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EFFECT OF VITAMIN D SUPPLEMENTATION ON KIDNEY FUNCTION IN ADULTS WITH PREDIABETES

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Abstract

Background: In clinical research, low serum 25[OH]D levels have been linked to increased levels of proteinuria and decreased levels of eGFR.

Objective: This study examined how vitamin D supplementation affected kidney outcomes in a pre-diabetic cohort.

Method: Adults who met two of the three glycemic parameters for pre-diabetes and were overweight or obese and at high risk of developing type 2 diabetes were randomised to receive 4000 IU of vitamin D3 daily versus a placebo. The mean length of therapy was 18 months. Kidney outcomes comprised deterioration in the Kidney Disease: Improving Global Outcomes (KDIGO) risk score (low, moderate, high, or very high) on two successive follow-up visits following the baseline visit, as well as mean fluctuations in eGFR & urine albumin-to Creatinine ratio (UACR).

Results: Among 600 participants (mean age 59 years, body mass index 33.1 kg/m2, serum 25(OH)D 29.3 ng/ml, eGFR87 ml/min per 1.73 m2, UACR 11 mg/g, 79.5% with hypertension). Over a mean follow-up of 18 months, there were 20 cases of KDIGO worsening in group A and 16 in the placebo group (hazard ratio, 0.79; 95% confidence interval [95% CI], (0.42 to 1.41). The mean difference in eGFR from baseline was -1.2 ml/min per 1.73 m2 (95% CI, 1.4 to 0.8) in the group A and 0.7 ml/min per 1.73 m2 (95% CI, 0.6 to 0.3) in the placebo group.

Conclusion: Vitamin D supplementation did not significantly influence advancing KDIGO risk scores, UACR, or eGFR in people with pre-diabetes who were not chosen based on blood 25(OH)D concentration.

Keywords: Vitamin D, Pre-diabetes, Kidney outcomes, Serum 25[OH]D levels, Glycemic parameters

Introduction

Pre-diabetes is defined by the American Diabetes Association (ADA) as a condition that raises the risk of type 2 diabetes and cardiovascular disease rather than as a disease[1]**.** Comorbidities, such as hypertension, are prevalent in people with pre diabetes and act as a moderator of risk for patient-relevant effects, such as renal disease. Furthermore, it has been proposed that low levels of circulating 25[OH]D are a risk factor for renal disease type 2 diabetes[2] and kidney disease[3-6]**.**
Many studies point to the possible Reno protective function of 1,25(OH)2D, or activated vitamin D. Preclinical research indicates that 1,25(OH)2D increases insulin sensitivity[7]**,** boosts endothelial function[8, 9], and helps control the renin-angiotensin system [9], which can all influence blood pressure and preserve renal vascular health [10]. Furthermore, in mice with vitamin D receptor deletion, hyperglycemia-induced renal damage can increase albuminuria and glomerulosclerosis[9]**.** While other research has shown no link [11, 12], human investigations have demonstrated that low circulating 25(OH)D concentration can predict all phases of kidney disease, from albuminuria to failure of the kidneys[3-6]**.** In the Third National Health and Nutrition Examination Survey (NHANES III), the incidence of albuminuria was boosted for each drop in quartile of blood Concentration of 25(OH)D[3]**.**In the Australian people cohort, It was shown that a blood 25(OH)D level lower than 20 ng/ dl has been independently linked with prevalent albuminuria[4]**.** Inadequate circulating 25(OH)D level was also related to advancement to kidney failure in the NHANES III cohort 6. Despite evidence indicating links between bad circulating 25(OH)D levels and kidney illness, few research studies have explored the efficacy of vitamin D treatment on renal outcomes.
This study aimed to assess the results of vitamin D supplementation on renal outcomes and the incidence of kidney damage in the pre-diabetes population.

Methods:

This study focuses on renal outcomes using a retrospective analysis. This single-centre, randomised trial examined the potential impact of vitamin D supplementation on persons with prediabetes. The institutional review board authorised the study; as it was retrospective, consent was unnecessary.
The study conducted at multiple centers including Fauji Foundation Hospital Rawalpindi and HBS Medical and Dental College Islamabad in the duration from June, 2023 to November, 2023. According to the ADA standards, eligible participants had to meet at least two of the three glycemic parameters for prediabetes: plasma glucose while fasting, 100–125 mg/dl; two hours following a 75-g oral glucose stress, plasma glucose 140–199 mg/dl; Hba1c in between 5.7%–6.4%. Minimum age of 25 was another requirement for enrollment in the study. Their body mass index should range from 22.5 to 42 kg/m2. Low serum 25(OH)D levels were not required for eligibility. A previous diagnosis of hyperparathyroidism, kidney stones, hypercalcemia, bariatric surgery, usage of anti-diabetic or weight-loss drugs, any glycemic parameter in the diabetes range, and an eGFR of below fifty ml/min per 1.73 m2 of body surface area were among the main exclusion criteria.
Two groups were randomly assigned to the participants. One soft gel containing 4000 IU of vitamin D3 (cholecalciferol) was given to group A, whereas group B did not receive a vitamin D3 pill. A computer produced the randomisation. Participants were advised to restrict the amount of vitamin D they took outside of the trial to 1000 IU daily from all dietary supplements and calcium to 600 mg per day. Follow-up appointments were made at month three, month six, and after every six months after that. Following an 8-hour overnight fast, blood and urine were collected for kidney outcomes at baseline, months 03, 06, 12, and 18.
Using the risk categories developed by the Kidney Disease: Improving Global Outcomes (KDIGO) organisation, we assessed the amount of time until kidney function deteriorated. Based on the urine albumin-to-creatinine ratio (UACR, mg/g) and estimated GFR (ml/min per 1.73 m2), there are four KDIGO risk categorisation levels. A two-visit sequence of at least one KDIGO risk category rise from baseline was considered a worsening of kidney function, as validated by KDIGO. Since previous research has indicated that vitamin D may impact both kidney parameters, time to deterioration in the KDIGO risk group was selected as a combined outcome to include both eGFR

and UACR. The following kidney endpoints were also analysed: time to meeting eGFR<60 ml/min per 1.73 m2 (among subjects with eGFR≥60 ml/min per 1.73 m2 at baseline); time to meeting UACR≥30 mg/g (among many participants with UACR<30 mg/g at baseline). These changes in eGFR and UACR were also considered continuous variables. Standardised protocols were utilised to measure height, weight, and blood pressure. The participant's medicines and dietary supplements were noted and examined at every follow-up visit. SPS version 21 was used for statistical analysis.

Results:

A total of 600 patients in our study met our inclusion criteria. They were divided into two groups. Group A received 4000 IU of vitamin D3 (cholecalciferol) daily, while Group B did not get 4000 IU of vitamin D3.

Table 1: Demographic details of participants

Variable	**Group A n=300**	**Group B n=300**	**P-VALUE**
Age, years	57±13	59±11	0.87
Male	160(53.3%)	157(52.33)	0.24
Female	140(46.7)	143((47.7%)	0.64
Family history of diabetes (first-degree relative), no. (%)	194(64.6)	214(71.3)	0.45
Smoking, no. (%)			
Current	34(11.3)	26(8.6)	0.71
No	169(56.6)	163(54.3)	0.26
Former	97(32.33)	111(37)	0.45
Physical activity, total MET hour/week (*Mean ±SD)*	111±169	113±161	0.45
Body mass index, kg/m^2 (*Mean±SD)*	32.3±5.1	33.5±4	0.34
Systolic BP, mm Hg	129±152	128±15	0.52
Diastolic BP, mm Hg	76±10	77±10	0.24
Hypertension, no. (%)[e]	231(77)	245(81.6)	0.25
Hemoglobin A1c, %	6±1.9	5.9±.2.4	0.42
Serum creatinine, mg/dl	0.7±0.5	0.9±0.3	0.65
eGFR category, no. (%)			
≥60 ml/min per 1.73 m^2	285(95)	289(96.3)	0.54
<60 ml/min per 1.73 m^2	15(5)	11(10.7)	0.41
eGFR, ml/min per 1.73 m^2 (*Mean±SD)*	86±16	85±17	
Urine albumin-to-creatinine ratio, mg/g (*Mean±SD)*	10±51	12±53	0.64
KDIGO classification, no. (%)			
Normal/low risk	271(90.3)	274(91.3)	0.32
Moderate risk	17(5.6)	15(5)	0.61
High risk	7(2.3)	9(3)	0.24
Very high risk	5(1.6)	2(0.6)	0.13
Serum 25-hydroxyvitamin D, ng/ml (*Mean±SD)*	29.8±11.2	28.8±12.2	0.43

Most of the study population in our study was males, as shown in Table 1. 64.6% of the population in Group A had a family history of diabetes. In comparison, this percentage was 71% in Group B.77% IN GROUP A were hypertensive, while 81.6% of the Group B population had a history of hypertension. Mean HbA1c in group A was 6±1.9 while in group B, it was 5.9±.2.4.Both groups were comparable in demographics, as shown in Table 1.

Table 2 Kidney Outcome

Variable	**Group A n=300**	**Group B n=300**	**Group A vs Group B Hazard Ratio**
Higher KDIGO risk (confirmed)	10(3.36)	16(5.3)	0.79 (0.42 to 1.41)
Higher KDIGO risk (confirmed and unconfirmed)	27(9)	31(10.3)	1.84 (1.43 to 1.14)
eGFR<60 ml/min per 1.73 m^2	29(9.6)	30(10)	1.24 (0.89 to 1.62)
UACR≥30 mg/g	21(7)	25(8.3)	0.72 (0.68 to 1.27)

Ten cases of confirmed deterioration in KDIGO risk score (increase in KDIGO risk category on two consecutive visits) were found in group A over a mean follow-up of eighteen months, while sixteen cases were found in group B (hazard ratio, 0.79; 95% CI, (0.42 to 1.41). There were more occurrences in both groups but no differences between them in a sensitivity analysis when the result included those whose KDIGO risk category had worsened at the last visit (and hence was unconfirmed) (hazard ratio, 1.84; 95% CI, 1.43 to 1.14). The incidence of UACR≥ 30 mg/g and eGFR<60 ml/min per 1.73 m2 are also shown in Table 2, and they did not differ among both groups.

Variable	Baseline	Month 3	Month 6	Month 12	Month 18
eGFR ml/min per 1.73 m^2 [b]					
	Group A				
	86±16	87±17	86±16	87±16	88±16
The difference compared with the baseline		-1.1	-0.9	-0.42	-0.3
	Group B				
	85±17	85±16	86±16	87±17	88±17
The difference compared with the baseline		-1.6	-0.3	-0.5	
P-value	**< 0.01**				
UACR, mg/g					
	Group A				
	10±51	11±55	12±61	13±45	14±54
The difference compared with the baseline		2.2	3.5	3.6	
	Group B				
	12±53	13±51	13±43	12±33	
The difference compared with the baseline		0.8	1.8	3.7	4.5
P-value	**0.25**				

Table 3: Variations in UACR and eGFR over time in both groups

Table 3 displays the mean change in UACR and eGFR at each FOLLOW-UP VISIT. In general, the mean eGFR declined more in the vitamin D group than in the placebo group, with a statistically significant difference of P= < 0.01. With all post-baseline data weighted equally, the average change throughout the follow-up period was indicated by this decline in eGFR. There was no statistically significant difference in the mean UACR change between the groups.

Discussion

Vitamin D3 supplementation did not significantly affect renal outcomes in individuals with pre-diabetes, including a combined kidney outcome based on the KDIGO risk category, combining eGFR and UACR values. Supplementing with vitamin D did not seem to help when eGFR and UACR were evaluated continuously as independent factors. Compared to the placebo group, the vitamin D group saw a statistically significant, but clinically less significant, decrease in eGFR of roughly one ml/min per 1.73 m2. This decline in eGFR is the average change throughout the follow-up period, weighted equally by all post-baseline data. A drop in eGFR with 1,25(OH)2D equivalents, such as paricalcitol, has been seen in specific previous investigations[13, 14]**.** It was hypothesised that this decrease was caused by a shift in creatinine metabolism instead of a natural decline in GFR. However, there is no evidence that cholecalciferol influences the metabolism of creatinine. Future vitamin D research might use a technique other than creatinine-based GFR assessment.

Few trials have examined the impact of vitamin D supplementation on renal outcomes, despite observational studies reporting links between low circulating 25(OH)D levels and kidney disease[3-6]**.** A recent research called the Vitamin D and Omega-3 Trial to Reduce the Risk and Treat Diabetic Kidney Disease (VITAL -DKD) found that supplementing older adults with established

diabetes with 2000 IU/d of vitamin D3 at five years of age did not significantly affect their eGFR or UACR when compared to a placebo [15]. Comparable to our study, most individuals had adequate circulating 25(OH)D level at baseline by current criteria[16] and normal renal function (mean eGFR of 86 ml/min per 1.73 m2). Interestingly, subgroup analyses in patients with lower 25(OH)D seem to support vitamin D intervention in our study and the VITAL-DKD trial.

Few research has examined renal disease incidents in people with pre-diabetes, and the majority have defined pre-diabetes using fasting glucose.[17, 18]). About 7% of participants in the present trial developed eGFR, 60 ml/min per 1.73 m2, and almost 8% had UACR.30 mg/g following an average 18-month follow-up. As a result, our research offers crucial information on the normal course of kidney function in pre-diabetes since comparable groups reporting both eGFR and UACR were absent from the literature. A disadvantage of the study is its brief trial period; neither the vitamin D nor the placebo group showed any clinically significant improvement in kidney parameters. Second, according to current guidelines, individuals were not chosen based on their vitamin D status, so the cohort would be regarded as having an adequate vitamin D level.

Conclusions

The study found that among those with high-risk pre-diabetes but lower baseline risk for adverse renal outcomes, vitamin D3 treatment had no meaningful effect on the course of kidney disease. Since baseline 25(OH)D concentrations were not used to select participants, we cannot rule out a Renal advantage for those who are vitamin D deficient.

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