

# ASSOCIATION OF VITAMIN D WITH RETINOPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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## ABSTRACT

**Objective:** The purpose of this study was to establish an association of vitamin D with diabetic retinopathy.

**Material and Methods:** This study was conducted at Endocrinology ward Hayatabad Medical Complex. It was a descriptive cross sectional study which was conducted for six months from January 2012 to June 2012 in which 100 patients after undergoing inclusion and exclusion criteria for having diabetes with and without retinopathy were enrolled

**Results:** Patients with diabetic retinopathy had lower vitamin D levels than those without diabetic retinopathy ( $P < 0.01$ ).

**Conclusion:** This study suggests that patients with diabetic retinopathy have low vitamin D levels.

**Key Words:** Vitamin D. Diabetes mellitus. Retinopathy.

## INTRODUCTION

Vitamin D was first identified and characterized in 1923 by Goldblatt and Soames<sup>1</sup>. It is an essential vitamin naturally produced by the body on exposure to sunlight. The best food sources of vitamin D are cod liver oil, fatty fish and egg yolk. Vitamin D concentration greater than 100nmols/l is desirable in normal healthy adults Vitamin D deficiency is characterized by circulating levels of 25 hydroxy vitamin D less than 50nmols/L. Concentrations ranging between 52-72 nmols/L are often considered insufficient<sup>2</sup>. The cause of low vitamin D levels include insufficient cutaneous synthesis (due to limited sunlight exposure or aging) inadequate intake and absorption of vitamin D, obesity or darker skin. Low vitamin D levels have been linked to poor health outcomes such as fractures, poor physical functions, diabetes, osteoporosis, cancer, cardiovascular, neurodegenerative, autoimmune and infectious diseases<sup>3</sup>. Several studies have demonstrated a link between vitamin D and the incidence of type2 diabetes<sup>4</sup>. Vitamin D protects the beta cells from cytokine mediated cell death<sup>5</sup> thereby reducing the risk of type 2 diabetes.

Diabetic retinopathy is the most frequent microvascular complication of diabetes mellitus resulting in blindness<sup>6</sup>. According to Pakistan National Blindness Survey, the prevalence of blindness in adults more than 30 years of age is 2.7% and out of these 15.3% have diabetic retinopathy<sup>7</sup>.

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In addition to its calciotropic functions, vitamin D has potent non classical effects including immunomodulatory, anti-inflammatory, anti-oxidant, anti angiogenic and anti-proliferative properties<sup>8</sup>. The vitamin D receptor is extensively expressed in retina including the endothelial cells in animals and human beings<sup>9</sup>. The plasma concentration of vitamin D has been inversely correlated with development of diabetic retinopathy<sup>10</sup>. The possibility is that vitamin D through its anti-inflammatory, anti-oxidant, anti-proliferative and anti angiogenic properties may protect diabetic retina<sup>11</sup>. Recent research has been done to show that vitamin D deficiency could lead to diabetic retinopathy in type2 diabetes<sup>12</sup>.

## MATERIAL AND METHODS

The study was conducted after approval obtained from Peshawar Medical College and Hayatabad Medical Complex ethical and research committee. All diabetic patients with or without retinopathy meeting the inclusion criteria were enrolled in the study through Endocrinology Ward HMC. A written informed consent was obtained after explaining purpose and benefits of the study.

The inclusion criteria included all type 2 diabetics admitted in endocrinology ward of Hayatabad Medical Complex with diabetes duration of 8-10 years. Exclusion criteria was Patients having known risk factors for the development and progression of diabetic retinopathy especially people who were hypertensive, pregnant and lactating women.

A detail history was taken followed by complete examination and routine set of investigation was done and preformed performa was filled. Investigations done included FBS<sup>13</sup>, Hb-A1c<sup>14</sup>, 25OH vitamin D<sup>15</sup> levels. Ret-

inopathy was diagnosed by using Canon CR-1 Mark II Digital retinal camera<sup>16</sup>.

Data was entered and analyzed into SPSS version 17. For descriptive analysis means and standard deviation were calculated such as age. Proportions were estimated for all the categorical variables such as sex, retinopathy. The appropriate measure for comparing cases and controls was done by odds ratio, confounding was evaluated using bivariate analysis and values were determined for risk using Chi square tests and fisher exact tests wherever appropriate. All the results were presented in the form of tables and graphs.

## RESULTS

The mean age of cases was 53±10.6 years and the mean age of controls was higher 54±8.5 years. Among gender distribution in cases 25 patients were males and 25 patients examined were females. Among controls 32 were males and 18 were females.

Fasting blood sugar was measured in two categories controlled and uncontrolled controlled were defined as those diabetics whose FBS levels were normal (70-100mg/dl) and uncontrolled were defined as those diabetics whose FBS was greater than 100mg/dl. Among cases 13(26%) subjects had controlled FBS levels and 37(74%) had uncontrolled levels. Among controls 14(28%) subjects had controlled FBS levels and 36(72%) had uncontrolled FBS levels. Odds ratio was 0.9 with 95% confidence interval of (0.37-2.18) which shows a protective effect of controlled sugar levels on diabetic retinopathy but P value was insignificant. (Table 1)

HBA1c levels in cases, 4(23%) subjects had good control and 46(55%) had poor to uncontrolled levels. Among controls 13(76%) subjects had good control and 37(44%) had poor to uncontrolled levels. Good glycemic control within last 3 months resulted in lesser retinopathy as compared to uncontrolled glycemic levels and the difference of glycemic control between people with and without retinopathy was statistically significant with a P-value of 0.03 (Table 2).

Among cases 18(94%) had low levels of vitamin D as compared to 32(39%) who had normal to high levels of vitamin D. Among controls 1(5%) had low vitamin D levels and 49(60%) had normal to high levels of vitamin D. Odds ratio was 18 with a 95% confidence interval of (2.4-29). This shows that retinopathy was 18 times more common in people with low vitamin D levels as compared to those with normal vitamin D levels. The P-value was highly significant (Table 3).

A relationship between glycemic control and vitamin D levels among cases and controls showed that among cases with good control 2(100%) had low vitamin D levels whereas in controls with good glycemic control vitamin D deficiency was seen in none. In cases with good glycemic control 2(13%) had normal to high levels of vitamin D and in controls 13(86%) had normal to high levels of vitamin D. Among cases having poor

**Table 1: Fasting blood sugar levels among Cases and Controls**

Cases and Control				
	Cases	Controls	Total	P-Value
Controlled FBS 70 -100 mg/ dl	13 (26.0%)	14 (28.0%)	27 (27.0%)	0.5
Uncontrolled FBS >100 mg/ dl	37 (74.0%)	36 (72.0%)	73 (73.0%)	
Total number	50 (100%)	50 (100%)	100 (100%)	

**Table 2: Glycemic levels among cases and controls**

HBA1c				
	Good Control 6.5%	Poor to uncontrolled >6.5%	Total	P-Value
Cases	4 (23.5%)	46 (55.4%)	50 (50.0%)	0.03*
Controls	37	36	73	
Total number	50	50	100	

\*P- Value is significant

**Table 3: Vitamin D levels among cases and controls**

VITAMIN D				
	Low levels	Poor to uncontrolled >6.5%	Total	P-Value
Cases with retinopathy	(<8.2ng/ml)	Normal to high (>8.2-37.4ng/ml)	Total	0.001*
Controls without retinopathy	1 (5.3%)	49 (60%)	50 (100%)	
Total number	19 (100%)	81 (100%)	100 (100%)	

\*P- Value is significant

glycemic control 16 (94%) had low vitamin D levels whereas only 1(5%) control had vitamin D deficiency. 30(45%) cases with poor glycemic control had normal to high vitamin D levels and 36(54%) controls had normal to high vitamin D levels'. P-value for poor to uncontrolled subjects was significant which means that vitamin D deficiency was more common in subjects having poor glycemic control in the last 3 months. (Table 4)

**Table 4: Glycemic control and vitamin D levels in cases and controls**

HBA1c		VITAMIN D			P-Value
		Low levels (<8.2ng/ml)	Normal to high (>8.2-37.4ng/ml)		
Good Control (<6.5%)	Cases & Controls	Cases (number)	(2) 100%	(2) 13.3%	0.06
		Controls (number)	0 0%	(13) 86.7%	
		Total (number)	(2) 100%	(15) 100%	
Poor to uncontrolled (>6.5%)	Cases & Controls	Cases (number)	(16) 94.1%	(30) 45.5%	0.001
		Controls (number)	(1) 5.9%	(36) 54.5%	
		Total (number)	(17) 100%	(66) 100%	

P-value was significant

**DISCUSSION**

Work has been done to establish a relationship between retinopathy in children and adolescents with type 1 diabetes<sup>17</sup>. Studies have also been conducted to establish a relationship between vitamin D levels and retinopathy in type 2 diabetes in different countries<sup>18</sup>. But still more work is needed regarding this aspect This is the first study done in Peshawar KPK to establish such a relationship.

A study conducted by H. Aksoy and colleagues in Ataturk university school of medicine Turkey examined serum 1,25 dihydroxy vitamin D,25 hydroxy vitamin D and parathormone levels in patients with diabetic retinopathy<sup>18</sup>. The study included 66 diabetic patients and 20 non diabetic healthy individuals. This study found a significant relationship between low vitamin D levels, and diabetic retinopathy. My study strongly goes in favor of the study done by H. Aksoy that vitamin D deficiency is associated with diabetic retinopathy. My study included equal number of patients 50 being cases and 50 being controls this was in contrast to the above mentioned study in which the number of cases were more than the number of healthy controls. The reason behind this may be that the incidence and thus prevalence of diabetes is increasing at an alarming rate in Turkey. According to a study conducted by Onat A and colleagues the annual incidence of diabetes in Turkey is 300,000<sup>19</sup>.

In my study vitamin D levels were compared to diabetic retinopathy. It was observed that diabetic retinopathy was 18 times more common in people with low vitamin D levels as compared to those having normal to high vitamin D levels. This novel association is also supported by other studies of adults with type 2 diabetes having low levels of vitamin D and retinopathy.

In my study FBS levels and HbA1c levels were also compared with diabetic retinopathy. Controlled FBS levels showed a protective effect on DR as odds ratio was 0.9 but P-value was insignificant. Good glyce-mic control over the last three months resulted in lesser retinopathy and this was statistically significant. In a

study conducted at Emory University of Atlanta Georgia, the patients also under went blood tests for glycated haemoglobin. Although there were differences in mean levels of HbA1c but these differences were not felt to be clinically important. This was contrary to my results which showed that 23% of cases and 76% of controls had good HbA1c levels whereas 46% of cases and 44% of controls had poor HbA1c levels. So conclusion drawn was that good glycemic control within last three months resulted in lesser retinopathy as compared to uncontrolled glycemic levels. I tried to establish a relationship between glycemic control and vitamin D levels. The confounding effect of duration of diabetes was controlled by careful selection of subjects with similar duration of diabetes that was 8-10 years. Among cases those having poor HbA1c levels 94% had low vitamin D levels and 45.5% had normal to high vitamin D levels. Among controls with poor HbA1c levels 5.9% had low vitamin D levels and 54.5% had normal to high levels.

This clearly shows that vitamin D deficiency is more common in subjects having poor glycemic control in the last three months. Low levels of vitamin D can be an offending factor responsible both for poor glyce-mic control and development of DR. In recent years researches have linked low vitamin D levels to insulin resistance and diabetes. Hence low vitamin D levels being responsible for causing poor glycemic control may play an indirect role in the development and progression of diabetic retinopathy as glycemic control is an important risk factor for DR. As vitamin D also decreases the levels of inflammatory cytokines that are up regulated in diabetes it may play an important role in prevention of DR. Furthermore the active metabolite of vitamin D calcitriol is a potent inhibitor of retinal revascularization.

Another study conducted at Jimma University hospital Ethiopia suggested that majority of patients with diabetic retinopathy had poor blood sugar levels. This study also goes in favour of my study that good glyce-mic control lowers the risk of DR.

## CONCLUSION

Diabetic retinopathy had low vitamin D levels. One study is not going to be a game changer, but it would certainly be grounds for more researches.

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### AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

- Khan F:** Conceive the idea.  
**Usman R:** Data collection, collection of references.  
**Wadud S:** Suggestions in laboratory works.  
**Zafar S:** Statistics analysis and compiling.  
**Adidenn Z:** Follow up and data collection.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.