ORIGINAL ARTICLE

A Cross-sectional Study on Vitamin D Status in Patients with Diabetic Nephropathy

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Abstract:

Background: Vitamin D deficiency is documented to be more prevalent in Type 2 Diabetes Mellitus (T2DM) and is associated with diabetic nephropathy. *Aim and Objective:* To investigate the vitamin D status in T2DM patients with and without nephropathy in eastern part of southern India. *Material and Methods:* This cross-sectional study included 150 study subjects. Routine laboratory measurements were done using commercially available kits on Vitros 5,1 FS auto analyzer from Ortho Clinical Diagnosis (OCD), United Kingdom, based on the principle of Reflectance Photometry. Serum 25-hydroxyvitamin D was measured by using chemiluminescence immunoassay methods. Results were analysed using IBM-SPSS version 20. *Results:* Vitamin D levels were observed to be lower in the diabetic nephropathy (18.44 ± 8.69 ng/mL) as compared to control (26.55 ± 7.88 ng/mL) and T2DM (19.64 ± 9.93 ng/mL) subjects and were correlated significantly with HbA1c and microalbumin. A markedly higher proportion of study subjects with vitamin D deficiency as well as insufficiency in T2DM and diabetic nephropathy group. *Conclusion:* Patients with type 2 diabetes and diabetic nephropathy had a low serum vitamin D level than healthy control. Vitamin D estimation in such patients may aid in the diagnosis and treatment as well as to prevent further complication.

Keywords: Type 2 Diabetes Mellitus, 25-hydroxyvitamin D, Diabetic Nephropathy, Micro-albuminuria, Lipid Profile

Introduction:

Diabetes Mellitus (DM) is a major public health issue in India. Statistics has shown that 61.3 million people with DM in 2011 and with an exponential increase to 69.9 million by 2025 probably landing at 79.4 million by 2030 [1]. Diabetes mellitus an endocrine disorder is characterized by pancreatic beta cell dysfunction, systemic inflammation and hyperglycaemia due to insufficient insulin production, insulin action, or both [2]. As the disease progresses, patients are at a higher risk for development of complications, such as retinopathy leading to blindness, nephropathy ending with renal failure, neuropathy resulting in nerve damage and atherosclerosis [3].

Diabetic Nephropathy (DN) is one of the major chronic microvascular complications in DM and a leading cause of End-Stage Renal Disease (ESRD), accounting for nearly half of all incident cases of ESRD in the developed world [4-5]. In 2014, the American Diabetes Association and the National Kidney Foundation reached an agreement in which DN was referred to as the chronic kidney disease due to DM, with a persistent estimated Glomerular Filtration Rate (eGFR) of < 60 ml per minute per 1.73m^2 or a urinary Albumin/Creatinine Ratio (ACR) of > 30 mg/gm for more than 3 months [4].

The pathogenesis of diabetic nephropathy is complex and thought to involve multiple pathways including activation of protein kinase C, stimulation of polyol pathway, formation of advanced glycosylation end products, increased oxidative stress and overproduction of free oxidative radicals and importantly, activation of the intrarenal Renin-Angiotensin System (RAS) [6]. Early alterations in diabetic nephropathy include glomerular hyper filtration, glomerular and tubular epithelial hypertrophy and the development of microalbuminuria, which is followed by thickening of glomerular basement membrane, accumulation of mesangial matrix and overt proteinuria, eventually leading to glomerulosclerosis and end stage renal disease [7].

Vitamin D is a fat soluble secosteroid obtained from diet as well as from skin. It is responsible for calcium and phosphate homeostasis [8]. Apart from calcium and phosphate homeostasis it plays a major role in multiple biological effects such as maintenance of immunity, vascular function, cardiomyocyte health, inflammation, insulin resistance and many more [9]. Vitamin D deficiency not only causes metabolic bone disease but also may increase the risk of many common chronic diseases. Studies have demonstrated vitamin D deficiency is prevalent in Type 2 Diabetes Mellitus (T2DM) patients and is found to be associated with diabetic nephropathy. Animal studies have suggested vitamin D deficiency and insufficiency have a potential role in the progression of kidney disease [10].

A low level of vitamin D is a prominent feature in patients with diabetic nephropathy [11]. Microalbuminuria is used as a guide for detection of nephropathy and shows increased prevalence with decreased vitamin D. Treatment with vitamin D in chronic kidney disease patient demonstrated an improved kidney function and decreased urinary albumin: creatinine ratio and improving the glomerular filtration rate [12]. Vitamin D has been shown to have renoprotective activity as vitamin D negatively regulates the RAS by suppressing renin expression [6]. Studies have also reported an independent association of vitamin D deficiency and a higher risk of the composite outcome in T2DM patients with diabetic nephropathy [13]. This has ignited a curiosity in us to investigate vitamin D status in T2DM patients with and without nephropathy in eastern part of southern India and to provide a new insight and methods for better management of ESRD.

Material and Methods:

This is a cross-sectional study carried out at R. L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, a constituent of Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, Karnataka India. This study was approved by the Institutional Ethics Committee and a written informed consent was obtained from all study subjects after being informed with the purpose of the study.

A total of 150 study subjects in the age group of 35-70 years of both genders were included. These study subjects were categorized into three groups each comprising 50 (n=50) study subjects: Group 1- Healthy controls; Group 2- Clinically proven T2DM and Group 3- T2DM with nephropathy. Patients with active urinary tract infection, chronic liver or heart diseases, malignancies, renal disease other than diabetic nephropathy, acute kidney injury along with patient on dialysis and taking vitamin D supplements were excluded from the study. The age and gender matched control

subjects were randomly selected from the general population. Clinical details such as anthropometric measurement (Age, gender, height, weight, systolic and diastolic blood pressure, pulse rate and diabetic duration) of all the study subjects enrolled in the study were obtained by one to one interview and the hospital medical records. Under strict aseptic condition and patient's comfortable position, 8 hours of fasting blood sample and 2 hours post-prandial blood sample were collected and split for analysis. A clean-catch midstream urine sample was collected into sterile container for estimation of Urinary Albumin Excretion (UAE).

Routine biochemical parameters including Fasting and post-prandial blood glucose, blood urea, serum creatinine, uric acid lipid profile [Total Cholesterol (TC), Triglyceride (TG) and High Density Lipoprotein-cholesterol (HDL-c), Low Density Lipoprotein-cholesterol (LDL-c), Very Low Density Lipoprotein-cholesterol (VLDL-c)] were analyzed using Vitros 5, 1 FS auto analyzer from Ortho Clinical Diagnosis (OCD), United Kingdom, based on the principle of reflectance photometry. Glycated Hemoglobin (HbA1C) was measured by high performance liquid chromatography method. Urinary albumin was measured by quantitative immunoturbidimetric method. Serum 25-Hydroxyvitamin D levels were measured using chemiluminescence immunoassay technique. A serum 25-hydroxyvitamin D level <20 ng/mL was considered as deficient. Statistical analysis was performed using IBM-SPSS statistical package 20. Normally distributed continuous values were expressed as Mean and Standard Deviation (SD) and compared using Analysis of Variance (ANOVA) test. Post *hoc* analysis was done by Bonferroni tests. Pearson correlation coefficient was used to demonstrate correlation between vitamin D with other parameters. The results with $p < 0.05$ were considered statistically significant.

Results:

A total 150 participants were enrolled for this study of which 105 were males and 45 were females. Mean ± SD value for anthropometric measurements and biochemical parameters of study subjects are shown in Table 1. Among these measures age, systolic blood pressure and diastolic blood pressure were significantly higher in T2DM and diabetic nephropathy patients as compared to control group. The mean duration of diabetes was higher in diabetic nephropathy subjects compared to T2DM group and it was 10 years and 4 months and was statistically significant.

The biochemical parameters in T2DM and T2DM with nephropathy study subjects were observed to be in higher range as compared to control group except Serum Glutamic Pyruvic Transaminase (SGPT) and Serum Glutamic Oxolacetic Transaminase (SGOT). Serum vitamin D concentration was significantly decreased in patients with T2DM and T2DM with nephropathy group as compared to the control group (19.64±9.93, 18.44±8.69, and 26.55±7.88 respectively). The same when observed in T2DM and T2DM with nephropathy, to our surprise there was no much difference and was not statistically significant. Serum calcium in control group was in the physiological reference of 9.08±0.33 mg/dL as compared to group III with T2DM with nephropathy which was 7.78±0.88 mg/dL and was statistically significant. About 1.03 mg/dL reduction in the serum calcium in group III may be contributed to the renal regulation mechanism of this molecule.

Table 1: Anthropometric Measures and Biochemical Parameters in Study Groups

Parameters	Group I (n=50)	Group II (n=50)	Group III (n=50)	F-value with Significance
Anthropometric Measurements				
Age (Years)	49.38 ± 11.13	57.16 ± 8.58	57.08 ± 9.35	10.5, p< 0.001[a,c]
BMI (Kg/m^2)	23.40 ± 3.62	24.03 ± 3.82	24.51 ± 4.19	0.99, p= 0.375
SBP (mmHg)	120.36 ± 5.59	125.6 ± 16.63	132.92 ± 14.45	11.55, p< 0.001[b,c]
DBP (mmHg)	78.96 ± 3.98	78.68 ± 8.84	84.20 ± 9.49	7.87, p= 0.001[b,c]
Diabetic Duration (Year)	-	6.02 ± 5.2	10.42 ± 8.22	10.2, p= 0.002[b]
Biochemical Parameters				
FBS (mg/dL)	93.74 ± 8.29	218.04 ± 63.84	149.24 ± 44.5	94.93, p< 0.001[a,b,c]
PPBS (mg/dL)	106.1 ± 19.11	290.74 ± 79.57	248.36 ± 59.4	137.2, p< 0.001[a,b,c]
HbA1C (%)	5.5 ± 0.48	10.9 ± 2.67	8.48 ± 2.2	93.01, p< 0.001[a,b,c]
Urea (mg/dL)	19.28 ± 5.9	25.38 ± 14.7	125.7 ± 48.19	208.04, p< 0.001[b,c]
SCr (mg/dL)	0.73 ± 0.2	0.69 ± 0.33	5.6 ± 2.85	146.1, p< 0.001[b,c]
UA (mg/dL)	4.66 ± 1.19	4.36 ± 2.17	8.15 ± 2.14	61.94, p< 0.001[b,c]
Calcium (mg/dL)	9.08 ± 0.33	8.89 ± 0.73	7.78 ± 0.88	52.17, p< 0.001[b,c]
Magnesium (mg/dL)	2.01 ± 0.18	1.7 ± 0.27	2.09 ± 0.49	18.54, p< 0.001[a,b]
Phosphate (mg/dL)	3.46 ± 0.48	3.44 ± 0.92	5.53 ± 1.87	43.37, p<0.001[b,c]
TC (mg/dL)	180 ± 37.98	166 ± 50.02	133 ± 41.9	15.31, p< 0.001[b,c]
TG (mg/dL)	170 ± 80.06	247.6 ± 130.5	167.26 ± 112.1	8.66, p< 0.001[a,b]
HDL-C (mg/dL)	42.9 ± 10.54	29.8 ± 9	29.16 ± 12.88	25.17, p< 0.001[a,c]
LDL-C (mg/dL)	101.7 ± 27.97	85.4 ± 41.13	70.68 ± 33.37	10.09, p< 0.001[c]
VLDL-C (mg/dL)	33.98 ± 16.02	51.14 ± 26.73	33.84 ± 23.55	9.7, p< 0.001[a,b]
Vit D (ng/mL)	26.55 ± 7.88	19.64 ± 9.93	18.44 ± 8.69	12.17, p< 0.001[a,c]
SGOT (U/L)	27.56 ± 9.12	28.72 ± 18.64	28.88 ± 17.04	0.108, p= 0.898
SGPT (U/L)	24.32 ± 10.24	28.86 ± 20.35	25.9 ± 17.1	0.982, p= 0.377
mALB (mg/L)	9.7 ± 7.7	56.6 ± 98.2	1101.8 ± 998.1	56.85, p< 0.001[b,c]

Values expressed in Mean ± SD. *p<0.05 considered as significant; *Group I: Healthy Control; Group II: Type 2 diabetes mellitus; Group III: Type 2 diabetic nephropathy; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; PPBS: Post Prandial Blood Sugar; HbA1C: Glycated Haemoglobin; SCr: Serum Creatinine; UA: Uric Acid; TC: Total Cholesterol; TG: Triglyceride; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; VLDL-C: Very Low Density Lipoprotein Cholesterol; Vit D: Vitamin D; SGOT: Serum glutamate-oxaloacetate transaminases; SGPT: Serum glutamate-pyruvate transaminases; mALB: Micro albumin] a- Group I vs Group II, b- Group II vs Group III, c- Group I vs Group III.*

Serum phosphate levels in the group I is in the physiological range compared to group III where it is grossly elevated with a value of 2.07 mg/dL. The same molecule we could not observe any difference in the group I and group II. This gross difference of serum phosphate between group I and group III cannot be compared with serum calcium as both these molecules are going in a reverse fashion and may be contributed to either hemoconcentration, elevated urea and serum creatinine levels or may be regulated by any other biochemical mechanism in addition to parat-hormone and which needs further evaluation at cellular level to understand the in-depth regulatory modalities.

TC and HDL-care grossly decreased in group III as compared to group I and group II. TG and LDL-c was decreased in group III compared to group I and group II. The significant decrease in the TC and HDL-c may be contributed to independent renal regulatory mechanisms as the liver enzymes are within the reference range and there is no hepatic involvement or affection by the elevated serum urea and creatinine levels. The unaltered TG levels in group III versus group I may be a contributory factor or secondary to the medical management of the nephropathy and which is correlated with the glycolytic regulatory metal ion magnesium.

Uric acid, a non-protein nitrogenous substance with a known potential as an oxidative stress parameter was grossly elevated to almost twice in group III as compared to group I. This was compared and correlated with the hypertensive status. Both systolic and diastolic hypertensions in group III were compared to group I however, found within the physiological range. The overview of the duration of diabetes of 10.42±8.22 years in group III and 6.02±5.2 years in group II indicates that a good diabetes mellitus monitoring may help postponement or nonoccurrence of diabetic nephropathy. We observed an elevated glycated hemoglobin level of 8.48±2.2% in group III compared to group I (5.5±0.48%). The same when observed in group II, a value of 10.9±2.67% which is comparable to the elevated glycemic measures FBS and PPBS which is in a higher range. The documented reduction of HbA1C in group III versus group II may be because of the awareness of the clinical consequences that the study subjects has landed with.

The microalbumin, a potent and known marker of diabetic nephropathy has been observed to be of a very higher value in group III as compared to group I and II. This magnitude of 114 times of elevated microalbumin in group III versus group I and 19 times more in group III compared to group II indicated the advanced renal damage and progression to end stage renal disease and also the extent of damage of the glomerular basement membrane.

Since our study included three groups and there is an absolute need for comparison between three groups, *post-hoc* Bonferroni analysis was performed and observed in group I versus group III.

a) The renal parameters were significant.
b) The lipid parameters except TG and VLDL-cwere significant and VLDL-c is a dependent lipid marker of TG.
c) Metal ions calcium and phosphate were significant but not magnesium.

Pearson's correlation of vitamin D versus the anthropometric and biochemical parameters were depicted in Table 2 which showed that

Table 2: Correlation of Vitamin D with the Clinical and Biochemical Parameters in T2DM (Group II) and Diabetic Nephropathy patients (Group III)

Variables	Type 2 DM (Group II)		Diabetic Nephropathy (Group III)	
	r value	p value	r value	p value
BMI	0.194	0.176	0.307	0.03*
SBP	0.301	0.034*	-0.245	0.086
FBS	0.278	0.05*	0.036	0.802
HbA1C	-0.103	0.478	0.025	0.865
Calcium	0.572	0.000*	0.31	0.028*
Phosphate	-0.002	0.989	-0.189	0.188
TG	-0.051	0.724	0.408	0.003*
HDL-C	0.172	0.232	-0.36	0.01*
mALB	0.08	0.582	-0.254	0.76

**p<0.05 considered as significant; BMI: Body Mass Index; SBP: Systolic Blood Pressure; FBS: Fasting Blood Sugar; HbA1C: Glycated Haemoglobin; TG: Triglyceride; HDL-C: High Density Lipoprotein Cholesterol; mALB: Micro albumin*

a) Increase systolic blood pressure, fasting blood sugar. Serum calcium showed positive correlation in group II.
b) Increased BMI, serum calcium and serum TG had a positive correlation in group III
c) HDL-C has a negative correlation. These data which are documented has given a clue that vitamin D mystery needs to be evaluated.
d) Fig. 1 depicting graphical representation of vitamin D versus HbA1c and microalbumin in the entire study population showed a negative correlation as shown in Fig. 1, indicated elevated HbA1c and microalbumin reduces the vitamin D. This can be linked to metabolism and regulation of vitamin D in the kidneys and 24-hydroxylase enzyme may have a role in this regard and needs further evaluation.

Depending upon vitamin D levels, study participants were categorised into subjects having sufficient (>30 ng/mL), insufficient (20-30 ng/mL) and deficient (<20 ng/mL) vitamin D level. Among all study participants (n=150), 70 (46.7%) study subjects were deficient, 54 (36%) insufficient and 26 (17.3%) had sufficient vitamin Das shown in Fig. 2. In this population with a good sunlight, millets being the staple diet and which is rich in calcium, with this area known for production of milk and consumption again contributing to the serum calcium has documented a decreased vitamin. This deficiency of vitamin D may be contributory to diabetes, diabetes with nephropathy, prediabetics or other molecules affecting the vitamin D metabolism such as the heavy metal ions and or fluoride which is high in the deep ground water this population is consuming.

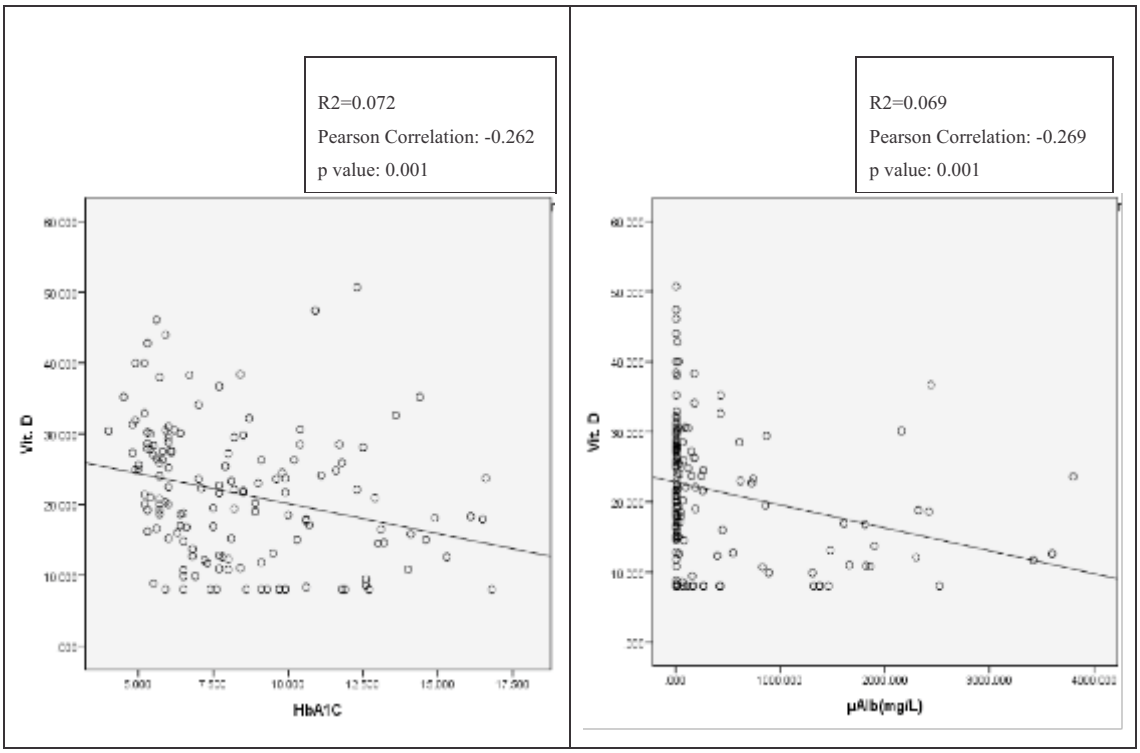

Fig. 1: Correlation of Vitamin D with HbA1c and Micro Albumin in Study Population
$p<0.05$ considered as significant; HbA1C: Glycated haemoglobin; µALB: Micro albumin

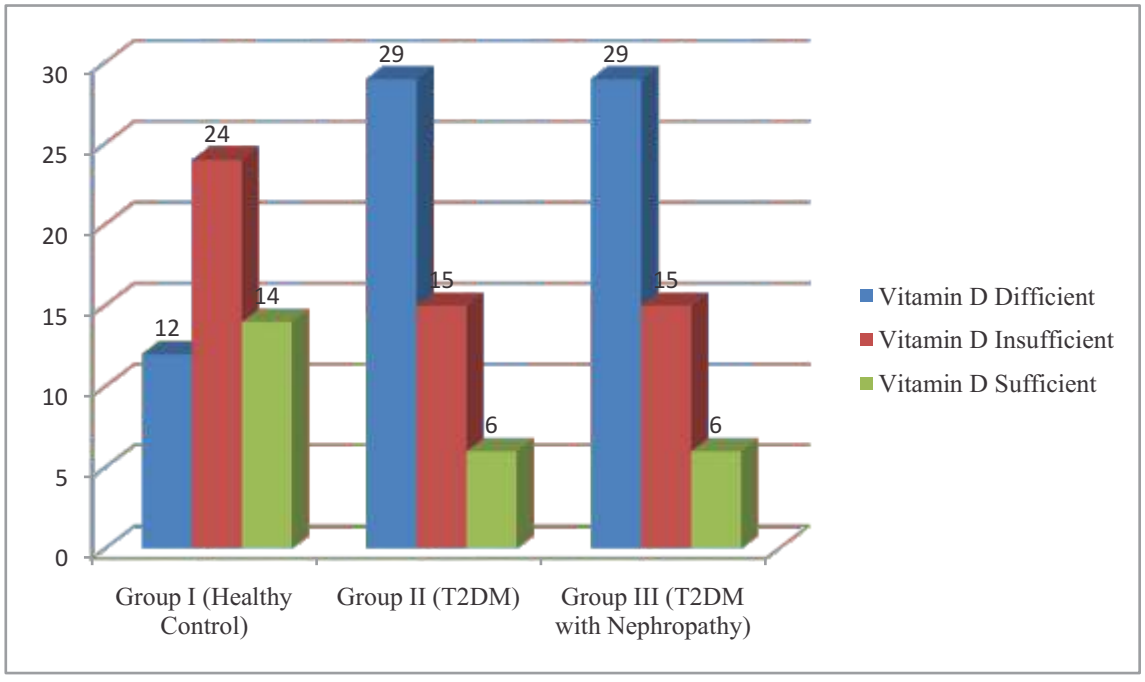

Fig. 2: Vitamin D Status in the Study Participants

Discussion:

Irrespective of geographical and socioeconomic status the prevalence of vitamin D deficiency among general Indian population is over 70% [14], while vitamin D deficiency is prevalent in 71.4% of people with type 2 diabetes in south India [15]. In the present study among anthropometric measurement mean age, systolic and diastolic blood pressure were higher in diabetic nephropathy than in control and T2DM study subjects. The average diabetic duration was almost double in nephropathy group when compared with T2DM group. We also observed a significant increase in diabetic profile parameters i.e. FBS, PPBS, HbA1C levels in T2DM and nephropathy group when compared with the control study subjects and similar results were shown by Patel and Kaila in 2019 [16].

Our study also showed a significant increase in TG in T2DM patients when compared with control study subjects indicating that increased blood sugar might have contributed to the elevated TGs. A significant reduction in HDL-c was observed in T2DM and T2DM with nephropathy subject. This results correlated with study conducted by Rai *et al*. in the year 2017 [17]. Altered lipid profile in T2DM is due to insulin resistance and defective insulin action on lipoprotein metabolism. It will also increase TG synthesis and promote quick breakdown of HDL-c [18]. DN which is considered as an independent risk factor for cardiovascular disease and altered lipid levels will increase the risk [17].

The prevalence of vitamin D deficiency is more common in diabetics compared with non-diabetics. The present study showed that serum vitamin D levels were lower in patients with diabetic nephropathy than in healthy control as well as in T2DM study subjects and a similar trend was shown in studies conducted by Peng *et al*. (2015) [6] and Xiao *et al*. (2016) [9]. However, there was no much difference observed in T2DM with nephropathy group. As renal functions decline in patients with DN, serum level of 1, 25 hydroxyvitamin D decreases progressively leading to active vitamin D deficiency. Low 25 hydroxyvitamin D levels in patients with CKD have been associated with a higher risk of all-cause mortality and faster progression of kidney disease [19]. In this study, decline in renal function was elucidated by increase in the blood urea and serum creatinine levels in patients with diabetic nephropathy when compared with control and T2DM study subjects. We also observed a declined trend in calcium level with vitamin D deficiency in the study population.

Vitamin D deficiency is a prominent feature in chronic kidney disease patients and was also elucidated a significantly higher incidence of vitamin D deficiency and insufficiency in diabetic nephropathy patients [4]. Among the study participants, 83% of patients were from T2DM and diabetic nephropathy group who had vitamin D deficiency and 55% of subjects with vitamin D insufficiency in the same study group. Our results are in agreement with the findings of study conducted by Gursoy *et al*. [20].

There was an inverse weak correlation between vitamin D and microalbumin level observed in diabetic nephropathy patients. However this correlation did not show statistical significance. A significant negative correlation was observed between Vitamin D with microalbumin level in total study population which was similar to previous study [9]. Increased urinary microalbumin might have decreased the serum albumin level and affected the serum vitamin D concentration.

Study conducted by Levin *et al*. has documented an independent association of low serum level of vitamin D with decrease in eGFR and a high urinary albumin: creatinine ratio in patient with diabetes, suggesting the involvement of vitamin D deficiency in the progression of DN [21]. Moreover, it has been also demonstrated that vitamin D reduces renin expression by inhibiting the renin gene promoter activity and supress high glucose induced angiotensinogen expression by blocking the nuclear factor-kappa B (NF-kB) signalling pathway and preventing RAS activation and hyper filtration which are characteristics of DN [22-23]. Thus, vitamin D is thought to be having a protecting role against development and progression of DN in type 2 diabetic patients.

A significant inverse correlation between HbA1c and serum vitamin D levels in the study population suggested a possible connection between glycaemic control and vitamin D metabolism. Vitamin D is thought to be involved in the pathophysiology of insulin resistance, insulin sensibility and β-cell function [9].

The effect of vitamin D on insulin secretion may be indirect as increasing intracellular calcium which could act as a mediator of insulin secretion and thus improve HbA1c level [24]. Studies conducted by Hutchinson *et al.* and Kositsawat *et al*. have observed a significant inverse correlation between HbA1c and serum vitamin D levels both in non-diabetic and in diabetic subjects [25-26] suggesting therapeutic effect of vitamin D on the diabetic control and thisneeds to be evaluated in further studies.

Findings of current study suggested that screening for vitamin D deficiency in patients with diabetes who are at higher risk of developing diabetic nephropathy may be of a greater benefit. The results of present study are limited by small sample size, confounding factors related to vitamin D deficiency and estimation and single-centric nature of study.

Conclusion:

Findings of our study suggested that patients with T2DM and diabetic nephropathy have a low serum vitamin D level than healthy control. An inverse significant correlation of vitamin D levels with microalbumin in diabetic nephropathy.

Determination of vitamin D status in T2DM with nephropathy may aid in the diagnosis and treatment as well as to prevent further complication.

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