients with diabetes mellitus type 2 and fifty-one patients without diabetes mellitus subjects. They analyzed the relation between serum 25- hydroxyl vitamin D(25-OHD) levels and Type 2 Diabetes, which found that stages of the 25-OHD have been extensively decreased inside the population with obvious microvascular changes. The prevalence of hypovitaminosis D (<20 ng/ml) turned to 70.6%. Serum concentrations of 25-OHD were related to HbA1c (P = 0.013), age (P = 0.070), and serum albumin (P < 0.001); however, they have been not related to BMI or the length of diabetes. [16]

5. Conclusion

Vitamin D decreases the expression of proinflammatory cytokines, a proliferation of immunocytes, and downregulate the vascular endothelial increase aspect (VEGF). Vitamin D deficiency or insufficiency, both play vast role for the development and progression of Diabetic Retinopathy.

The study demonstrates a negative correlation among the severity of the grades of diabetic retinopathy and serum vitamin D values. Most participants in the study with mild NPDR and moderate NPDR had vitamin D insufficiency ranges, which reduced to vitamin D deficiency stages in severe NPDR and PDR. On reading the statically assessments, a P-value of <.001 suggests deviation from normality, for that reason showing a good sized relation between vitamin D ranges and the grades of retinopathy. Parameters such as RBS, FBS, PPBS, HbA1c with p value>0.001 showed a positive correlation as well.

Consequently, it's miles essential to look at the affiliation of overall vitamin D with the grades of diabetic retinopathy and its use as a predictor to understand the severity of diabetic retinopathy.

Limitations of our study were that the patients lacked the follow-ups and patients were not evaluated to study the benefit vitamin D supplementation in diabetic retinopathy. Longer follow up is necessary to document whether the beneficial effect of such supplementation is seen in diabetic retinopathy and also to re-evaluate the serum vitamin D levels.

6. Source of Funding

None.

7. Conflict of Interest

None.

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