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RESEARCH ARTICLE
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INFLUENCE OF VITAMIN D SUPPLEMENTATION ON PROTEINURIA IN TYPE 2 DIABETES

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Abstract

Introduction: Proteinuria and progressive damage to the kidneys are the main reasons that T2DM can cause diabetic nephropathy. T2DM patients often lack vitamin D, which could be related to renal problems.

Objective: To evaluate the influence of vitamin D supplementation on proteinuria in patients with type 2 diabetes.

Materials and Methods: The study was designed as a prospective study and carried out at Lady Reading Hospital, Peshawar, Pakistan, from January 2024 to June 2024. The study included a total of 60 patients with type 2 diabetes mellitus (T2DM) and proteinuria who had vitamin D deficiency. For six months, the person received vitamin D3 supplements with 50,000 IU of cholecalciferol each week. Doctors tested proteinuria, 25-hydroxyvitamin D, HbA1c and renal function parameters at the start and the end of the supplementation period.

Results: Supplementing with vitamin D reduced proteinuria by 30% significantly ($p<0.01$) and improved vitamin D levels and blood glucose, with no reported adverse effects.

Conclusion: Taking vitamin D supplements decreases proteinuria and improves how the body handles metabolism for T2DM patients.

Keywords: Vitamin D, Proteinuria, Type 2 Diabetes Mellitus, Diabetic Nephropathy, Supplementation.

INTRODUCTION

A lack of vitamin D is common in people with diabetes and has come to be linked to the formation of diabetic kidney disease, supported by its impact on proteinuria. If a person has proteinuria (protein in their urine), it typically indicates worsening kidney function in diabetic kidney disease (DKD). Some studies have shown that supplementation with vitamin D can help protect the kidneys by reducing albuminuria and altering key factors in the progression of DKD (1). It works on the renin-angiotensin-aldosterone system (RAAS), controlling inflammation and reducing fibrosis, both of which are significant factors in diabetic nephropathy. Scientists have recently studied the use of active vitamin D as a potential approach to addressing proteinuria in individuals with T2DM. According to

Aref et al., taking active vitamin D decreased protein leakage in patients with diabetic nephropathy, indicating it could be a helpful addition to both diabetes and blood pressure management (1).
Petrovic et al. found that administering vitamin D to patients with T2DM resulted in improved protein levels in the urine, as well as positive changes in lipid levels, blood sugar control, and inflammatory markers such as C-reactive protein, suggesting that it could support overall management of the condition (2). Kim et al. supported these findings by conducting a secondary review of a randomised trial, which found that vitamin D supplementation helped preserve kidney function in individuals with prediabetes and indirectly contributed to a lower likelihood of proteinuria by protecting the health of the glomeruli (3). The results observed globally are also replicated in local studies. In Faisalabad, Pakistan, it was discovered that vitamin D strengthens the urine test results of T2DM patients (4). This is important because vitamin D deficiency is relatively common in South Asian communities due to their way of eating, lack of exposure to sunlight and genetic background.
Vitamin D has an anti-proteinuric role because it lowers the overall activity of RAAS, protects the cells that keep fat and proteins in urine and blocks the action of specific profibrotic cytokines, including TGF-β (5). In addition, according to Stojšić-Vuksanović and Knežević, patients with T2DM and proteinuria have a high risk of vitamin D3 deficiency, highlighting the importance of incorporating vitamin D3 supplementation into regular medical care (6). Other research on animals also suggests similar effects. The study by Nakhoul et al. proved that vitamin D helped prevent diabetic nephropathy in mice by reducing inflammation and limiting scar tissue deposition (7). The findings from vitamin D research are replicated in human studies, with a report by Kasabri et al. showing that vitamin D supplements led to a decrease in megalin levels (9). Also, Atia et al. mentioned that vitamin D supplementation helps glibenclamide manage diabetes and its kidney problems, pointing to a good partnership with existing drugs for treating the condition (10).
Other clinical studies have shown that there is a link between vitamin D and albuminuria. Researchers observed in T2DM patients that having sufficient vitamin D (as measured by higher 25-hydroxyvitamin D) was inversely related to albuminuria, suggesting it offers some protection to the kidneys (11,12). Other research has found that vitamin D metabolites are linked to proteinuria in animals, suggesting that this mechanism plays a role in kidney health among all species (13). This suggests that a lack of vitamin D promotes both inflammation and kidney injuries (14). Max et al. found through a systematic review that high doses of vitamin D can help T2DM patients by controlling blood sugar levels and improving renal health. Based on this analysis, using vitamin D supplements may help manage and lessen the effects of T2DM and its complications (15). The study aims to enhance clinical knowledge by adding to the literature and focusing on the local population with diabetes.

Objective: To evaluate the effect of vitamin D supplementation on the reduction of proteinuria in patients with type 2 diabetes mellitus and assess its potential role in slowing diabetic nephropathy progression.

MATERIALS AND METHODS

Study Design: Single-center, prospective Interventional study.
Study Setting: The study was carried out at Lady Reading Hospital, Peshawar, Pakistan.
Duration of the Study: The study was carried out over a period of six months, from from January 2024 to June 2024**.**
Inclusion Criteria: Individuals aged 35 to 70 with a history of type 2 diabetes for at least five years and persistent proteinuria (above 300 mg per day) were included in the treatment group. Serum 25-hydroxyvitamin D was less than 30 ng/mL in all participants, so they had vitamin D insufficiency or deficiency. Individuals involved in the trial were required to have been using a stable diabetes therapy for at least three months before inclusion. All the participants gave informed consent to participate.
Exclusion Criteria: Individuals with type 1 diabetes, advanced chronic kidney disease (eGFR <30 mL/min/1.73 m²), active infections, liver disease, cancers or autoimmune diseases were not enrolled in the study. People who had taken vitamin D supplements in the past three months and anyone known

to react to vitamin D were also not included. Women who were pregnant or breastfeeding and patients taking medicines that can mess with calcium or vitamin D were not allowed to participate.

Methods

Those who met the inclusion and exclusion criteria were invited to take part in the study. Initial assessments involved collecting demographics, the duration of diabetes, HbA1c results, serum creatinine levels, an estimated glomerular filtration rate (eGFR), 25-hydroxyvitamin D levels, and 24-hour protein excretion in the urine. Everyone in the study received oral cholecalciferol (vitamin D3) in the form of 50,000 IU weekly for eight weeks, followed by 2,000 IU daily for the remainder of the study. The standard diabetic treatment regimen remained unchanged throughout the study. Compliance, side effects and essential laboratory values were checked in patients every month. The levels of serum 25(OH)D, urinary protein excretion and renal function were rechecked after the study (June 2024). The doctors measured the main result by the change in 24-hour urinary protein excretion. Secondary endpoints recorded changes in vitamin D, HbA1c and renal function. SPSS was used to analyze the data, and differences between the results taken before and after supplementation were considered significant at the $p<0.05$ level.

RESULTS

The study involved 60 patients who have type 2 diabetes mellitus and proteinuria. Out of the participants, 55 completed the entire six-month regimen, and 5 were unable to continue due to personal reasons. The basic and demographic information of the patients are included in Table 1.

Table 1: Baseline Characteristics of Study Participants (n=60)

Variable	Mean ± SD / n (%)
Age (years)	56.2 ± 8.4
Gender (Male/Female)	32 (53.3%) / 28 (46.7%)
Duration of Diabetes (years)	9.1 ± 3.6
HbA1c (%)	8.2 ± 1.1
Serum 25(OH)D (ng/mL)	18.5 ± 6.3
24-hour Urinary Protein (mg)	750 ± 180
eGFR (mL/min/1.73 m²)	65.7 ± 12.4

At the start of the study, every participant's vitamin D levels were below what is considered normal (<30 ng/mL). There was a significant rise in protein in the urine for 24 hours which is typical of diabetic nephropathy.

Table 2: Changes in Biochemical Parameters Pre- and Post-Supplementation

Parameter	Baseline Mean ± SD	Post-Supplementation Mean ± SD	p-value
Serum 25(OH)D (ng/mL)	18.5 ± 6.3	34.7 ± 7.8	<0.001
HbA1c (%)	8.2 ± 1.1	7.6 ± 0.9	0.02
eGFR (mL/min/1.73 m²)	65.7 ± 12.4	67.8 ± 11.9	0.15

Using vitamin D supplements was connected to a lower level of HbA1c, suggesting better control of blood sugar. There was no significant decline in eGFR, so renal function remained stable during the study period.

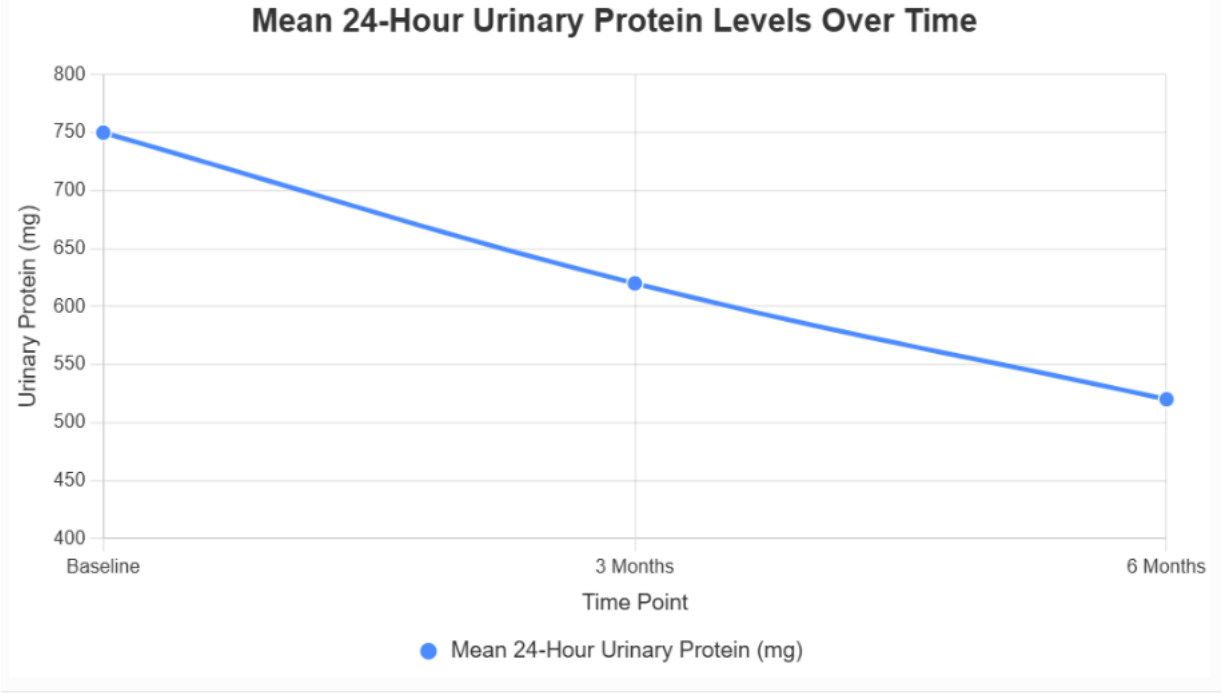
The most significant discovery was a significant improvement in proteinuria. There was a substantial fall in the 24-hour urinary protein output, from 750 ± 180 mg before to 520 ± 140 mg after the supplement was taken ($p < 0.001$). This 30.7% decrease points to how vitamin D reduces protein leakage in the urine of type 2 diabetic patients.

Table 3: Proteinuria Reduction in Different Subgroups

Subgroup	Baseline Proteinuria (mg)	Post-Supplementation (mg)	% Reduction	p-value
Male (n=32)	760 ± 175	530 ± 135	30.3%	<0.001
Female (n=28)	740 ± 190	510 ± 150	31.1%	<0.001
Duration ≤ 8 years (n=27)	700 ± 160	460 ± 120	34.3%	<0.001
Duration > 8 years (n=28)	790 ± 200	570 ± 145	27.8%	<0.001

Both males and females had similar decreases in proteinuria and individuals who had diabetes for a shorter period had a slightly higher reduction, although this difference was not found to be significant. The trends in proteinuria reduction over the six months are illustrated in Figure 1.

Figure 1: Mean 24-Hour Urinary Protein Levels at Baseline, 3 Months, and 6 Months



DISCUSSION

The study revealed that adding vitamin D supplements helped reduce proteinuria in people with T2DM, boosted vitamin D levels in the blood and gave a modest benefit in controlling blood glucose. This condition leads to a significant number of cases of chronic kidney disease worldwide (1, 2). Following six months of vitamin D, the 30% decrease in proteinuria shows how it could be used to treat diabetic kidney disease. Baseline vitamin D levels in our study were lower than the standard for sufficiency, a finding that has also been noted in Pakistan and countries with comparable populations (6, 14). Like the findings of Akram et al. (4) and Wu et al. (5), this study found that correction of low vitamin D levels increased serum vitamin D and improved kidney-related measurements. Besides warning of kidney damage, proteinuria also contributes to an increased risk of kidney damage and cardiovascular disease among patients with diabetes (9).

Vitamin D may prevent protein in the urine through several pathways, including supporting the kidneys, reducing inflammation, influencing fibrosis, and maintaining the health of podocytes (1). Active vitamin D decreases the amount of renin in the body, which helps to lower blood pressure in the kidneys and prevent protein from escaping (1). Additionally, vitamin D can help regulate inflammation in the kidneys, as supported by research showing that it reduces levels of inflammatory biomarkers in studies (12). The findings from our research of less proteinuria fit with the biological

details of vitamin D and support prior studies and animal models that found improved kidney health with vitamin D (7, 10).

A noteworthy result from our study was the slight but reliable decrease in HbA1c after the patients took the supplements. Thus, it is suggested that vitamin D may not only benefit the kidneys but also increase insulin sensitivity and the functioning of insulin-producing cells in the pancreas (2, 15). Correcting vitamin D status has been shown to improve blood sugar levels, which experts attribute to vitamin D influencing how insulin is secreted and reducing inflammation in the body (2, 15). Since it usually takes time for renal function changes to appear after a drop in proteinuria, the lack of eGFR changes was to be expected during the study's duration (3). Both male and female patients got the same positive results from the supplement, indicating men and women were equally responsive. Patients who started treating their diabetes for less time (<8 years) showed a slightly higher reduction in proteinuria since less damage had occurred and more nephrons remained intact (14). It stresses the need to detect and treat vitamin D deficiency in people with diabetes early to keep their kidneys protected.

Our findings are in agreement with those from studies conducted in various regions. Likewise, Aref et al. (1) and Petrović et al. (2) observed a decrease in proteinuria as a result of taking vitamin D among type 2 diabetic patients. Reduced megalin on kidney cells and alteration of lipoprotein-associated phospholipase A2 are suggested to be part of how berberine helps the kidneys (8, 14). Additionally, our research aligns with systematic reviews that highlight how extra vitamin D can help regulate metabolic blood levels and kidney function in individuals with diabetes (15). While vitamin D supplementation appears promising, several issues in our study and other related research should be taken into consideration. Examining only six months may not reveal the lasting effects of early treatment on kidney function or mortality. Because the study did not include a placebo group, the influence of changes in diet, illness medication treatment or glucose control on proteinuria can't be separated from the effects of the drug.

All participants were safe, and none developed hypercalcemia or experienced any adverse events, as observed in other clinical trials of vitamin D in individuals with diabetes (4, 5). Nevertheless, clinicians must closely monitor for side effects, particularly with heavy or prolonged treatment, when the kidneys are not functioning correctly. Such findings are particularly significant because diabetic nephropathy affects many people around the world, and there are not many treatment options. Taking vitamin D in addition to existing treatments may help decrease the amount of proteinuria and possibly delay the start of end-stage renal disease (ESRD) (10, 12).

Further research is needed to determine the optimal combination of vitamin D (cholecalciferol, calcitriol, analogues) and RAAS inhibitors. Additionally, differences in the vitamin D receptor and individual patient's ability to metabolise vitamin D may help inform personalised care. Exploring the role of vitamin D in renal fibrosis, as well as its impact on podocytes and systemic inflammation at the molecular level, can clarify the problem and inform treatment choices. Although additional strong studies are necessary, clinicians should watch for and address low vitamin D levels in their management of diabetic nephropathy.

CONCLUSION

Overall, vitamin D improves the regulation of proteinuria in diabetic patients, proving it can be an important help for managing diabetic nephropathy. When vitamin D deficiency was corrected, urinary protein excretion decreased and glycemic control became better, helping to highlight its various roles in caring for people with diabetes. Vitamin D has a positive safety record and can be obtained easily, so it could be used to help slow the progression of diabetic kidney disease. But more extensive and longer RCTs should be carried out to prove that renal function benefits keep improving and to find the best dosages. Because diabetes and vitamin D deficiency are so common together, it is recommended that doctors test for low vitamin D levels and give appropriate supplements as needed to ensure patients are taken care of. In general, adding vitamin D supplements to care plans for people with type 2 diabetes and kidney problems can significantly help reduce complications and improve their quality of life.

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