

## Vitamin D3 effect on Albuminuria in Type 2 Diabetes Mellitus patients in Northern Andhra Pradesh, India

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DOI: <https://doi.org/10.17511/ijmrr.2020.i04.06>

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**Introduction:** Vitamin D deficiency is a common disorder in diabetic patients and may be a risk factor for the progression of diabetic nephropathy. The present study aimed to assess the effects of a large dose of parenteral. Vitamin D on 24 hours albuminuria in T2DM patients. **Methods:** This prospective single-center study included 80 vitamin D deficient [25(OH) D <50 nmol/l] T2DM patients with an adequate glycemic control (HbA1c < 7.0%). Without any changes in anti-hyperglycemic or antihypertensive drugs, these patients were given a single high dose (600000 IU) of parenteral Vitamin D3. Then the changes in Vitamin D levels and 24 hours albuminuria were seen on follow up at 3 months. **Results:** Vitamin D3 supplementation improved 24 hours albuminuria. In the present study, Twenty-four-hour urinary albumin excretion decreased from 210.4 ± 101.2 to 204.6 ± 104.5. In males, it changed from 221.8 ± 99.7 to 216.1 ± 100.3 and in females, it changed from 192.3 ± 108.5 to 186.7 ± 113.1. There was a negative association of albuminuria with Vit D levels in the present study. **Conclusion:** Vitamin D3 supplementation significantly reduces 24-hour urinary albumin excretion in T2DM patients with Vitamin D3 deficiency.

**Keywords:** Albuminuria, RAS -Renin-Angiotensin System, T2DM-Type 2 Diabetes Mellitus, Vitamin D

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Manuscript Received  
2020-06-07

Review Round 1  
2020-06-23

Review Round 2  
2020-07-15

Review Round 3

Accepted  
2020-08-25

Conflict of Interest  
No

Funding  
Nil

Ethical Approval  
Yes

Plagiarism X-checker  
8%

Note



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## Introduction

Diabetic nephropathy is the leading cause of chronic renal disease and a major cause of cardiovascular mortality. Diabetic nephropathy is staged based on albuminuria and it is a marker for kidney injury [1].

In the pathogenesis of diabetic nephropathy, multiple pathways are engaged and the intrarenal RAS is activated [2].

Vitamin D3 negatively regulates the renin-angiotensin system (RAS) as it suppresses renin biosynthesis [3].

Therefore constant low vitamin D levels can worsen renal injury in diabetic patients. Vitamin D is vital for maintaining podocyte health, preventing epithelial-to-mesenchymal transformation, and suppressing inflammation [4].

Replacement with pharmacologic dosages of vitamin D receptor agonists has consistently shown a reduction in albuminuria [5] and glomerular inflammation and decreases in the renal fibrosis progression [6]. Emerging evidence in patients with nephropathy shows that vitamin D

Can reduce albuminuria even in the presence of angiotensin-converting enzyme inhibition [7]. In addition to reducing proteinuria, Vitamin D reduces insulin resistance [8], blood pressure, inflammation, and preserves podocyte loss, providing biologic plausibility to the notion that the optimum Vitamin D levels are renoprotective [9,10].

The present study aims to evaluate the effect of Vitamin D in reducing albuminuria in type 2 diabetic patients with Vit D deficiency.

## Methods

**Study design:** Prospective cohort study over a period of two years

**Study setting:** Department of Medicine, Great Eastern Medical School, and Hospital, Srikakulam, Andhra Pradesh over a period of two years from June 2018 to June 2019.

**Inclusion criteria:** All Type 2 diabetic patients who fulfill the following were included in the study.

01. Adequate Glycemic Control (Hba1c < 7).
02. Albuminuria (> 30 mg/ 24 hours).
03. Vitamin D Deficiency (< 50 nmol/l).

### Exclusion criteria

01. Uncooperative patients or unwilling to give informed written consent.
02. Vit D or Calcium supplements consumption in the previous 3 months.

**Participants:** 80 consecutive Type 2 Diabetes Mellitus patients who presented to our department and fulfilled the inclusion criteria.

**Statistical method:** Statistical analyses were performed using SPSS 20. The difference in mean levels of vitamin D and albuminuria before and after treatment with parenteral vitamin D were determined by paired samples T-test. Results were considered significant with a P-value of less than 0.05.

The study was approved by the ethics committee of the institute. 80 patients of T2DM with Vitamin D deficiency and adequate glycemic control were taken into study. Patients fulfilling the inclusion criteria were apprised of the type of study being carried out and their written consent was obtained. Vitamin D {25(OH) D} and 24 hours urinary albumin levels were obtained at the baseline. One single dose 600000-unit vitamin D3 was given intramuscularly and changes in 24 hours albuminuria were seen on follow up at 3 months.

## Results

The study included a total of 80 vitamin D deficient [25(OH) D <50 nmol/l] T2DM patients with adequate glycemic control. 50 out of 80 participants (62.5%) were above 50 years of age.

After supplementation with a single high dose (600000 IU) of parenteral Vitamin D3, 25(OH) D levels increased from  $32.94 \pm 3.84$  to  $57.21 \pm 4.84$  nmol/l. In males, it improved from  $34.68 \pm 4.08$  to  $58.04 \pm 4.86$  nmol/l and in females from  $32.44 \pm 3.94$  to  $56.92 \pm 4.72$  nmol/l (Table 1).

**Table-1: Vitamin D levels in all patients before and after supplementation.**

Variables	Mean $\pm$ SD	
	Vit D (basal)	Vit D ( After 3 months )
All Cases	$32.94 \pm 3.84$	$57.21 \pm 4.84$
Males	$34.68 \pm 4.08$	$58.04 \pm 4.86$
Females	$32.44 \pm 3.94$	$56.92 \pm 4.72$

Twenty-four-hour urinary albumin excretion decreased from  $210.4 \pm 101.2$  to  $204.6 \pm 104.5$ . In males, it changed from  $221.8 \pm 99.7$  to  $216.1 \pm$

100.3 and in females it changed from 192.3 ± 108.5 to 186.7 ± 113.1 (Table 2).

**Table-2: 24 hours of albuminuria levels in all patients before and after vitamin D supplementation.**

Variables	Mean ± SD	
	Albumin (basal)	Albumin ( After 3 months)
All Cases	210.4 ± 101.2	204.6 ± 104.5
Males	221.8 ± 99.7	216.1 ± 100.3
Females	192.3 ± 108.5	186.7 ± 113.1

## Discussion

Diabetic nephropathy is the most common cause of chronic kidney disease and end-stage renal disease, about 30% to 35% of dialysis patients have diabetes [11]. Diabetes is also the most common cause of renal replacement therapy requirements, in the United States [12].

Nephropathy is the serious complication of diabetes, defined by the development of proteinuria. Proteinuria is the main predictor of chronic kidney disease progression and it is now recognized as the first therapeutic target in the management of chronic kidney disease [13-17]. Drugs that block the renin-angiotensin-aldosterone system (ARBs) are effective in reducing proteinuria and slowing down the progression of the disease. ARBs are the first step in renoprotective antiproteinuric treatment. However their antiproteinuric effect is usually suboptimal and residual proteinuria continues to be a target for treatment, with additional renoprotective agents.

Clinically, many drugs have been tested to reduce residual proteinuria, and others are being tested. Growing evidence supports a potential role for vitamin D receptor (VDR) activation in reducing proteinuria. Vitamin D deficiency is highly prevalent in patients with chronic kidney disease even in the early stages [18-23]. In several studies, vitamin D deficiency is related to albuminuria, lower glomerular filtration rate and chronic kidney disease progression [18, 20, 24-27], Vitamin D metabolites inhibit the renin-angiotensin system and prevent the glomerulosclerosis. Vitamin D also decreases insulin resistance and decreases blood pressure as well [28,29].

Recently some studies were carried out regarding the effect of Vitamin D supplementation on reducing proteinuria in diabetic patients. However, the results of these studies are controversial. Therefore, the

Current study aimed to evaluate the effect of Vitamin D in reducing proteinuria in type 2 diabetic patients with Vitamin D deficiency. Out of 80 diabetic patients included in the study, 50 (62.5%) were above 50 years of age. This is by the epidemiological evidence of hypovitaminosis D being more prevalent in the elderly [30] because they produce 75% less cutaneous vitamin D3 than young adults. After supplementation with parenteral Vitamin D3, circulating levels of 25-hydroxy vitamin D were adequate in patients at follow up. So cholecalciferol via intramuscular route has effective and immediate response resulting in improved levels. There was a significant decrease in urinary albumin excretion on the follow up after Vitamin D was replenished.

Ahmadi [31] et al, in a clinical trial on diabetic patients with diabetic nephropathy and Vitamin D deficiency, found that Vitamin D prescription for three months had no effect on decreasing proteinuria. Kim [32] et al in the study on 63 diabetic patients with nephropathy and low Vitamin D levels found that repletion with cholecalciferol could decrease albuminuria. They concluded that dietary Vitamin D in patients with diabetic nephropathy may have a beneficial effect in delaying the progression of the disease. Ali Momeni [33] et al randomly enrolled 60 diabetic patients with proteinuria and Vitamin D deficiency or insufficiency in two equal groups. They saw that there was no difference between Vitamin D level in the case and control group at the beginning of the study, however, at the end of the study Vitamin D levels were significantly higher in the case group.

There was no difference in proteinuria between the case and control group at the beginning and the end of the study, while a significant difference between the changes of proteinuria before and after the study were seen in two groups. Bonakdaran [34] et al, found a significant correlation between microalbuminuria and vitamin D deficiency. Therapy with calcitriol had a beneficial effect on the albumin excretion rate, although this change was not significant. De Zeeuw [35] et al, in a study on diabetic patients, showed that 2 mg/day of paricalcitol also of rennin-angiotensin aldosterone blockers, could decrease proteinuria. Molina P [36] et al, conducted a study on nondialysis chronic kidney disease patients with albuminuria, low vitamin D, and high parathyroid hormone levels. They found that cholecalciferol administration led to a significant rise in mean vitamin D levels and

Urinary albumin-to-creatinine ratio significantly decreased at 6 months in the cholecalciferol group, and there was no change in the control group. Huang [5] et al, in a study, found that deficiency of Vitamin D was associated with microalbuminuria and administration of cholecalciferol significantly decreased albuminuria in the early stages of treatment. They concluded that conventional doses of cholecalciferol may have antiproteinuric effects on diabetic patients. Agarwal [37] et al, conducted a study in patients with residual proteinuria and stage 2-4 chronic kidney disease (CKD). They found a significant decrease in proteinuria in patients treated with paricalcitol compared with the control group, after 24 weeks of treatment. The authors concluded that the antiproteinuric effect of paricalcitol is a potential pharmacological action that requires further investigation. Fishbane [38] et al published a study comparing paricalcitol with placebo in patients with stage 2-3 CKD, over a follow-up period of six months. The decrease in the urine protein to creatinine ratio was significant in the paricalcitol group compared placebo group. Liu [39] et al found in a study of 50 patients with IgA nephropathy and residual proteinuria >0.8g/day that patients receiving calcitriol twice weekly had a significant decrease in proteinuria of compared with placebo, after 48 weeks of follow-up. In the National Health and Nutrition Examination Survey (NHANES III) [40], it was found that higher proportions of individuals with nephropathy have vitamin D deficiency than individuals without nephropathy. This suggests that optimum vitamin D levels should be maintained to prevent albuminuria and diabetic nephropathy. The present results were similar to most of the available studies in the literature. Thus it can be concluded that the prescription of Vit D in diabetic patients with nephropathy and Vit D deficiency may decrease proteinuria. The main limitation of this study is the sample size. Because of the sample size, this study can't be attributed to all the population. More such studies have to be done for a better outcome.

## Conclusion

The findings of the present study have potentially important public health implications as vitamin D supplementation can ameliorate albuminuria in type 2 diabetes which is the major cause of end-stage renal disease. This study encourages the design and conduct of studies that further explore the roles of Vitamin D in the nephropathy of T2DM patients for longer durations of follow up.

## What does the study add to the existing knowledge

In the current study, it is found out that Vitamin D3 supplementation significantly reduces 24-hour urinary albumin excretion in T2DM patients with Vitamin D3 deficiency. Hence more studies have to be done with a good sample size and longer duration of follow up to confirm this.

## Author's contribution

**Dr. P. Sreedevi:** Manuscript preparation

**Dr. T. Venugopal Rao:** Formulated the aims and objective of the study

**Dr. B. Annaji:** Data collection

**Dr. K. Sudheer:** Data analysis

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