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A Study on Correlation of Vitamin D Level in Diabetic Retinopathy

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Abstract

India is called the capital of diabetes mellitus and many people are suffering from microvascular and macrovascular complication and vitamin d supplement may prevent the complication and delays it. Diabetes mellitus (DM) is a large public health problem which affects more than 300 million individuals in the world, with significant morbidity and mortality worldwide. In addition to the deleterious effects of the disease itself, its long-term complications can conspicuously decrease the quality of life of diabetes patients. This was a prospective study including 50 subjects of type 2 Diabetes Mellitus admitted to hospital after meeting the inclusion criteria and exclusion criteria. Patient consent was taken and patient vitamin D was done and patient underwent fundoscopy after which the vitamin D level was correlated with fundoscopic findings. When compared with vitamin D level it was found that 29 of control 100% had adequate vitamin D level and in cases 13 (61.9%) had deficiency which was stastically significant. Vitamin D level can be used as a marker in predicting the complication of type 2 Diabetes Mellitus. Supplementation of it may delay the progression towards the complication of type 2 Diabetes Mellitus. We found that in type 2 Diabetes Mellitus patient vitamin D also plays as a risk factor and contribute in causing type 2 Diabetes Mellitus and correlation of vitamin D level and if found to be deficient then supplementing may delay the complication of microvascular and macrovascular complication.

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Key Words
Type 2 diabetes mellitus, vitamin D level, fundoscopy

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INTRODUCTION

Diabetes mellitus (DM) is a large public health problem which affects more than 300 million individuals in the world, with significant morbidity and mortality worldwide. In addition to the deleterious effects of the disease itself, its long-term complications can conspicuously decrease the quality of life of diabetes patients. Diabetes patients with uncontrolled or poorly-controlled blood glucose are at high risk of microvascular complications[1].

Diabetic retinopathy (DR) is among the most common diabetic complications, and is the leading cause of blindness among working-aged individuals worldwide. The prevalence of DR varies from 20-80% in different studies. Recent estimates suggest that the number of people with diabetic retinopathy will increase to 191 million by 2030. Diabetic retinopathy has a complex process. Many risk factors for DR have been established, such as poor glycaemic control, long duration of diabetes, smoking, inflammation, obesity, and hypertension. Stratton *et al*. have given evidence that poor glycaemic control and long duration of diabetes are independent risk factors of DR[2].

Praidou *et al.* found that increased physical activity is associated with less severe levels of DR, independent of the effects of HbA1c and body mass index (BMI). However, detailed pathophysiological mechanisms and other DR risk factors are not fully clarified.

Vitamin D is a multi-functional fat-solute metabolite required for humans' growth and development. Vitamin D deficiency (VDD) is seen across all ages, races and geographic regions[3].

Due to the wide functionality of vitamin D and because vitamin D deficiency is epidemic, Vitamin D's non-classical functions are gaining more attention for the close association between vitamin D deficiency and cancers, infectious diseases, autoimmune diseases, diabetes and diabetic complications[4].

The prevalence of vitamin D deficiency is high in type 2 diabetes mellitus (T2DM) patients. Vitamin D receptors are expressed extensively in the retina and an animal study showed that calcitriol was a potent inhibitor of retinal neovascularization in an oxygen-induced ischemic retinopathy mouse model. This evidence indicated that vitamin D may play a role in the pathogenesis of diabetic retinopathy.

While there are accumulating studies on the effect of vitamin D on diabetic retinopathy, the association between vitamin D and diabetic retinopathy are conflicting. According to some studies, vitamin D deficiency is associated with an increasing risk of diabetic retinopathy[5].

Patrick *et al*. found an association between serum 25-hydroxyvitamin D concentration and diabetic retinopathy in a cohort of 1790 type 2 diabetes patients. Inukai *et al*. reported that serum 25-hydroxyvitamin D (25(OH)D) levels were decreased in type 2 patients with retinopathy when compared with type 2 patients who had no microangiopathy.

However, others suggested that no significant differences in vitamin D status were found between type 2 diabetes with or without diabetic retinopathy. Alam *et al.* found no association between serum 25(OH)D levels and the presence and the severity of diabetic retinopathy[6].

MATERIALS AND METHODS

Source of Data: 50 subject with diagnosis of type 2 diabetes mellitus attending KIMS Hospital.

Sample Size: 50 subject after considering inclusion and exclusion criteria was taken up for study.

Sampling Method: Purposive sampling.

Type of Study: Cross sectional study.

Inclusion Criteria:

- Patient diagnosed of type 2 diabetes mellitus
- Age more than 18 years

Exclusion Criteria:

- Pregnant and lactating mother
- Patient on vitamin D supplements

Method of Collection of Data: Informed consent was taken. Information was collected through structured Performa for each subject. Study was carried out by making two groups, one group had type 2 diabetes mellitus with retinopathy and HbA1C level >7 and other group had type 2 diabetes mellitus with no retinopathy and HbA1c level <7.

Qualified subjects was undergoing detailed history, clinical examination including relevant investigation. Statistical test data was analysed using appropriate statistical method.

RESULTS AND DISCUSSIONS

It is the comparison vitamin D in case and control study and out of 50 patient using student t test and found to have 21 patients as cases who had vitamin D level below 15 and control of 29 patient had good vitamin D level of more than 20.

In (Table 4)-comparison of Vitamin D level in case and control study out of 50 patient using chi square test is found to have cases with 21 and in that 13 had 61.9% deficiency of vitamin D and 38.1% had sufficient level. In control it was found out that 29 patient had 100% of sufficient vitamin D level.

Comparison of vitamin D level with the fundus status of 50 patient, using One-way ANOVA test and result found to be 29 patient who had normal fundus

Table 1: Comparison of mean Vitamin D levels betweencCases and control using Independent student t test

Groups	N	Mean	SD	Mean Diff	95% CI for the Diff.		p-value
					Lower	Upper	
Cases	21	12.81	4.33	-7.47	-9.47	-5.46	<0.001*
Control	29	20.28	2.71				

*-Statistically Significant.
Note: Cases means subjects with NPDR and Control means normal subjects.

Table 2: Comparison of Vitamin D Levels between cases and controls using Chi Square Test

Variable	Category	Cases		Control		c2 Value	p-value
		n	percentage	n	percentage		
Vitamin D	Vitamin D Deficiency	13	61.9	0	0.0	24.260	<0.001*
	Adequate	8	38.1	29	100.0		

*-Statistically Significant.
Note: Cases means subjects with NPDR and Control means normal subjects.
Vitamin D-Deficiency = <20 ng/ml, Adequate = >20 ng/ml.

Table 3: Comparison of mean Vitamin D levels different fundus status using One-way ANOVA Test

Fundus	N	Mean	SD	Min	Max	p-value
Normal	29	20.28	2.71	14	24	<0.001*
Mild NPDR	15	13.60	4.42	8	24	
Moderate NPDR	6	10.83	3.71	6	16	

*-Statistically Significant.

Table 4: Multiple comparison of mean difference in Vitamin D levels b/w diff. fundus status using Tukey's Post hoc Analysis

(I) Fundus	(J) Fundus	Mean Diff. (I-J)	95% CI for the Diff.		P-value
			Lower	Upper	
Normal	Mild NPDR	6.68	4.05	9.30	<0.001*
	Mod. NPDR	9.44	5.74	13.15	<0.001*
Mild NPDR	Mod. NPDR	2.77	-1.23	6.76	0.23

*-Statistically Significant.

had vitamin D level >20.15 patient with mild NPDR changes found to have vitamin D level less than 13mg/dl. Remaining 6 patient with moderate NPDR found to have vitamin D level<10mg/dl it is the comparison of mean difference of vitamin D level and fundus using Tukey's post hoc analysis and found to have normal fundus with vitamin D level more than 20ng/ml and patient with less than 20ng/ml found to have mild NPDR and patient who had less than 10ng/ml found to have moderate to severe NPDR changes in fundus.

The characteristic feature of diabetic retinopathy is the appearance of vascular lesion of increasing severity, ending up in the growth of new vessels (neo-vascularisation). Vitamin D has anti inflammation properties and inhibits vascular smooth muscle cell growth and affects on the expiration of transforming growth factor beta 1 vitamin D is an important regulator of hundreds of genes regulating key biological processes from cell division to apoptosis.

It is well known that poor glycaemic control is a risk factor for the development and progression of DR, and vitamin D deficiency has been shown to impair insulin synthesis and secretion in animal models of diabetes. On the other hand, an optimal concentration of vitamin D is strongly proven to be necessary for efficient insulin secretion and function and vitamin D receptor (VDR) are ubiquitously expressed in every human tissue, including retina. Active vitamin D mediates its biological function by binding to vitamin D receptors. Vitamin D receptors have been found to be associated with insulin secretion and sensitivity and have been identified in pancreatic beta cell.

Additionally, some genes associated with the development of diabetic retinopathy have been found, such as Bsm1, rs2228570 and TT So, vitamin D status is related with the development and progression of diabetic retinopathy among type2 diabetic patients. Robinson *et al*.[7] in his study found that vitamin D were significantly lower in those diabetes who had microvascular complication. Aksoy *et al*.[8] also showed that the mean vitamin D3 concentration fell with increasing severity of diabetic retinopathy.

Payne *et al*.[9] demonstrated that patient with DR were deficient in vitamin D and that diabetic subjects, especially those with proliferative diabetic retinopathy (PDR). Suzuki *et al.* showed the existence of PDR was significantly associated with the decreased in serum vitamin D concentration. Even in the study on type 1 DM, Kaur *et al*.[10] found that retinopathy prevalence was higher in cases with vitamin d deficiency versus sufficiency. Chaychi *et al.*[11] in his study found that patient with diabetic polyneuropathy had a lower mean serum vitamin D level. Soderstrom *et al.*[12] demonstrated vitamin D insufficiency is associated with the adjusted composite measure of neuropathy. Lee and Chen in their study on use of vitamin D has analgesic for neuropathic pain found that all patient were vitamin D insufficient and mean vitamin D level was 18ng/ml. Diaz *et al*.[13] in their study found that 30.7% of adults with diabetes have neuropathy, 48.9% have vitamin D deficiency and 36.6% have vitamin D insufficiency. Kim *et al.* in their study found that mean vitamin D level was 18.4+/-9.8 in diabetic nephropathy and 86% of subjects were vitamin D insufficient and 46% were deficient.

Oh *et al.* found that in early stage 3CKD mean vitamin D level was 20.4ng/ml and 29.9% were deficient in vitamin D. the results obtained in our study compare well with those obtained in above studies. Thus in conclusion, mean vitamin D level are significantly lower in Type 2 DM, vitamin D deficiency (<20ng/ml) in type 2 DM is significantly associated with the any of the individual microvascular complication i.e. neuropathy, retinopathy and nephropathy and type 2 DM with the decrease in vitamin d levels have significantly increasing prevalence of combination of microvascular complication[14].

There is an epidemic of vitamin D deficiency around the world. From this meta-analysis, the prevalence of vitamin D deficiency was high among type 2 diabetes patients, although it may vary from different latitude, ethnicity, body mass index, season and supplementation of vitamin D.

VDD was consistent with previous studies. For patients with diabetes, the association with vitamin D deficiency and risk of developing diabetes has been acknowledged. Vitamin D deficiency is associated with an increased risk for diabetes.

In patients with diabetic retinopathy, the level of serum 25(OH)D was lower than patients without diabetic retinopathy. The characteristic feature of diabetic retinopathy is the appearance of vascular lesions of increasing severity, ending up in the growth of new vessels (neovascularization).

Vitamin D has anti-inflammation properties and inhibits vascular smooth muscle cell growth and effects on the expression of transforming growth factor ß1. Vitamin D is an important regulator of hundreds of genes regulating key biological processes from cell division to apoptosis. It is well known that poor glycaemic control is a risk factor for the development and progression of DR and vitamin D deficiency has been shown to impair insulin synthesis and secretion in animal models of diabetes.

On the other hand, an optimal concentration of vitamin D is strongly proven to be necessary for efficient insulin secretion and function and vitamin D receptors (VDR) are ubiquitously expressed in every human tissue, including retina. Active vitamin D mediates its biological function by binding to vitamin D receptors. Vitamin D receptors have been found to be associated with insulin secretion and sensitivity and have been identified in pancreatic beta cells.

Additionally, some genes associated with the development of diabetic retinopathy have been found, such as *Bsm1, rs2228570* and *TT. So*, vitamin D status is related with the development and progression of diabetic retinopathy among type 2 diabetes patients. Increasing studies have given more evidence of this. Annwelier *et al.* found that the serum 25(OH)D levels were associated with optic chiasm volume and in a vitro experiment, vitamin D was found to inhibit neovascularization in retinal tissue in a model of ischemic retinopathy.

What is more, proof of the VDR polymorphisms related with diabetic retinopathy was found. Hong *et al*. showed that patients with the B allele (BB or Bb) of Bsm1 polymorphism in VDR were associated with lower risk of diabetic retinopathy compared to patients without the B allele (bb) in Korean type 2 diabetic patients.

Bucan *et al*. showed that the bb genotype in VDR has a higher risk of developing diabetic retinopathy. Zhong *et al.* found that rs2228570 was associated with increased risk of diabetic retinopathy in Han Chinese type 2 diabetes patients. Benjamin *et al*. reported that the anticipation of retinopathy onset is significantly associated with the exaggeration of oxidative stress biomarkers or decrease of antioxidants in African type 2 diabetics and supplementation with vitamin D should be recommended as complement therapies of T2DM.

Therefore, low serum 25(OH)D levels are association with an increased risk of diabetic retinopathy, but more studies are required to identify the mechanism of the relationship between vitamin D and diabetic retinopathy fully.

It is well known that one of the two major sources of vitamin D is cutaneous synthesis by solar ultraviolet B radiation and the other is dietary intake.

The cutaneous synthesis of vitamin D is affected by many factors, such as season, latitude, time of day, skin pigmentation, the amount of skin exposed and whether makeup with sunscreen is used, so serum 25-hydroxyvitamin D levels vary between areas and persons. Hence, dietary vitamin D supplementation and physical activity might be a feasible way for patients with diabetes to maintain sufficient 25-hydroxyvitamin D levels.

Physical activity may increase blood 25-hydroxyvitamin D concentrations as a consequence of an associated increase in sunlight exposure. Praidou *et al.* reported that increased physical activity is associated with less severe levels of diabetic retinopathy, independent of the effects of HbA1c and BMI. Lee *et al.* showed that 3 months of vitamin D supplementation improved neuropathic symptoms by 50% in diabetic patients whose 25-hydroxyvitamin D status was deficient at baseline.

However, there has yet to be a dietary vitamin D supplementation trial on diabetic retinopathy. Thus, large randomized controlled trials researching on reducing diabetic retinopathy in type 2 diabetes are needed to accurately evaluate the potential benefits of these low-cost interventions in the future.

Diabetic retinopathy may develop and progress to advanced stages without producing any immediate symptoms to the patient. Screening for DR is essential in order to establish early treatment of sight-threatening retinopathy and has been demonstrated to be successful at achieving vision loss. Considering the heavy burden of DR and the association between serum 25(OH)D level and diabetic

retinopathy, low 25(OH)D levels may help us to find more early-stage diabetic retinopathy patients.

Therefore, screening low 25(OH)D levels may be a potential simple way for screening diabetic retinopathy among type 2 diabetes in primary hospitals-especially where there is a shortage of ophthalmic equipment or ophthalmologists.

CONCLUSION

- It is also found that patient who had found to have vitamin D deficiency were found to have microvascular complication like diabetic retinopathy i.e. mild NPDR
- It is also seen from the study that patient who had uncontrolled blood glucose level and vitamin D deficiency had developed the complication at the earliest i.e. moderate-severe NPDR and proliferative DR

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