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Association between Serum 25- Hydroxyvitamin D and Urinary Albumin in Type 2 Diabetes Mellitus

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Abstract

Background: Diabetic kidney disease (DKD) is the most common long-term microvascular complication and the leading cause of chronic kidney disease and end-stage renal disease. The main clinical manifestations of DKD are progressive albuminuria and decline in renal function. Vitamin D is transported through the human body in the bloodstream by binding to vitamin D binding protein (VDBP). The complex formation of VDBP/25-dihydroxyvitamin D, its filtration, and the reabsorption of this complex in the proximal renal tubular cells are critical for the retrieval and activation of vitamin D. People with renal damage, like diabetic patients with DKD, have increased urinary VDBP concentrations. This urinary loss of VDBP might have an effect on vitamin D levels. Inthis study, we determined the association between 25-hydroxyvitamin D (25OHD) level and urinary albumin in patients with type 2 diabetes mellitus.

Materials and Methods: This cross sectional analytical study included 108 patients with type 2 diabetes mellitus (type 2 DM). They were classified into two groups based on the level of urinary albumin-to-creatinine ratio (UACR). UACR < 30 mg/g was defined as normoalbuminuria, while UACR levels between 30–300 mg/g was defined as microalbuminuria. Serum 25OHD levels among two UACR groups were compared. The relationship between albuminuria and 25OHD was analysed.

Results: Vitamin D deficiency is more in type 2 DM with microalbuminuria than normoalbuminuria. The percentage of patients with vitamin D deficiency (<30 ng/mL) in the microalbuminuria group was significantly greater than that in the normoalbuminuria group (87 % vs. 40.7 %, P < 0.05). We also got significantly negative correlation between serum 25(OH)D concentrations and urinary albumin: creatinine ratio (UACR) ($r = -0.315$) $p < 0.001$.

Conclusion: This study states that an association exists between Vitamin D deficiency and microalbuminuria in type 2 diabetes. The prevalence of vitamin D deficiency in type 2 diabetes patients with albuminuria was overtly higher than that in patients without albuminuria. Thus, from the study we can conclude that patients with DKD are more likely to be vitamin D deficient than those without DKD.

Keywords: Diabetic kidney disease, microalbuminuria, Type 2 diabetes mellitus, Vitamin D deficiency

Introduction

Diabetes mellitus (DM) is a major global health concern, and one of the four noncommunicable diseases targeted for action by world-leading governments[1]. According to the International Diabetes Federation (IDF), there are currently 363 million people with diabetes worldwide and this number is expected to increase to 700 million by the year 2045.[2]

Vitamin D deficiency is worldwide an increasing medical problem. The fat-soluble prohormone vitamin D plays an important role in calcium and bone metabolism, cell proliferation and differentiation, and immunoregulation. The human body has two main sources of vitamin D: diet (20%) and exposure of the skin to sunlight (80%). Vitamin D is metabolized to 25(OH)D in the liver, followed by another hydroxylation in the kidneys that results in 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1,25(OH)2D reflects the reserve status of vitamin D. The production of 1,25(OH)2D3 in the kidneys is regulated by the plasma parathyroid hormone and serum calcium and phosphorous concentrations. Vitamin D is transported through the human body in the bloodstream by binding to vitamin D binding protein (VDBP). VDBP is a low-molecular-weight protein of 58 kDa, which predicts the bioavailability of 25(OH)D in the bloodstream. The complex formation of VDBP/25(OH)D, its filtration, and the reabsorption of this complex in the proximal renal tubular cells are critical for the retrieval and activation of vitamin D. People with renal damage, like diabetic patients with DKD, have increased urinary VDBP concentrations[3]. This urinary loss of VDBP might have an effect on vitamin D level[4].

Diabetic kidney disease (DKD) is the most common long-term microvascular complication and the leading cause of chronic kidney disease and end-stage renal disease. The main clinical manifestations of DKD are progressive albuminuria and decline in renal function. The pathophysiological changes of DKD are likely attributable to the metabolic and hemodynamic abnormalities; however, the exact underlying mechanisms are complex and may involve multiple pathways. Studies have demonstrated that the activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the causation of progressive renal injury in DKD. Vitamin D inhibits the activation of RAS by down-regulating renin expression and thus plays a protective role in DKD[5].

Studies on associations between vitamin D and albuminuria are inconsistent. Therefore, the current

study was carried out to evaluate the association between vitamin D deficiency and albuminuria in type 2 DM.

Material and Methods

Subjects

This cross sectional study was conducted in the department of Biochemistry of Indira Gandhi Government Medical College, Nagpur during September 2022 to August 2023. The study included 108 patients of diabetes mellitus attending Diabetic outpatient Medicine department who were diagnosed with type 2 DM as per the American Diabetes Association criteria[6]. All the patients were in the age group of 40- 65 years and were on antidiabetic treatment. Patients with hepatic disease, kidney disease, or hyperparathyroidism, patients who are on insulin, corticosteroids and vitamin D or calcium supplementation, pregnant and lactating women and those not willing to participate were excluded from the study. Because 1,25(OH)2D has a short half-life (approximately 15 h), 1,25(OH)2D levels are not considered a good indicator of vitamin D levels. As 25(OH)D is more stable in the blood than 1,25(OH)D, blood concentrations of 25(OH)D are 500 to 1000 times higher than 1,25(OH)2D concentrations. Therefore, to evaluate vitamin D deficiency and insufficiency, serum 25(OH)D concentrations are considered an adequate biomarker[7]. A normal level of vitamin D is defined as a 25(OH)D concentration greater than 50 ng/mL, vitamin D insufficiency is defined as a 25(OH)D concentration of 30–50 ng/mL, vitamin D deficiency is defined as a 25(OH)D level less than 30 ng/mL[8]. The diabetic patients were further classified based on their urinary albumin-to-creatinine ratio (UACR) into two groups: Group 1 included diabetic patients (n = 54) with UACR< 30 mg/g (normoalbuminuria) and group 2 included diabetic patients (n = 54) with UACR between 30-300 mg/g (microalbuminuria). Sample size was calculated based on the data obtained from previous studies using n-Master software. The study was approved by institutional Ethics Committee.

Sample collection

Fasting and 2-hour post-prandial venous blood samples were collected from all the individuals after an informed consent. Serum was separated and analysed for fasting and post-prandial blood glucose levels, HbA_{1c} levels and 25 Hydroxy Vitamin D levels. Glucose was measured by glucose oxidase-peroxidase method on Tranasia XL-640 autoanalyzer. HbA_{1c} and serum 25 Hydroxy Vitamin D levels were measured by Fluorescence immunoassay. Urinary albumin was measured by Pyrogallol red method and urinary creatinine by Jaffe's method. UACR is calculated by formula: UACR (mg/g) = Urine Albumin (mg/dL) / Urine Creatinine (g/dL). The measured variables were expressed in mean and standard deviation. Vitamin D levels were compared between 2 groups by using independent sample t-test. Statistical analysis was done using SPSS software version 29.

Result

The mean age in patients with type 2 diabetes mellitus was 56.9 ± 5.4 years. The majority of the participants were older than 50 years. The males were predominant in our study. The mean duration of DMT2 was 9.1 ± 3.7 years.

Table 1: Shows socio-demographic and clinical profile of type 2 diabetic patients. Vitamin D levels were lower (25.7 ng/ml ± 10.3) in patients with diabetes mellitus.

Parameters	Mean	Std. Deviation
Age (years)	56.9	5.4
Duration (years)	9.1	3.7
HBA1C (%)	8.1	0.8
Creatinine (mg/dl)	0.9	0.2
UACR (mg/g)	95.5	87.6
Vitamin D(ng/ml)	25.7	10.3

Table 2: Shows gender distribution of diabetic patients:

Gender	Frequency	Percent
Female	44	40.7 %
Male	64	59.3 %

Table 3: Shows that out of total 108 patients,70 patients (64.8 %) were deficient, 37 patients (34.3 %) were insufficient in vitamin D and only 1 patient (0.9 %) was having normal vitamin D level.

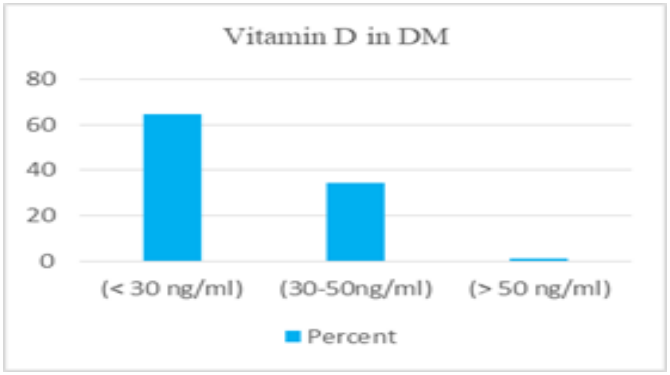
Vitamin D	N =108	Percent
(< 30 ng/ml)	70	64.8
(30-50ng/ml)	37	34.3
(> 50 ng/ml)	1	0.9

Table 4: Shows socio-demographic and clinical profile in group 1 and group 2 diabetic patients. Vitamin D deficiency is more in type 2 DM with microalbuminuria (group 1) than with normoalbuminuria (group 2).

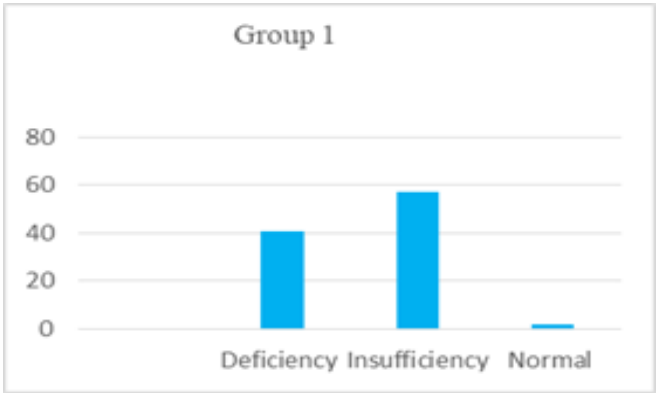
Parameters	Group 1	Group 2
Age (years)	54 ± 4.2	59.7 ± 4.3
Duration (years)	6.7 ± 1.8	11.5 ± 2.8
HBA1C (%)	7.9 ± 0.8	8.3 ± 0.8
Creatinine (mg/dl)	0.7 ± 0.1	1 ± 0.2
UACR (mg/g)	23.3 ± 5.4	167.7 ± 69.5
Vitamin D (ng/ml)	31.5 ± 9.9	20.5 ± 8.9

Table no 5: Shows vitamin D in group 1 and Group 2 Diabetic patients. The percentage of patients with vitamin D deficiency (<30ng/ml) in the microalbuminuria group was significantly greater than that in the normoalbuminuria group (87 % vs. 40.7 %, P < 0.05). The percentage of patients with vitamin D insufficiency (30-50 ng/ml) in the normoalbuminuria group was significantly greater than that in the microalbuminuria group (57.4 % vs. 12.9 %, P < 0.05). Only 1.8% of patients were having normal levels of vitamin D.

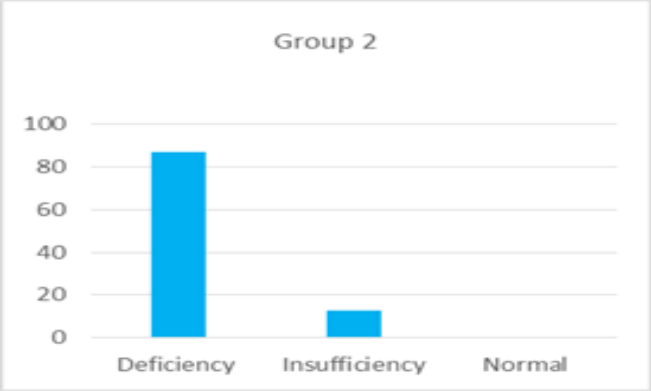
Vitamin D (ng/ml)	Group 1 UACR < 30	Group 2 UACR > 30	p-value
Deficiency (<30)	22 (40.7 %)	47 (87 %)	P < 0.05
Insufficiency (30 – 50)	31 (57.4 %)	7 (12.9%)	P < 0.05
Normal Levels (>50)	1 (1.8%)	0	Not significant



Graph 1: shows percentage of diabetic patients having deficiency, insufficiency and normal levels of vitamin D



Graph 2: shows percentage of group 1 diabetic patients having deficiency, insufficiency and normal levels of vitamin D



Graph 3: shows percentage of group 2 diabetic patients having deficiency, insufficiency and normal levels of vitamin D

We also got significantly negative correlation between serum 25(OH)D concentrations and urinary albumin: creatinine ratio (UACR) ($r = -0.315$) $p < 0.001$.

Discussion

In our study, vitamin D levels were lower in patients with diabetes mellitus. There are various possible mechanisms by which hypovitaminosis D increases risk of diabetes mellitus. Vitamin D receptor (VDRs) in pancreatic βcells play an important role in the progression of type 2 DM. Vitamin D deficiency is related to insulin secretion, insulin resistance, and βcell dysfunction in the pancreas. The secretion of pancreatic insulin is inhibited by vitamin D deficiency in the diabetic animal model. Administration of vitamin D restores glucose stimulated insulin secretion and promotes βcell survival by modulating the generation and effects of cytokines. Insulin secretion is also influenced by calcium concentration and flux through the βcells. Vitamin D regulates the function of calbindin, a calcium binding protein found in pancreatic βcells, and acts as a modulator of depolarization stimulated insulin secretion via regulation of intracellular calcium. PTH, which has its concentration regulated by vitamin D, is associated with insulin synthesis and secretion in the pancreas. Insulin sensitivity is also associated with vitamin D. By stimulating the expression of insulin receptors, vitamin D regulates insulin sensitivity[7].

The major contribution of this study is the finding an association between vitamin D and urine ACR, an index of diabetic nephropathy. In our study, patients with DKD are more vitamin D deficient than those without DKD which is consistent with the findings of other studies[9,10,11,12,13,14,15].

There are the several plausible mechanisms that explain the decreases in vitamin D. The complex of 25(OH)D and VDBP leaks with proteinuria. Uptake of 25(OH)D decreases due to down-regulation of megalin levels[7]. Megalin and cubilin, endocytic receptors in proximal tubule cells, are involved in the reabsorption of vitamin D binding protein from glomerular filtrates and the subsequent intracellular conversion of 25-hydroxyvitamin D2 to biologically active 1α,25-dihydroxyvitamin D3. Dysfunction of these receptors, which is commonly found in patients with diabetic nephropathy, even at early stages, may explain why vitamin D deficiency is often complicated in these patients[16].

This study suggested independent association of vitamin D with albuminuria. The question is whether vitamin D deficiency leads to albuminuria or albuminuria causes vitamin D deficiency. Our study measures 25(OH)D, which is the circulating metabolite produced in the liver that is later metabolized in the kidneys to 1,25(OH)2D. Therefore, it is difficult to establish cause and effect relationship between vitamin D deficiency and albuminuria in DKD and more studies are needed to find out it.

Conclusion

This study states that an association exists between Vitamin D deficiency and microalbuminuria in type 2 diabetes. The prevalence of vitamin D deficiency in type 2 diabetes patients with albuminuria was overtly higher than that in patients without albuminuria. Thus, from the study we can conclude that patients with DKD are more likely to be vitamin D deficient than those without DKD.

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