THE EFFECT OF VITAMIN D SUPPLEMENTATION ON ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background

Proteinuria is the hallmark of diabetic kidney disease. Patients with Diabetes mellitus is deficient in Vitamin D compared to normal people, which has some beneficial effects on albuminuria.

Objectives

To assess the effect of Vitamin D supplementation on albuminuria in diabetic patients.

Materials and Methods

In this prospective case-control study, we collected 80 diabetics with albuminuria from the 1st of May, 2022 to the 1st of September, 2022 at Shar Teaching Hospital, Sulaimaniyah, Iraq. All patients had type two diabetes mellitus, albuminuria (urinary Albumin/Creatinine of > 30 mg/g, morning sample, twice) and Vitamin D deficiency (less than 30 ng/ml). All were on Angiotensin-converting enzyme inhibitors or Angiotensin two receptor blockers. They were divided into 2 groups: Cholecalciferol supplementation is given in group one (50000 IU weekly for 2 months), and no treatment is given in group two. After eight weeks: the urine Albumin/Creatinine ratio and serum vitamin D were measured in both groups.

Results

All patients completed the study course. Those with vitamin D supplementation showed a significant lowering of albuminuria compared to control (31% vs 3% reduction, p value 0.001), which was parallel to the significant increase in the vitamin D level in the treatment arm (≈ 6.25 ng/ml vs 0.5 ng/ml in the control arm). The response was slower in smokers in the treatment group. Baseline status of blood glucose, gender and age did not affect the outcome.

Conclusion

Vitamin D deficiency may exacerbate albuminuria and supplementation has beneficial effects on proteinuria in diabetic nephropathy. The interference of inflammatory process and plasma renin activity can explain the effect. Further studies with larger sample sizes and longer duration may be needed for confirmation of the efficacy.

Keywords: *Albuminuria, Diabetic nephropathy, Vitamin D..*

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INTRODUCTION

The prevalence of diabetes mellitus among the population is increasing nowadays [1] and nephropathy is one of its common and deleterious complications, which can be diagnosed by the detection of proteinuria and is classified based on its severity and stages [2].

There are many mechanisms explaining hyperglycemia-induced nephropathy, which include: High blood pressure with increased intraglomerular pressure, defective carbohydrates and lipid metabolism with increased profibrotic factors like TGF-B and fibroblasts, oxidative stress, and advanced glycation end products [3,4].

Measures for prevention of proteinuria include: lifestyle modifications (diet, smoking cessation, weight reduction, and exercise), sodium restriction, blood pressure and glucose controlling [2,5].

According to the guidelines; Blockage of renin-angiotensin-aldosterone system [Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin 2 receptor blockers (ARB)] and Sodium Glucose transporter 2 (SGLT2) inhibitors together with GLP-1 agonist and statins are recommended as treatment of diabetic kidney disease. (5,6)

Despite these measures; the progression of proteinuria and cardiovascular complications can't be retarded in diabetics, this raises the hypothesis of interference of other factors in progression of diabetic nephropathy. Diabetic patients are more deficient in Vitamin D level compared to general population, and this can lead to adverse outcomes like cardiovascular disease, diabetic nephropathy and deterioration of chronic kidney disease.This association was reported in many studies, and can be explained by the dysfunction of the vitamin D hydroxylase enzyme that takes part in the first hydroxylation process of the vitamin D activation [7].

The role of supplementation with vitamin D in diabetic kidney disease is not well established yet; it's shown in some trials on animals that the expression of renin, angiotensin and angiotensin 1 receptor in the kidneys are increased in vitamin D knockout mice than in wild type mice who were diabetic. There is also increased inflammatory substance TGF-B expression more in diabetic vitamin D knockout mice [8-12].

It's also shown in many trials on humans that correction of vitamin D is associated with lowering albuminuria and further renal damage in diabetics; however, these trials were on small sample-sized populations and also some other trials showed non-promising results [13-15] .This study aimed to assess the effect of vitamin D supplementation on proteinuria in diabetics who are deficient in vitamin D levels.

PATIENTS AND METHODS

Our prospective case control study was conducted among eighty patients from the 1st of May,2022 to September,2022, at the Shar teaching hospital/ Sulaimaniyah/ Iraq. All of the patients had type two diabetes mellitus, with albuminuria (urinary albumin/ creatinine ratio (ACR) of >30 mg/g morning sample, twice) and vitamin D deficiency (less than 30 ng/L) and were on their regular ACEI or ARB, which have their antiproteinuric effect. After explanation and taking written informed consent from them; they were divided into two arms: one group was exposed to vitamin D analogue; Cholecalciferol 50000 IU weekly for 8 weeks in addition to their treatment, and the other group left with their conventional treatment. After 8 weeks; we measured urine Albumin/creatinine ratio and serum vitamin D level in both groups. The serum vitamin D level was measured by chemilumiscent immunoassay (CLIA) method and the albumin/creatinine ratio by immunoturbidimetric and kinetic colorimetric assays. The results in the two groups was compared and subjected to SPSS 22. The data were analyzed for comparison of the arms using line graphs. A p-value of <0.05 is regarded as significant. All information remained confidential, so written informed consents were taken from all the patients. The inclusion criteria included: patients with diabetes and proteinuria, on their antiproteinuric agents (either ACEI or ARB), and deficient in vitamin D level. The exclusion criteria were: patients with non-diabetic proteinuria, non proteinuric diabetics, those who are not on their antiproteinuric agents, and those who refuse to be enrolled in the study. The study was completed under permission of Kurdistan Higher Council of Medical Specialties

Table 1. basic characteristics of the involved patients.

Variable	Control arm (no Vit D therapy)	Treatment arm (Vit D therapy)	p-Value
No. of patients	40	40	
Mean age(yr)	54.8±9.83	55.2±11.91	**0.87**
HbA1C	7.8±0.66	8.13±0.85	**0.07**
Gender			
Male	25(%62.5)	26(%65)	**1**
Female	15(%7.5)	14(%35)	
Smoking			
Yes	14(35%)	16(%40)	**0.8**
No	26(65%)	24(%60)	
Mean eGFR (ml/min/1.73m2	>60	>60	**??**
Baseline ACR (mean)	53.5±19.48	69.40±25.47	**0.02**
Baseline S.vit D(mean)	16.5±4.7	17.5±.6	**0.3**

RESULTS

A total of eighty (80) patients were collected between May, 2022 and September 2022, all completed the study visits. Baseline characteristics of the participants are expressed in Table 1; both arms were relatively matched in their baseline characteristics except for the significant difference in baseline ACR in the treatment group versus the control.

A significant decrease in albuminuria is noted in the Vitamin D therapy group; from 69.40±25.47 at the baseline to 47.77±21.20 at 8 weeks and a mean reduction of - 21.62±19.41 (%31)(p-value <0.001) . group. (53.5±19.48 Vs 52.15±18.43, p-value 0.75), similar differences is noticed in regard to changes in Vit D level between the two arms is shown in Table (2). When a cut-point of 20% reduction in ACR from baseline were assigned a significant difference in the number and rate of the two groups was identified 23(%57.5) in treatment Vs 2(5%) in Control arm with p-value of < 0.001 as shown in table 2.

When a model of logistic regression analysis was performed among all responders with ≥20% reduction in ACR, Vit D therapy and being non-smoker were strong predictors of ACR reduction to a aforementioned value. See table 3 The response was significantly slower in the smokers compared to non-smokers in the treatment group as is shown in Figure (2).

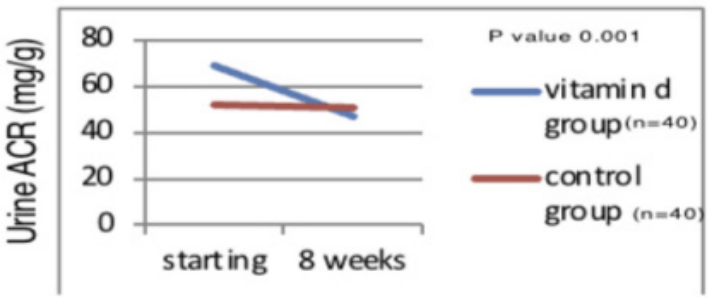

Figure 1. comparing urine ACR in the treatment vs control group.

Table 2. Mean change in Vit D and urinary Albumin-Creatinine Ratio (ACR) for both groups from baseline to last visit.

Variable	Control arm		Treatment arm		p-Value
Vit D Baseline(mean)	16.5±4.7	p-vale 0.6	17.5±0.6	p-value 0.001	**0.3**
Vit D at 2 momths(mean)	17.02±4.28		23.80 ± 6.33		**0.001**
Mean Vit D change	+ 0.52±2.13		+ 6.25±5.02		**0.001**
ACR Baseline(mean)	53.5±19.48	p-vale 0.75	69.40±25.47	p-vale 0.001	**0.02**
ACR at 2 months (mean)	52.15±18.43		47.77±21.20		
Mean ACR change	- 1.66±6.62(3%)		- 21.62±19.41 (%31)		**0.001**
No.(%) ACR reduction by ≥20%	2(5%)		23(%57.5)		**0.001**

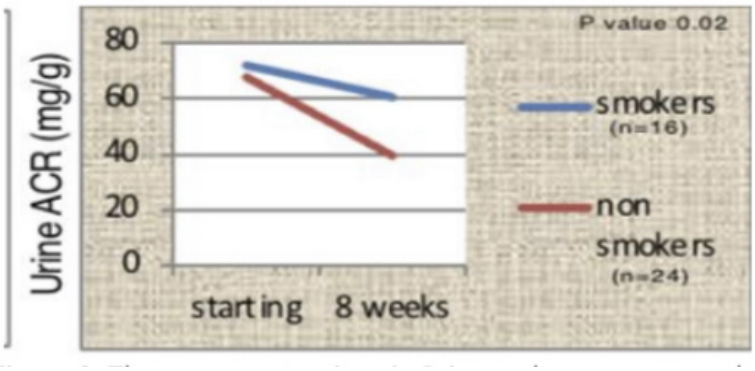

Figure 2 . The response to vitamin D in smokers and non-smokers.

Table 3. Logistic regression analysis for predictors of ACR reduction by ≥%20.

Factors	B	Standard error	Wald test	Degree of freedom	Significance	Odds ratio
Age	-.015	.035	.182	1	.669	.985
Vit D therapy	4.502	.974	21.351	1	.000	90.159
Gender	-.300	.848	.126	1	.723	.741
Smoking	-2.978	.891	11.166	1	.001	.051
HbA1C	-.091	.495	.034	1	.854	.913
Constant	-.794	4.344	.033	1	.855	.452

DISCUSSION

Vitamin D deficiency nowadays is an important health concern, and its prevalence in the diabetic patients is more than healthier populations as shown in many studies. The effect of its deficiency on diabetic kidney disease is still a matter of debate [21-24].

In our study; Treatment with vitamin D in patients who were deficient in this substance led to a significant decrease in proteinuria (p valve 0.001) that was parallel to the significant raise in serum vitamin D level in the treatment group, which could be due to the vitamin D's involvement in the RAS system as well as it's anti inflammatory activity [25,26].

This outcome is also seen in some regional and international studies. This result is similar to the outcome of a study that is done in Iran by Momeni et al in 2017 among 60 patients which showed that normalization of vitamin D is associated with lowered proteinuria (p value 0.0001) [27].

Fishbane et al in 2009 completed a randomized trial showed that Paricalcitol administration to patients with proteinuric kidney disease led to a significant reduction in protein excretion (p value 0.04) [28] .Also the similar effect of Paricalcitol was found among 281 diabetic patients on ACEI/ARB by de Zeeuw et al in VITAL study; after 24 weeks of the administration, the urinary ACR reduced in the treatment group versus placebo group (16% vs 3%) [13].

Molina P et al, published a study on the effect of the vitamin D analogue on proteinuria in stage 3 and 4 chronic kidney disease. There was a significant decrease in albuminuria in the treatment group compared to the control within 6 months (53% vs 7%) [29].

Some other studies; however, showed no significant change in the results. In a study done by Ahmedi among a number of patients with albuminuria and vitamin D deficiency, divided into treatment and control group. The administration of vitamin D, although resulted in normalization of vitamin D level, there was no significant change in albuminuria [16].

A systematic review and a meta-analysis published by Derakhshanian et al have shown that although vitamin D deficiency showed significant adverse relationship with progression of diabetic nephropathy (p value 0.002); the supplementation with this substance showed non-significant result of lowering albuminuria (p value 0.51) [30] .Snijder on the other hand; in a study showed no significant relationship between level of vitamin D and blood pressure and renin level [31].

During our study; we have noticed that the effect of vitamin D is slower in smokers. This could be due to some deleterious effects of smoking on diabetic nephropathy. In the literature; it's shown that smoking increases the carboxyhemoglobin level, prothrombotic factors, and stimulated platelet activation, which induces inflammation, oxidation, and poor endothelial cell function, which in turn leads to glomerulosclerosis, and tubular atrophy [32].

This effect of smoking is also demonstrated in other studies; in 2017, Ning Jiang et al published a meta-analysis which showed that smoking may increase the probability of diabetic nephropathy in diabetics irrespective of the major risk factors like hypertension, duration of the diabetes and body mass index [33].

CONCLUSION

The low vitamin D level may exacerbate diabetic kidney disease and supplementation has beneficial effects on proteinuria in diabetic nephropathy. However, further controlled studies with larger sample size is needed for confirmation, and the potential adverse effects of this vitamin in chronic kidney disease like hypercalcemia and hyperphosphatemia should be put in consideration.

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