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ORIGINAL ARTICLE

Vitamin D and diabetic retinopathy in above 40 years old patients; Study of Tertiary Eye Care Hospital Jamshoro.

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ABSTRACT… Objective: To estimate the relationship between serum level 25-hydroxyvitamin (25 (OH) D) and diabetic retinopathy (DR) in type 2 diabetic elders. **Study Design:** Prospective, Observational study. **Setting:** Institute of Ophthalmology, Liaquat University of Medical & Health Sciences Jamshoro. **Period:** July 2020 to September 2021. **Material & Methods:** After completing the clinical examination, all participants were sent to the laboratory to investigate the blood level of Vitamin D (Vita D), glycated hemoglobin, glucose fasting/random; and urea and creatinine. For statistical analysis, the Statistical Package for Social Sciences (SPSS) version 20 was used. The serum level of 25 (OH) D was assessed with logistic regression analysis to evaluate the relationship with diabetic retinopathy. **Results:** Collected blood variables indicated that the mean level of Vita D was lower in subjects with proliferative Diabetic Retinopathy (PDR) and Non-PDR (NPDR) as compared to No DR (NDR) (14.10 ± 1.20, 21.10 ± 1.91, 23.29 ± 2.10 $P < 0.001$repectivly). In the results of logistic regression analysis, we found 25 (OH) D cut off levels < 20 ng/mL as a significant predictor for diabetic retinopathy with odds ratio (OR), 2.91 and 95 % confidence intervals (95 % CIs) (95% CI) 0.91- 5.91; p-value=0.001. It also revealed a strong association of diabetes duration with diabetic retinopathy with OR 3.91 (95% CI 1.89 – 11.91); p-value=0.001. **Conclusion:** With the reference to this research we can suggest that the deficiency of Vitamin D is another comorbid progression of diabetic retinopathy.

Key words: Diabetic Retinopathy, Prospective Study, Retinal Disease, Vitamin D Deficiency.

INTRODUCTION

It has been known that since the last century diabetes is a health issue in developed and developing countries. One report has been published in 2017 by International Diabetic Federation and stated that there are four hundred and fifty-one million people with Diabetic Mellitus (DM) all over the world. It may increase up to six hundred and ninety-three million by the year 2045.[1] Macular edema and retinopathy in diabetic people are the leading cause of blindness all over the world[2], especially in the working-age of a group. The long period of diabetes mellitus, the high glucose level in the blood, and hypertension are the strong risks factors for DR[3] not only these; but obesity, smoking and inflammation, hyperlipidemia, anemia, microalbuminuria, and increased growth factors are also having a strong association with DR.[4] For the last two decades we know that the Vitamin D hormone is necessary for humans' growth and development, it has pleiotropic functions[5] like calcium and phosphorus absorption and their homeostasis.[6] Progressive DR can be kept under control with the help of the following properties of Vita D; 1) Anti-proliferative, 2) Anti-oxidant, and 3) Antiangiogenesis.[7,8] Some epidemiological studies on the way stated that some nutritional factors may influence the risk of diabetic retinopathy.[9] An unusual hypothesis regarding Vitamin D is "it is a modifiable risk factor in the advancement of DR"[10], some studies have accumulated evidence on this hypothesis[11] but multiple research denies it.[12] Vitamin D deficiency (VDD) has become a pandemic globally[13] and it is

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also a serious health issue in Pakistan. It has been estimated that approximately 63.4% to 78.3% population of big cities in Pakistan has VDD.[14] Due to the prevalence of VDD in our country we investigated the impact of vitamin D on diabetic disease.

MATERIAL & METHODS

This prospective and observational research was carried out on elder subjects with type 2 diabetes in the institute of ophthalmology LUMHS Jamshoro during the period from July 2020 to September 2021 the research was conducted after getting approval from the Local Ethics Committee of the Institute (LUMHS/RECIOL-16). The sample for this study composed of 100 patients. Verbal and written consent was obtained from all participants before induction and each subject was informed that there are no hazards to this research.

Inclusion Criteria

All patients aged above 40 years and confirmed to be type 2 DM with and without DR were included in the study.

Exclusion Criteria

Each participant was evaluated for DME with ocular coherence tomography and for diabetic retinopathy, we got red color fundus photograph and results of fundus fluorescence angiography (FFA) with a fundus camera, then diabetic retinopathy was classified as defined by ETDRS;

- NO Diabetic Retinopathy (NDR)
- Non-Proliferative Diabetic Retinopathy (NPDR)
- Proliferative Diabetic Retinopathy (PDR)

The following data were collected through a questionnaire proforma;

- Personal Biodata; such as gender, body mass index (BMI) (kg/m^2), and age.
- Clinical Biodata; as; hypertension (mmHg), duration of diabetes, and kidney disease.
- Relevant blood investigations including glycated hemoglobin A1C (HbA1C), random blood glucose (RBG), fasting blood glucose (FBG), Vitamin D, blood urea (BU), and Blood creatinine (BCr) were carried out through the Diagnostic and Research laboratory LUMHS Jamshoro.

For statistical analysis, the Statistical Package for Social Sciences (SPSS) version 20 was used. Data of different variables were collected in terms of mean SD±, number, and percentage. The mean of continuous variables (like; duration of diabetes, level of Vita D, and HbAIc) was compared with an independent t-test and the relationship between these categories was assessed with chi-square. The relationship between continuous variables was assessed with Pearson's correlation (*r*, *p*). Independent predictor(s) for the severity of diabetic retinopathy was assessed using logistic and linear regression analysis. The ORs and 95 % CIs for NPDR and PDR with the status of serum level of vitamin D was also calculated by the Logistic regression method. $p < 0.05$ was considered statistically significant.

RESULTS

Demographic, clinical characteristics, and laboratory investigations of hundred study patients are shown in Table-I. The subjects without diabetic retinopathy were younger as compared with diabetic retinopathy and no age difference was found between the diabetic retinopathy group (NDR 46.4±8.2 v/s PDR 47.9 ± 7.8 years, $P = 0.89$), however, the patients with NDR had significant short duration (years) of diabetes as compared to NPDR and PDR (11.3 ± 6.9 v/s 18.7 ± 11.7 v/s 20.0 ± 10.5, respectively). The mean HbA1c was lower in subjects without retinopathy as compared to NPDR and PDR (7.9 ± 1.6 v/s 9.6 ± 1.7 versus 10.9 ± 1.5, $P < 0.001$ respectively). Patients with NPDR and PDR had higher BMI as compare NDR (32.7 ± 9.8 v/s 29.7 ± 8.0 v/s 25.9 ± 6.1 $p = 0.003$ respectively).

Study outcomes have shown that the 25 (OH) D cut-off levels less than 20 ng/mL were strongly associated with diabetic retinopathy and it can be enlisted in risk factors for the progression of the disease.

Variables	NDR	NPDR	PDR	P-Value
Age (years)	42.50 ± 1.6	46.4±8.2	47.9 ± 7.8	0.89
Gender Female (n /%) Male (n /%)	 08 /36.4 14 /64.1	 13 /59.0 9 /41.0	 06 /27.0 16 /73.0	
Duration of Diabetes	11.3 ± 6.9	18.7 ± 11.7	20.0 ± 10.5	< 0.001
BMI (Kg/m^2)	25.9 ± 6.1	29.7 ± 8.0	32.7 ± 9.	0.003
Blood Pressure (mmHg) Systolic Diastolic	 136.5 ±20.7 79.2 ±13.7	 139.6 ±25.3 82 ±12.0	 140.6 ±25.3 8.2 ±12.0	
HbA1c (%)	7.9 ± 1.6	9.6 ± 1.7	10.9 ± 1.5	< 0.001
FBG (mg/dL)	142 ± 10.12	161.50 ± 11.12	180.90 ± 10.0	< 0.01
RBG (mg/dL)	217.15 ± 15.20	251.0 ± 13.4	261.0 ± 12.28	< 0.01
25 (OH) D (ng/mL)	23.30 ± 2.01	18.10 ± 1.90	14.10 ± 1.20	< 0.001
BU (mg/dL)	34.26 ± 2.09	45.15 ± 3.39	48.02 ± 2.56	< 0.01
BCr (mg/dL)	0.89 ± 0.0	1.01 ± 0.27	1.65 ± 0.08	< 0.01

Table-I. Demographic and clinical data of study patients

We compared the blood level of Vita D between diabetic retinopathy and non-diabetic retinopathy groups and found a decrease in subjects of diabetic retinopathy (PDR, 14.10 ± 1.20 v/s NPDR 21.10 ± 1.91, v/s NDR 23.29 ± 2.10;).

Correlation and Regression Analyses

The serum level of 25 (OH) D was negatively correlated with HbA1c ($r = -0.20$, $P = 0.049$) also with older age ($r = -0.18$, $P = 0.06$) and with BMI ($r = -0.2$, $P = 0.04$) but not with duration of diabetes. logistic regression model was used to adjust the glycated hemoglobin, age, BMI and diabetic duration to get 25 (OH) D cut off levels that was < 20 ng/mL, as strong indicator for diabetic retinopathy (OR, 2.91 / 95% CI, 0.91-5.91); p-value=0.001 and logistic regression analysis also revealed strong association of diabetes duration with diabetic retinopathy with OR 3.91 (95% CI 1.89 – 11.91); p-value=0.001.

In this study, we found different and higher values of hypertension, FBG/RBG, BU, and B Cr in progressive DR as compared to NDR but logistics regression analysis did not find any correlation with diabetic retinopathy.

DISCUSSION

In the 21st century, the deficiency in Vita D is a common public health issue and its prevalence varies across the different populations[15], the described percentage of vitamin D deficiency among Type 2 diabetic patients ranged from 63.5% to 91.1%.[16] Vascular Endothelial Growth Factors and inflammatory processes are the key factors for the appearance of DME and proliferative retinopathy in diabetic participants. Recent studies have shown that a good level of Vitamin D can hamper the progression of DR by inhibiting inflammatory, angiogenesis, and proliferation of endothelial cells.[17] The different meta-analyses stated that the multiple patients with a low level of Vita D (< 20 ng/mL) had an experience of increased risk of DR than those without DR.[18] Luo et al and Nadri et al and national study in their studies also indicated the progression of diabetic retinopathy with serum level of V D < 20 ng/mL (OR = 2.03, 95% CI: 1.07–3.86 / OR = 1.11, 95% CI: 1.06–1.16 respectively).[5,19] Zoppini et al also stated that "the VDD may lead to severe microvascular complications (OR 0.758; 95% CI 0.607 to 0.947)".[20] Results of our study strongly correlated with the results of current studies, we also found 25-OHD cut off levels < 20 ng/mL as a strong indicator for diabetic retinopathy (OR= 2.91, 95% CI, 1.02- 5.91, p-value=0.001).

In one study the level of HbA1c in relation to Vita D has been evaluated.[21] We also evaluate the comparison of vitamin D blood level with HbA1c in study subjects that was inversely related to each other which means the vitamin D insufficiency was seen to be more in the subjects with higher HbA1c and we have a resemblance in results with

the research of Dave et al and Iqbal K.[22,23] The results of these studies show favorable matching with the results of our study.

It has been reported by many researchers that a long duration of diabetes and higher figures of HbAlc may influence the progression of DR in type 2 diabetes.[24] One cohort study denied the negative relation between serum level of vitamin D and progression of diabetic retinopathy.[3] One study reported that the increased numbers of participants with VDD have severity in DR, but when the relationship between retinopathy severity and serum Vita D level was analyzed with a regression model no significant result was found.[13] One large cross-sectional study reported a. The comparative analysis of national (OR= 2.01, 95% CI, 1.02- 3.91, p-value=0.001)[25] and international studies (OR = 2.03, 95% CI: 1.07–3.86 / OR = 1.11, 95% CI: 1.06–1.16 respectively) indicated the negative correlation of 25(OH) D level with the progression of proliferative diabetic retinopathy[5,19], we also observed the same results in our study.

CONCLUSION

With the reference to this research we can suggest that the deficiency of Vitamin D is another comorbid progression of diabetic retinopathy. It can be managed able with vitamin D supplements.

LIMITATIONS

1. **Implementation of the data collection.** Because it is a hospital-based study and the number of patients is small.
2. **Sample size. The** sample size is small which may decrease the efficacy of the results.
3. **Lack of previous national studies in the research area. Therefore,** the scope and depth of discussions in this paper on the national level are compromised.
4. Lack of financial support. With good finances, we can research on large scale.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Mahtab Alam Khanzada	He did substantial contribution to the conception & design of the article and interpretation of data for final approval.	
2	Nouman Ahmed Shaikh	He partiicpated in article writing and revising it critically forthe contents of the submitted data.	
3	Ghulam Hyder Sahito	he participated in study design, data gartehring and analysis.	
4	Mona Liza Mahesar	She performed it basic examination of all study patients and gathered basic clinical data.	
5	Azfar Ahmed Mirza	He did FFA of study patients.	
6	Imtiaz Ahmed Gilal	He maintained the record of FFA and color fundus photograph.	