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Role of Vitamin D in Type 2 Diabetes Mellitus and Its Impact on Diabetic Retinopathy

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ABSTRACT

Background: The prevalence of Diabetes mellitus is increasing worldwide with nearly more than 1 million new cases every year,associated with lot of mortality and morbidity. Along with maintainance of calcium homeostasis,Vitamin D is shown to have many nonskeletal effects with recent advances in the studies. Vitamin D has been found to have an important role in pancreatic insulin secretion and insulin action as well. The studies showing effect of vitamin D on diabetes mellitus and Diabetc retinopathy are controversial. So there is the need to study effect of vitamin D on Diabetes mellitus and its impact on Diabetic retinopathy.

Aim: To find the association between Vitamin D and type 2 diabetes mellitus and its effect on diabetic retinopathy

Materials and Methods: Study was conducted in Department of Biochemistry Gadag Institute of medical sciences Gadag.60 patients with type 2 diabetes mellitus were compared with 60 controls,after taking an informed consent.Vitamin D estimated by Chemiluminescence Immuno Assay method. Fasting and post prandial blood sugar was estimated by GOD-POD method.Indirect ophthalmoscope was used to assess Retinopathy

Results: vitamin D was highly significant in patients with type 2diabetes mellitus with proliferative diabetic retinopathy as compared with healthy controls. The study showed a negative correlation between vitamin D and diabetic retinopathy.

Conclusion: Decreased vitamin D levels are statistically highly significant in proliferative diabetic retinopathy. Hypovitaminosis D is negatively correlated with diabetic retinopathy.So the supplementation of Vitamin D in diabetics may improve the glycemic control of the patients and decrease the rate of morbidity and mortality.

Keywords: Hypovitaminosis D, Diabetic reinopathy ,calcium homeostasis, insulin.

INTRODUCTION

Diabetes mellitus is associated with considerable morbidity and mortality with its prevalence increasing every year [1, 2]. Incidence of type 2 Diabetes mellitus in India is 7.1%. There are many modifiable and non modifiable risk factors that have been found to be associated with type 2 diabetes mellitus but the identification of easily modified risk factor is very much needed to reduce the incidence of type 2 diabetes mellitus [3]. T2DM is associated with insulin resistance to the cells and decreased insulin secretion due to beta cell dysfunction [4]. Vitamin D plays an important role in maintaining the calcium homeostasis and its deficiency is associated with many diseases, including cancer, cardiovascular disease, and type 2 diabetes[5]. There is growing body of evidence that shows vitamin D deficiency is

an important contributing factor in development of both type 1 and type 2 diabetes. The β-cell present in the pancreas which secretes insulin are known to have vitamin D receptors on them [6]. Several studies have proved that treatment with vitamin D in type 2 diabetes mellitus patients is found to improve the glucose tolerance also the insulin resistance [7,8]. Vitamin D deficiency will lead to reduced insulin secretion [9]. Many Studies have shown that vitamin D has an indirect effect on the insulin secretion, probably by the effect of calcium on insulin secretion. Vitamin D is found to bring up the levels of calcium, which leads to normal influx of calcium through the cell membranes, so decreased vitamin D may bring down the calcium levels and its ability to affect the insulin secretion [10]. Although this is known to be the proposed mechanism, the studies showing relation between vitamin D and Diabetes mellitus are still controversial. The available epidemiological study evidences are to the limited extent. Several studies performed to detect effect of calcium and supplementation of vitamin D on glucose metabolism have shown mixed results [11-15]

Vitamin D, effects on the immune system and on angiogenesis plays a important role in the pathogenesis of diabetic retinopathy . Vitamin D brings up an anti-inflammatory effect brought about by decreasing the proliferation of lymphocytes, natural killer cells, and several pro-inflammatory cytokines as well(32). many studies have shown that , calcitriol, is an inhibitor of retinal neovascularisation studied in a mouse oxygen-induced ischemic retinopathy model(33). Hence it is important to know the impact of Vitamin D in diabetic retinopathy.

MATERIALS AND METHODS:

Source of data**:** This is a cross sectional study conducted in Department of Biochemistry Gadag Institute of Medical Sciences, Gadag. 60 type 2 Diabetes mellitus cases were selected from among the patients referred by the physicians to the clinical Biochemistry department and 60 healthy controls from the general population were enrolled in the study according to the inclusion and exclusion criteria mentioned below. This study was approved by the Ethical and Research Committee of Gadag Institute of medical sciences and all the subjects gave an informed consent before undergoing further investigations.

Inclusion criteria: Type 2 Diabetes mellitus cases having fasting blood sugar(FBS) of more than 120 mg/dl and post prandial blood sugar (PPBS) of more than 180 mg/dl were included in the study.

Exclusion criteria: diabetes mellitus type I cases, Obese individuals, patients with history of smoking, gestational diabetes mellitus cases, patients with hepatic failure, cases with pancreatic diseases or other systemic diseases,cases on supplementation with vitamin D, patients on medications known to alter vitamin D metabolism like phenytoin, rifampin or Phenobarbital, cases with parathyroid disorders like hyperparathyroidism or hypoparathyroidism altering vitamin D levels were excluded from the study.

Venous blood samples were collected from the subjects after 12 hours of fasting, with all the aseptic precautions. Sample was centrifuged and serum was separated and was used for the estimation of FBS and Vitamin D levels. Blood sample was again collected after one and a half hour of food to estimate PPBS. FBS and PPBS estimation was done by Glucose oxidase peroxidise (GODPOD) method [16]. Vitamin D estimation was done by Chemiluminescence Immuno Assay (CLIA) method [17]. Ophthalmic examination with dilated fundoscopy was done to assess the status of retinopathy

STATISTICAL ANALYSIS:

Statistical analysis is done by using Mean, Standard deviation, P value to assess the statistical significance, Spearman correlation coefficient to assess the correlation between vitamin D and type 2 diabetes mellitus and retinopathy.

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RESULTS:

Table-1: Comparison of biochemical parameters between type 2 diabetes mellitus cases and healthy controls

Variable	Type 2 diabetes mellitus Patients (Mean±SD)	controls (Mean±SD)	P value	Statistical significance
FBG(mg/dL)	171.7±39.3	85.2±9.5	0.003	HS
PPBG(mg/dL)	220±41.6	98.2±11.6	0.0012	HS
VIT D(ng/ml)	16.3±2.6	57.6±14.5	0.001	HS

Table-2: shows the spearman correlation between the different parameters among type 2 diabetes mellitus cases.

VARIABLE	r VALUE
Vit D and FBG	-0.736
VIT D and PPBG	-0.595

Table -3: comparison of parameters among diabetic retinopathy cases

variable	Diabetes with no retinopathy (n=22)	Diabetes with non proliferative Diabetic Retinopathy (n=18)	Diabetes with proliferative Diabetic Retinopathy (n=20)	P value
FBG(mg/dL)	122±30.2	140±28.2	175± 26.6	0.004
PPBG(mg/dL)	180±20.6	212±22.4	230±32.4	0.0024
VIT D(ng/ml)	16.2±1.4	14±2.1	10±1.9	0.0014

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Fig-1: shows the mean 25 OH Vitamin D in the study group

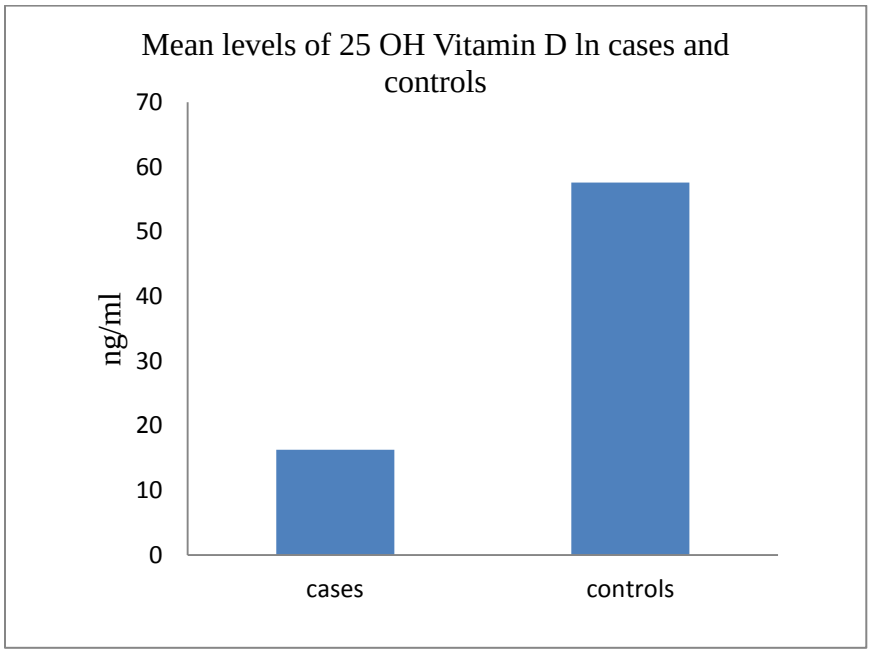

Fig-2: shows the mean fasting blood glucose and post prandial blood glucose in the study group

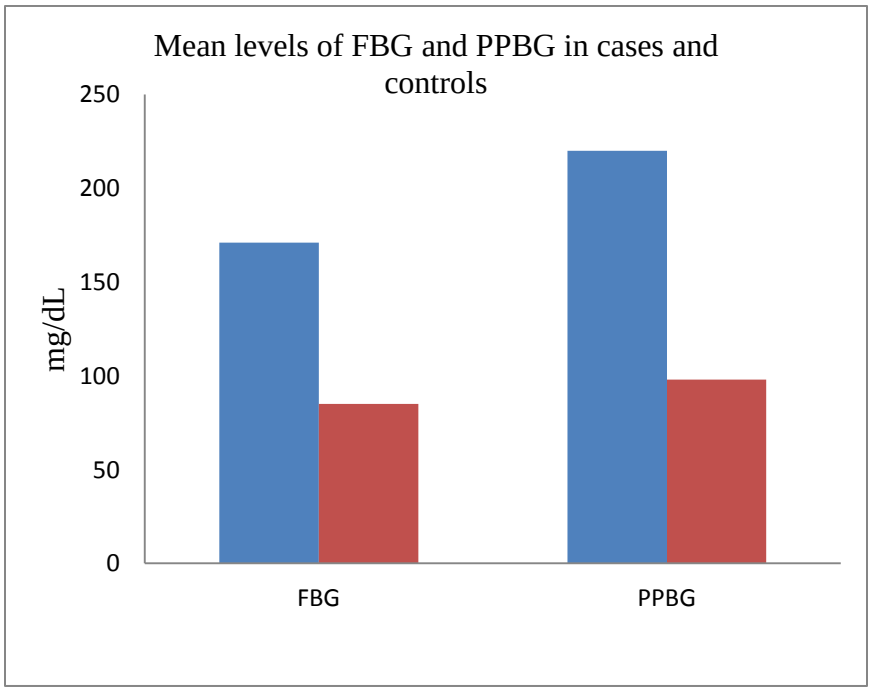

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Fig-3: shows the relationship between vitamin D and fasting blood glucose which showed a negative correlation

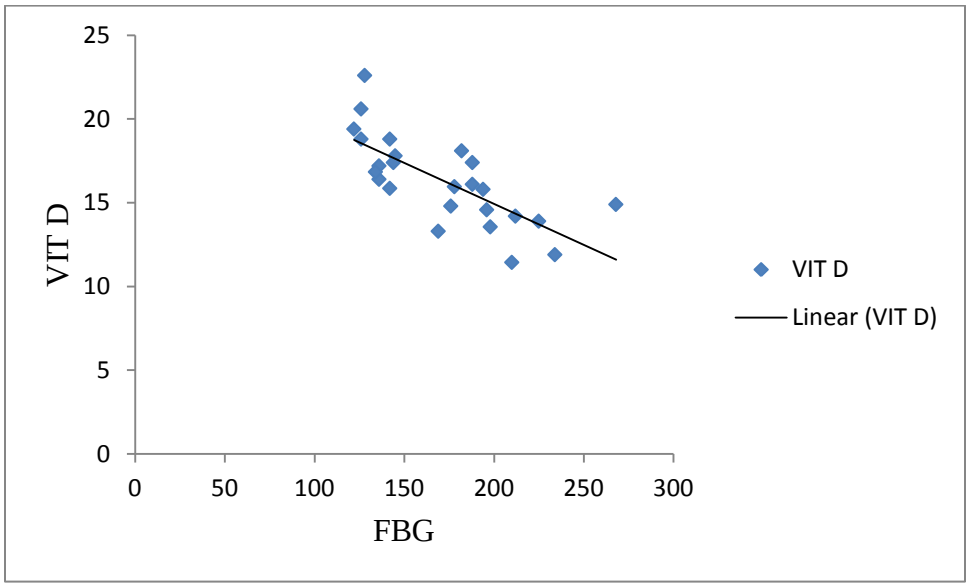
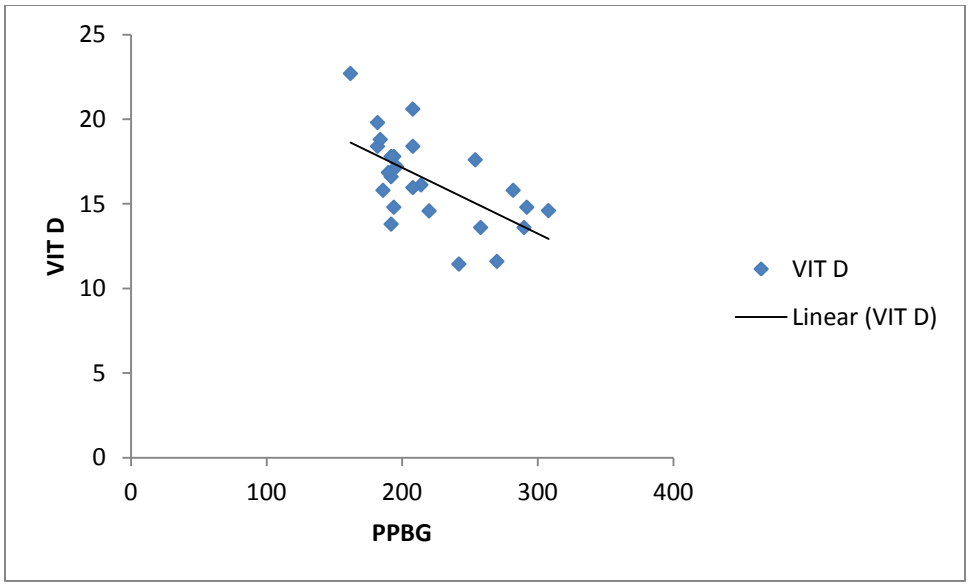


Fig-4: shows the relationship between vitamin D and post prandial blood glucose which showed a negative correlation



DISCUSSION:

Present study showed statistically highly significant mean values of fasting blood glucose levels, post prandial blood glucose, 25 OH Vitamin D in type 2 Diabetes mellitus cases when compared to the healthy controls. Our study showed similar results as Nita G et al (18) who showed significant relation between the cases and controls, their study also included insulin resistance. Results of our study are similar to study done by Jessica et al (19) who showed the significant influence of vitamin D in type 2 diabetes mellitus . Study of Enju Liu et al (20) showed high vitamin D levels have 40% decreased risk of type 2 diabetes mellitus which was similar to our study as we proved decreased vitamin D levels in type 2 diabetes mellitus. Study done by Mohammad Ali et al (21) showed vitamin D concentration was significantly lower in diabetic patients as compared with healthy individuals which was similar to our study. In a study performed by Mukherjee Brijesh(22) showed a negative correlation between vitamin D levels and diabetes and showed that poorly

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controlled diabetics had lower values of vitamin D their findings were similar to our study. Our study showed same results as study done by Akio Nakashima et al (23) who concluded that vitamin D levels are decreased in diabetes mellitus. The results of our study are similar to study done by Bang-an luo et al (24) who concluded that decreased vitamin D levels are related with increased incidence of diabetes mellitus and its complication that is diabetic retinopathy.

Our study is different from the study done by Jennifer g. Robin et al (25) who could not find any relation between 25(OH)D and type 2 diabetes mellitus but our study showed significant relation. Results of our study are also different from the study done by Lise lotte N et al (26) who showed that low 25(OH)D levels was not significantly associated with the incidence of diabetes mellitus but our study showed significant correlation between type 2 diabetes mellitus and vitamin D levels.

Our study is also similar to study done by Ian H.et al(27) , Joanna Mitri(28) who showed that vitamin D levels are significantly reduced in type 2 diabetes mellitus. They also supplemented vitamin D and found that this supplementation improved the status of type 2 diabetes mellitus.

Our study showed that vitamin D levels decreases with progression of retinopathy from diabetes with no retinopathy to diabetes with non proliferative retinopathy to diabetes with proliferative retinopathy. Our study is similar to the study done by pyane et all (34). Findings of our study is similar to the study done by Dave Mayur et all (35) who showed that vitamin D levels goes on decreasing with increasing grades of Diabetic Retinopathy

Though it is been found that the vitamin D levels are decreased in type 2 diabetes mellitus the exact mechanism underlying this hypothesis is not clear. Possible mechanism include the direct effects of vitamin D on islet cells of pancreas and secretion of insulin by them which is based on nuclear VDRs receptors present on them that can effect insulin sensitivity by stimulation of insulin receptor expression on them. Other proposed mechanism is that the regulation of intracellular calcium is dependent on vitamin D , the vitamin D–dependent calcium-binding protein that is needed for post insulin receptor effects in the tissue which respond to insulin and also by indirectly affecting the secretion through inflammatory processes (29-30). Other mechanism is inadequate vitamin D may lead to increased serum PTH hormone , which is found to have an inverse association with insulin sensitivity in case of healthy adults (31). At the genetic level VDR gene polymorphisms is found to have an association with variation in insulin secretion which may affect glucose metabolism (32). vitamin D has effect on the immune system. vitamin D decreases the production of many pro-inflammatory cytokines, like IL-2, IL-6, IL-8, IL-12, and TNF-α.11 Vitamin Dbrings about an anti-inflammatory effect brought about by decreasing the proliferation of helper T-cells, cytotoxic T-cells and natural killer cells. It also causes vascular endothelial dysfunction by increased vascular endothelial cell expression of the pro-inflammatory transcription factor, nuclear factors(36). Vitamin D contributes to diabetic retinopathy by angiogenesis mechanisms. Calcitriol is a inhibitor of retinal neovascularization and inhibits retinal endothelial cell capillary morphogenesis by decreasing the activity of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF).The complications of diabetic retinopathy which include macular edema and neovascularization, are brought about by decreased production of VEGF (37).

CONCLUSION:

Our study indicates that there is a definite correlation between Vitamin D levels and type 2 diabetes mellitus and poorly controlled diabetics have further lower values of Vitamin D as compared with healthy controls. It is well known that the patients with poorly controlled diabetes mellitus are more prone to develop complications. So the supplementation of Vitamin D in diabetics may improve the glycemic control of the patients and can decrease the rate of morbidity and mortality and can also improve the quality of life.

LIMITATIONS OF STUDY:

Limitations of our study include small sample size. Our study is cross sectional study , there is also a need for a prospective study including large population group to correlate the changes of vitamin D with different levels of progress of type 2 diabetes mellitus and its complications. Seasonal changes were not included in our study as it is going to affect the synthesis of vitamin D by sunlight.

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