

# Effect of parenteral vitamin D (D<sub>3</sub>) on albuminuria in T<sub>2</sub>DM patients

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## Abstract

**Background:** Vitamin D deficiency is a common disorder in diabetic patients and may be a risk factor for progression of diabetic nephropathy. The aim of our study was to assess the effects of large dose of parenteral Vitamin D on 24 hours albuminuria in T2DM patients. This is a first study of its kind, where we used single large dose parental vitamin D. **Methods:** This prospective single center study included 50 vitamin D deficient [25(OH) D <50 nmol/l] T<sub>2</sub>DM patients with an adequate glycemic control (HbA<sub>1c</sub> < 7.0%). Without any changes in anti-hyperglycemic or antihypertensive drugs, these patients were given a single high dose (600000 IU) of parenteral Vitamin D<sub>3</sub>. Then the changes in Vitamin D levels and 24 hours albuminuria were seen on follow up at 3 months. **Results:** Vitamin D<sub>3</sub> supplementation improved 24 hrs albuminuria. In this study twenty-four hour urinary albumin excretion decreased from 200.4 ± 103.3 to 198.4 ± 105.0 mg/24 hrs (p value 0.015). In males it changed from 212.1 ± 95.4 to 209.6 ± 96.9 (p value 0.046) and in females it changed from 188.6 ± 111.3 to 186.8 ± 112.9. (P value 0.041). There was a negative association of albuminuria with Vit D levels in our study with p value =0.001 at 3 months of follow up. **Conclusion:** Vitamin D<sub>3</sub> supplementation significantly reduces 24 hour urinary albumin excretion in T2DM patients with Vitamin D<sub>3</sub> deficiency.

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

## Introduction

Diabetic nephropathy is the leading cause of chronic renal disease and a major cause of cardiovascular mortality. Diabetic nephropathy is staged on the basis of 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 D<sub>3</sub> negatively regulates the renin-angiotensin system (RAS) as it suppresses renin biosynthesis [3]. Therefore constant low vitamin D level can worsen the renal injury in the 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 have consistently shown 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 reduce insulin resistance [8], blood pressure, inflammation and preserve podocyte loss, providing biologic plausibility to the notion that the optimum Vitamin D levels are renoprotective [9,10].

## Aims & Objectives

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To evaluate the effect of Vitamin D in reducing albuminuria in the type 2 diabetic patients with Vit D deficiency

**Variables:** Age, Gender, Fasting Blood Glucose, Postprandial Blood Glucose, HbA1c, Albuminuria, Vitamin D and Calcium.

## Methods

**Study design:** Prospective cohort study over a period of one year

**Study setting:** Department of Medicine SKIMS Medical College & Hospitals Srinagar over a period of one year from Nov 2015 to Nov 2016.

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

- 1) Adequate Glycemic Control (Hba1c < 7).
- 2) Albuminuria (> 30 mg/ 24 hours).
- 3) Vitamin D Deficiency (< 50 nmol/l).

### Exclusion criteria

- 1) Uncooperative patients or unwilling to give informed written consent.
- 2) Vit D or Calcium supplements consumption in previous 3 months.

**Participants:** 50 consecutive Type 2 Diabetes Mellitus patients who presented to our department and fulfilled the inclusion criteria.

**Data source:** Department of medicine, SKIMS Medical College & Hospitals Srinagar, Jammu & Kashmir, India

**Statistical method:** Statistical analyses were performed by 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 clinical research and ethics committee of institute. 50 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 hr urinary albumin levels were obtained at the baseline. One single dose 600000 unit vitamin D3 was given intramuscularly and changes in 24 hrs albuminuria were seen on follow up at 3 months.

## Results

Study included a total of 50 vitamin D deficient [25(OH) D <50 nmol/l] T<sub>2</sub>DM patients with an adequate glycemic control. 30 out of 50 participants (60%) were above 50 years of age. After supplementation with single high dose (600000 IU) of parenteral Vitamin D<sub>3</sub>, 25(OH) D levels increased from 33.34 ± 4.19 to 56.12 ± 4.70nmol/l. In males it improved from 33.99 ± 4.10 to 56.58 ± 4.89nmol/l and in females from 32.70 ± 3.94 to 55.65 ± 4.55 nmol/l (p value <0.001) (Tab 1).

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

Variables	Mean ± SD		p-value	Remarks
	Vit. D (basal)	Vit. D (3 months)		
All cases	33.34 ± 4.19	56.12 ± 4.70	< 0.001	S
Male	33.99 ± 4.10	56.58 ± 4.89	< 0.001	S
Female	32.70 ± 3.94	55.65 ± 4.55	< 0.001	S

**Table-2: 24 hrs albuminuria levels in all patients before& after vitamin D supplementation**

Variables	Mean ± SD		p-value	Remarks
	Alb. (basal)	Alb. (3 months)		
All cases	200.3 ± 103.3	198.2 ± 1054.8	0.005	S
Male	212.1 ± 95.4	209.6 ± 96.9	0.046	S
Female	188.6 ± 111.3	186.8 ± 112.9	0.041	S

Twenty-four-hour urinary albumin excretion decreased from  $200.4 \pm 103.3$  to  $198.4 \pm 105.0$  (p value 0.015). In males it changed from  $212.1 \pm 95.4$  to  $209.6 \pm 96.9$  (p value 0.046) and in females it changed from  $188.6 \pm 111.3$  to  $186.8 \pm 112.9$  (p value 0.041) (Tab 2).

## 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 requirement, 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 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 the 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 we aimed to evaluate effect of Vitamin D in reducing proteinuria in the type 2 diabetic patients with Vitamin D deficiency.

Out of 50 diabetic patients included in the study, 30 (60%) were above 50 years of age .This is in accordance to the epidemiological evidence of hypovitaminosis D being more prevalent in elderly [30] because they produce 75% less cutaneous vitamin D<sub>3</sub> 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 not any effect on decreasing of 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 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 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 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 in addition of rennin-angiotensin-aldosterone blockers, could decrease proteinuria. Molina P [36] et al, conducted a study on non-dialysis chronic kidney disease patients with albuminuria, low vitamin D and high parathyroid hormone levels. They found that cholecalciferol administration led to 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 paricalcitol group compared placebo group. Liu [39] et al found in 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 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.

Our results were similar with most of the available studies in literature. Twenty-four-hour urinary albumin excretion decreased from  $200.4 \pm 103.3$  to  $198.4 \pm 105.0$  (p value 0.015). In males it changed from  $212.1 \pm 95.4$  to  $209.6 \pm 96.9$  (p value 0.046) and in females it changed from  $188.6 \pm 111.3$  to  $186.8 \pm 112.9$  (p value 0.041). Thus we concluded that prescription of Vit D in diabetic patients with nephropathy and Vit D deficiency may decreased proteinuria.

## Conclusion

The findings of our study have potentially important public health implications as the 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 nephropathy of T2DM patients for longer durations of follow up.

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**Permission of IRB:** Yes

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