SERUM VITAMIN D LEVELS IN DIABETICS AND ITS CORRELATION WITH DIABETIC RETINOPATHYAnurag Chaurasia¹, Sourabh Jain²¹Associate Professor, Department of Medicine, S. S. Medical College, Rewa, Madhya Pradesh.²Senior Resident, Department of Medicine, S. S. Medical College, Rewa, Madhya Pradesh.**ABSTRACT****BACKGROUND**

Diabetes mellitus continues to be a tremendous health burden in India. Diabetes is also the leading cause of new blindness in patients 20 to 74 years of age. Diabetics are 25 times more likely to become legally blind than Non-Diabetics. Vitamin D may play a role in the pathogenesis of diabetic retinopathy through its anti-inflammatory effect and calcitriol is a potent inhibitor of retinal neovascularisation in an oxygen-induced ischaemic retinopathy model. Given these associations, we sought to determine the relationship between vitamin D insufficiency and diabetic retinopathy.

Aims and Objectives- To estimate the serum Vitamin D levels in Diabetics and to establish the correlation between the serum Vitamin D levels and Diabetic Retinopathy.

MATERIALS AND METHODS

Diabetics either attending OPD or admitted in Department of Medicine, SGMH, Rewa, were assessed during Jul 2014 - Jun 2015. They were tested for HbA_{1c} levels and serum Vitamin D and labelled insufficient for Vitamin D when serum levels were < 30 ng/mL. They also underwent fundoscopic examination and were classified into No Background Diabetic Retinopathy (BDR), Non-Proliferative Diabetic Retinopathy (NPDR) of mild, moderate, severe and very severe grade and Proliferative Diabetic Retinopathy (PDR).

RESULTS

Diabetic subjects had lower Vitamin D levels than non-diabetic subjects (20.7 ± 6.91 ng/mL versus 27.51 ± 5.53 ng/mL, $p < 0.0001$). The mean Vitamin D levels were as follows: No diabetes or ocular disease- 28.90 ± 4.70 ng/mL, no diabetes with ocular disease- 25.60 ± 6.12 ng/mL, no BDR- 25.3 ± 5.63 ng/mL, NPDR (mild, moderate)- 18.66 ± 4.39 ng/mL, NPDR (severe, very severe) PDR- 16.45 ± 7.42 ng/mL. Vitamin D levels demonstrated statistical significance between the body mass index, presence of Macrovascular disease, HbA_{1c} and serum creatinine.

CONCLUSION

This study suggests that diabetic subjects, especially those with NPDR (severe and very severe grade) and PDR have lower Vitamin D levels than those without diabetes.

KEYWORDS

Diabetes Mellitus, Diabetic Retinopathy, Vitamin D.

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BACKGROUND

Diabetes mellitus is an "Iceberg disease." Diabetes mellitus is accepted as a worldwide epidemic with an estimated increase in prevalence from 2.8% in 2000 to 4.4% by 2030.¹

The incidence of this disease continues to rise all over the world. Diabetes is recognised to be common in Asian Indians. The magnitude of problem is further compounded by various catastrophic microvascular and macrovascular complications targeting the vital organs in the body.

DM is the leading cause of blindness between the ages of 20 and 74. The gravity of this problem is highlighted by the finding that individuals with DM are 25 times more likely to become legally blind than individuals without DM. Blindness

in Diabetes is primarily the result of progressive diabetic retinopathy and clinically significant macular oedema. While it has been well established that intensive blood glucose control can lower the risk of microvascular complications from diabetes, the pathophysiology of retinopathy progression is not completely understood.²⁻⁴

As of the current data, more than 50% of world's population is vitamin D insufficient.⁵ The pathogenesis of various diseases like cardiovascular, cancer, Alzheimer's disease, Parkinson's disease, etc. has shown the role of vitamin D insufficiency in the further development of disease.^{6,7}

The anti-inflammatory effect of vitamin D is due to its anti-proliferative effects on lymphocytes, natural killer cells and reduction of a number of pro-inflammatory cytokines.¹⁰ Also, Calcitriol inhibits retinal neovascularisation as shown in some animal models.⁸ All these evidences provoked us to check the implication of vitamin D insufficiency in Diabetic Retinopathy.

MATERIALS AND METHODS

Type 2 Diabetic patients older than 18 years of age attending OPD and those admitted in Department of Medicine, S. S.

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Medical College and associated S. G. M. Hospital, Rewa (M. P.) from July 2014 to October 2015 were included in the study to minimise seasonal bias. Those with type 1 diabetes, younger than 18 years, taking vitamin D supplements, on medications such as Rifampicin and phenobarbital were excluded.

Patients were screened to determine their diabetes status, age, sex and addiction. Patients underwent routine ophthalmic examination including dilated funduscopy and were included in the study if they were able to be matched into a study. Attempts were made to keep the study groups equally matched according to age (within 10 years) and sex. Once enrolled, completed a medical history questionnaire and had their blood tested for haemoglobin A_{1c}, serum creatinine and 25-hydroxyvitamin D (25(OH)D). Haemoglobin A_{1c} levels were also measured using high performance liquid chromatography (HPLC). The 25(OH) vitamin D levels were measured from serum samples via an automated competitive immunoassay detected by chemiluminescence. The form of vitamin D measured is 25 (OH) vitamin D total. It is a comparative study which included a total of 220 subjects which were divided into five distinct groups based on their diabetes status and retinopathy findings-

1. Subjects without Diabetes or any ocular disease.
2. Subjects without Diabetes but had some other form of ocular disease, such as uveitis or macular degeneration.
3. The no background diabetic retinopathy (No BDR) group consisted of subjects with type 2 diabetes, but no evidence of diabetic retinopathy.
4. Subjects in the Non-Proliferative Diabetic Retinopathy (NPDR) group had evidence of retinopathy, such as microaneurysms, cotton-wool spots, intraretinal haemorrhages or macular oedema, but no evidence of retinal or iris neovascularisation. This group included patients with mild-to-moderate NPDR.
5. The PDR group consisted of subjects with neovascularisation on the optic disc, retina or iris, with or without vitreous haemorrhage or prior panretinal photocoagulation. This group also included patients with severe to very severe NPDR.

Demographic variables were categorised as following: age was grouped by decades of life (18 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 90 years); and Body-Mass Index (BMI) was grouped as well (less than 25.0 kg/m², 25.1 to 29.9 kg/m², 30.0 to 34.9 kg/m² and greater than 35 kg/m²). For those subjects with diabetes, duration of diabetes was categorised into groups (less than 5 years, 5 to 10 years, 10 to 15 years and greater than 15 years). Laboratory variables were grouped as following: haemoglobin A_{1c} (less than 6.0, 6.0 to 6.9, 7.0 to 7.9, 8.0 to 8.9, 9.0 to 9.9, greater than 10.0), and serum creatinine (less than 0.5 mg/dL, 0.5 to 1.0 mg/dL, 1.0 to 1.49 mg/dL, 1.50 to 1.99 mg/dL and greater than 2.0 mg/dL).

The presence of hypertension or macrovascular disease was also recorded. Subjects were considered to have macrovascular disease if they had ever been diagnosed with a myocardial infarction, cerebrovascular accident if they had undergone coronary artery bypass grafting surgery or a cardiac stenting procedure. Additionally, the duration of diabetes, which was defined as the interval between their

diagnosis of type 2 diabetes and the time of their enrolment into this study and insulin usage was recorded for each diabetic patient.

Fundus Photographs

Mild NPDR

Moderate NPDR

Severe NPDR

PDR

Statistical Considerations

One-way Analysis of Variance (ANOVA) and the chi-square test were used to compare the means and percentages for patient characteristics across study groups. One-way ANOVA was used to compare mean 25 (OH) D across levels of patient characteristics. The mean 25 (OH) D pair wise comparison between levels of the patient characteristics was tested using Tukey's multiple comparison procedure. Vitamin D was analysed as a dichotomous variable with a level less than 30 ng/mL used to label insufficiency. Chi-square test was used to compare the percentages of subjects with vitamin D insufficiency across the various patient characteristics. All the statistical calculations were performed using SPAS and GraphPad InStat 3.

RESULTS

Subject characteristics in the 5 Study Groups and Vitamin D

The mean vitamin D levels are significantly lower in Diabetics as compared to Non-Diabetics in the age group 40 - 49 and age more than 70 years. The mean age in group with no background retinopathy is 49.6 ± 11.28 years, whereas in group with severe and very severe NPDR and PDR is 65.00 ± 11.4 years and the difference in the age among the five groups is statistically significant ($p < 0.0001$).

The mean vitamin D levels were higher in females (24.35 ± 7.33 ng/mL) as compared to males (22.75 ± 7.26 ng/mL). But these results were statistically insignificant ($p = 0.116$). There is no significant difference in the distribution of male and female subjects in the 5 study groups ($p = 0.43$).

The mean vitamin D levels are significantly more ($p < 0.0001$) in patients with lesser BMI (mean vitamin D level of 28.23 ± 3.24 ng/mL in BMI < 20) than those with higher BMI (mean vitamin D level of 19.73 ± 8.15 ng/mL in BMI > 30). The BMI was significantly higher in those with higher grades of retinopathy. It is 23.52 ± 3.70 in no background retinopathy group and 26.37 ± 3.43 in those with severe - very severe NPDR and PDR ($p < 0.0001$).

Characteristic	Mean Vit D	P value	Vit D Insufficient (%)	P value
Diabetics (n = 120)	20.7 ± 6.91	< 0.0001	91 (110/120)	< 0.0001
Non-Diabetics (n = 100)	27.51 ± 5.53		68 (68/100)	

Table 1a. Mean Vitamin D Levels and % age Insufficiency in Vitamin D among Diabetics and Non-Diabetics

The mean vitamin D level in Diabetics (20.7 ± 6.91 ng/mL) is significantly less than that in non-diabetics (27.51 ± 5.53 ng/mL) ($p < 0.0001$). Also, diabetics have significantly higher proportion of subjects with vitamin D insufficiency (91.3%) as compared to Non-Diabetics (68%).

5 Study Groups	Mean Vit-D	P value	Vit-D Insufficient (%)	P value
No DM no ocular ds (n = 58)	28.90 ± 4.70	< 0.0001	72.4% (42/58)	$\chi^2 26.5$ $p < 0.0001$
No DM with Ocular ds (n = 42)	25.60 ± 6.12		71% (30/42)	
No BDR (n = 40)	25.3 ± 5.63		80% (32/40)	
Mild - Mod NPDR (n = 42)	18.66 ± 4.39		95% (40/42)	
SEV - V.SEV NPDR + PDR (n = 38)	16.45 ± 7.42		100 (38/38)	

Table 1b. Mean Vitamin D Levels and % age Insufficiency in Vitamin D in 5 Study Groups

The above table shows a significant and steady decline in mean serum vitamin D levels with increasing grades of Diabetic Retinopathy. The mean levels are 25.3 ± 5.63 ng/mL in No Background Retinopathy Group, 18.66 ± 4.39 ng/mL in group with mild-to-moderate NPDR and 16.45 ± 7.42 ng/mL in severe and very severe NPDR and PDR. Also, the proportion of diabetics with vitamin D insufficiency is significantly more with increasing grades of Retinopathy.

	Mean 25 (OH) D Level	P value	Vitamin D Insufficiency	P value
Duration of Diabetes				
< 5 (n = 24)	22.86 ± 6.01	0.005	91.66 (22/24)	0.08
5 - 10 (n = 54)	20.77 ± 6.28		88.89 (48/54)	
10 - 15 (n = 18)	17.56 ± 3.44		100 (18/18)	
>15 (n = 40)	17.65 ± 7.83		100 (40/40)	
Glycated Haemoglobin (HbA _{1c})				
< 6	28.08 ± 4.75	< 0.0001	68.96 (40/58)	< 0.0001
6 - 6.9	25.88 ± 6.51		67.74 (42/62)	
7 - 7.9	22.80 ± 5.78		92.85 (26/28)	
8 - 8.9	18.6 ± 7.45		91.66 (22/24)	
9 - 9.9	17.81 ± 7.02		100 (24/24)	
> 10	17.52 ± 6.49		100 (22/22)	
Insulin Usage				
Yes	17.40 ± 7.54	0.0006	90.47 (38/42)	0.79
No	21.91 ± 6.10		91.9 (68/74)	
Table 2a. Diabetic Profile and Vitamin D				

Table 2a. Diabetic Profile and Vitamin D

The mean vitamin D levels is significantly more ($p = 0.005$) in subjects with lesser duration of Diabetes (mean vitamin D level of 22.86 ± 7.10 ng/dL in less than 5 years' duration) as compared to those with longer duration of Diabetes (mean level of 17.65 ± 6.98 ng/dL in more than 15 years' duration).

The mean vitamin D levels are significantly more in subjects with lesser HbA_{1c} levels (28.08 ± 4.75 ng/mL in

HbA_{1c} < 6) than those with higher HbA_{1c} (17.52 ± 6.49 ng/mL in HbA_{1c} > 10). Also, proportion of subjects with vitamin D insufficiency is more those with higher HbA_{1c}.

The mean vitamin D levels in Diabetics on Insulin therapy is significantly lower (17.40 ± 7.54 ng/mL) than those on oral hypoglycaemics ($p = 0.0006$).

	No Ocular DS No DM (n = 58)	No DM with Ocular DS (n = 42)	No BDR (n = 40)	Mild-Mod NPDR (n = 42)	Sev-V. Sev NPDR + PDR (n = 38)	P value
Duration of Diabetes			4.84 ± 6.32	8.90 ± 4.91	15 ± 5.71	< 0.0001
HbA _{1c}	5.90 ± 0.45	5.9 ± 0.40	8.28 ± 1.89	8.63 ± 2.15	9.06 ± 1.5	< 0.0001
Type of Treatment OHA			36 (90%)	28 (66.67%)	20 (50%)	0.0005
Insulin			4 (10%)	14 (33.34%)	20 (50%)	

Table 2b. Diabetic Profile in the Study Groups

The mean duration of Diabetes was significantly more in subjects with higher grades of retinopathy ($p < 0.0001$). It was 4.84 ± 6.32 years in No BDR group, 8.90 ± 4.91 years in group with mild-to-moderate NPDR and 15 ± 5.71 years in group with severe to very severe NPDR and PDR.

The HbA_{1c} levels were significantly higher in those with higher grades of retinopathy. Mean HbA_{1c} is 8.28 ± 1.89 in subjects with no background retinopathy group and $9.06 \pm$

1.5 in subjects with severe to very severe NPDR and PDR ($p < 0.0001$).

The proportion of subjects on Insulin treatment significantly increases ($p = 0.0005$) with increasing grade of Diabetic Retinopathy.

	Mean 25 (OH) D Level	P value	Vitamin D Insufficiency	P value
Serum Creatinine Levels				
< 1	25.04 ± 6.71	< 0.0001	96 (154/192)	0.005
1 - 1.5	22.57 ± 7.26			
1.5 - 2	18.75 ± 8.96		100 (28/28)	
> 2	17.24 ± 6.69			
Hypertension				
Present	21.84 ± 7.67	0.0268	81.23 (52/64)	0.589
Absent	24.19 ± 7.06		80.77 (126/156)	
Macrovascular Disease (CAD)				
Present	20 ± 7.00	< 0.001	86.36 (38/44)	0.818
Absent	24.15 ± 7.19		79.54 (140/176)	
Absent	24.15 ± 7.19		79.54 (140/176)	
Table 3a. Co-morbidities and Vitamin D				

Table 3a. Co-morbidities and Vitamin D

The mean Vitamin D levels decreases significantly ($p < 0.0001$) with the rise in mean serum creatinine levels. Also, vitamin D insufficiency was proportionally and significantly higher in the subjects with deranged serum creatinine levels.

The mean serum vitamin D levels were significantly lower in Hypertensives (21.84 ± 7.67 ng/mL) than in non-hypertensives (24.19 ± 7.06 ng/mL).

The mean serum vitamin D levels were significantly lower in subjects with coronary artery disease (20 ± 7.00 ng/mL) than those without it (24.15 ± 7.19 ng/mL).

	No Ocular DS, No DM (n = 58)	No DM with Ocular DS (n = 42)	No BDR (n = 40)	Mild-Mod NPDR (n = 42)	Sev-V. Sev NPDR + PDR (n = 38)	P value
Sr. Creatinine	0.80 ± 0.23	0.99 ± 0.20	1.49 ± 1.55	$1.10 \pm .39$	1.44 ± 1.06	< 0.0001
Hypertension						< 0.0001
Present	4	24	6	14	16	
Absent	54	18	34	28	22	0.0001
Macrovascular Disease						
Present	8	10	14	16	22	
Absent	50	32	26	26	16	

Table 3b. Co-morbidities in the 5 Study Groups

The above-mentioned table shows that mean creatinine levels were more in diabetics as compared to non-diabetic population. Among diabetics, the levels were significantly more with increasing grades of retinopathy.

The prevalence of Hypertension increase with increasing grade of retinopathy ($p < 0.0001$). Mean SBP/DBP was $137.23 \pm 31.5/80.95 \pm 12.6$ and $151.89 \pm 36.38/90.52 \pm 20.94$ mmHg

in patients with mild-to-moderate NPDR and severe-to-very severe NPDR and PDR respectively.

The prevalence of macrovascular disease increases with increasing grade of retinopathy (p value 0.0001).

DISCUSSION

The mean vitamin D levels were higher (insignificantly- p 0.116) in females (24.35 ± 7.33 ng/mL) as compared to males (22.75 ± 7.26 ng/mL)- a finding similar to study by Payne et al, 2010⁹ and Joergensen et al 2010.¹⁰ There is no significant difference in the distribution of male and female subjects in the 5 study groups (p 0.43).

The mean vitamin D levels are significantly more (p < 0.0001) in patients with lesser BMI (mean vitamin D level of 28.23 ± 3.24 ng/mL in BMI < 20) than those with higher BMI (mean vitamin D level of 19.73 ± 8.15 ng/mL in BMI > 30). Payne et al 2011⁹ found similar result and stated higher the BMI lower the mean vitamin D levels. Obesity has been shown to affect vitamin D levels, possibly through vitamin D sequestration in fat deposits.

The BMI was significantly higher in those with higher grades of retinopathy. It is 23.52 ± 3.70 in no background retinopathy group and 26.37 ± 3.43 in those with severe to very severe NPDR and PDR (p < 0.0001). Fawzia et al 2012¹¹ reported average BMI of 33.1 ± 1.1 kg/m² and 32.5 ± 1.1 kg/m² in patients with PDR and NPDR respectively and Juutilainen et al 2007⁹ found average BMI of 29.5 ± 5.5 kg/m² and 31.3 ± 5.5 kg/m² in patient with no background retinopathy and proliferative retinopathy respectively. Although in India among newly detected, diabetic lean diabetics are common but in present study majority of patients included already had diabetes for a long duration along with associated complications.

Mean Vitamin D Levels and % age Insufficiency in Vitamin D among Diabetics and Non-Diabetics

This study showed a significant and steady decline in mean serum vitamin D levels with increasing grades of Diabetic Retinopathy. Also, the proportion of diabetics with vitamin D insufficiency is significantly more with increasing grades of Retinopathy. Tukey-Kramer multiple comparison test shows significant difference in vitamin D in between group 1 with group 2, 3, 4 and 5 and group 2, 3 and 4 with group 5 (p < 0.001). Payne et al⁹ found results comparable to this study.

Out of 120 Diabetics 80 developed Retinopathy, of which 78 were vitamin D insufficient. Vitamin D insufficiency was significantly associated with Diabetic Retinopathy (p 0.0023). Also, subjects with vitamin D insufficiency are at risk of having retinopathy 9.75 times that of vitamin D sufficient subjects (Odds Ratio 9.75; 95% C.I. 1.96 to 48.46).

Diabetic Profile and Vitamin D

The lower level of mean vitamin D in subjects with longer duration of Diabetes perhaps reflect that hyperglycaemia is implicated in vitamin D insufficiency as the glycaemic status worsens over time in most of the Diabetic patients.

The mean vitamin D levels were lower in subjects with higher HbA1c. Also, proportion of subjects with vitamin D insufficiency is more in those with higher HbA1c. Zoppinni et al 2013¹² also found that Glycated Haemoglobin is inversely related to Serum Vitamin D Levels in Type 2 Diabetics.

The lower mean vitamin D levels in Diabetics on Insulin therapy again reflects the poor glycaemic control in these patients in addition to the longer duration of Diabetes.

Diabetic Profile in the Study Groups

The higher grades of retinopathy in patients with longer duration of Diabetes is attributed to the chronic alteration in retinal microvasculature as a result of metabolic disturbances.

The HbA1c levels were significantly higher in those with higher grades of retinopathy. These results were similar to study by Fawzia et al 2012¹³ (mean HbA1C levels was 9.0 ± 10.9 years for PDR and 8.09 ± 1.1 for NPDR group). In the CURES eye study (Pradeepa et al 2010)¹⁴ found that for every 2% elevation of HbA1C, the risk of DR increased by a factor of 1.7. These changes stem from poor glycaemic control causing retinal vascular damage.

The proportion of subjects on Insulin treatment significantly increases (p 0.0005) with increasing grade of Diabetic Retinopathy. The likelihood of Insulin treatment necessity increases with the duration of Diabetes due to the exhaustion of beta cells of pancreas and due to development of Diabetic Nephropathy, which precludes the use of oral hypoglycaemic agents.

Co-morbidities and Vitamin D

The mean Vitamin D levels decreases significantly (p < 0.0001) with the rise in mean serum creatinine levels. This result is comparable to study of Payne et al, 2010.¹²

The vitamin D insufficiency is proportionally but insignificantly more in Hypertensive patients and vitamin D insufficiency does not pose any risk for development of Hypertension (odds ratio 1; 95% C.I. 0.49 to 2.17).

Subjects with vitamin D insufficiency are at risk of developing Coronary Artery Disease 1.63 times that of vitamin D sufficient subjects (Odds Ratio 1.63; 95% C.I. 0.64 to 4.15).

Co-morbidities in the 5 Study Groups

The prevalence of Hypertension increase with increasing grade of retinopathy (p < 0.0001), a result similar to that in study by Fawzia et al 2012¹⁴ (mean SBP/DBP was $142.2 \pm 4.4/91.69 \pm 2.9$ and $141 \pm 1.8/91.1 \pm 1.1$ mmHg in patients with NPDR and PDR respectively). Shrote et al 2015¹⁵ found significant relation between hypertension and retinopathy.

The prevalence of macrovascular disease increases with increasing grade of retinopathy (p value 0.0001). Rosenson et al 2011¹⁶ found that retinopathy was associated with approximately 1.7 fold increased risk for cardiovascular events and over two-fold increased risk for coronary events.

CONCLUSION

The most significant and outstanding finding of the study is that serum vitamin D level were significantly lower in Diabetics, specially in those with severe and very severe NPDR and PDR when compared to non-diabetics. Vitamin D play a protective role through its effects on glycaemic control and hypertension, both significant risk factors for the development and progression of diabetic retinopathy.²⁻⁴ It is possible that treating vitamin D insufficiency may lead to an improvement in blood sugar and blood pressure control, which could ultimately slow the progression of retinopathy.

We, therefore, propose 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 if found insufficient so as to possibly prevent or even retard the progression of what has become the leading cause of blindness in the early adulthood till late ages.

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