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Evaluating the effects of uric acid level reduction on serum vitamin D level in hemodialysis patients

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Abstract

Introduction: The role of vitamin D in metabolism, bone-mineral regulation, and anti-oxidation effect has drawn researchers' attention toward its exact role in hemodialysis.

Objectives: In this study, the effect of uric acid level reduction on serum 25-hydroxy vitamin D levels in hemodialysis patients was assessed.

Patients and Methods: This study is a triple-blind clinical trial conducted on 81 hemodialysis patients suffering from asymptomatic hyperuricemia. Serum uric acid levels were assessed at the start of the study. Then patients were divided randomly into two groups of intervention and control. The intervention group received 100 mg of allopurinol tablets daily for two months. The control group received placebo tablets for the same duration. At the end of the study, 25-hydroxyvitamin D and uric acid levels were assessed. Data were analyzed using SPSS software and chi-square, independent t test, Mann-Whitney U, and Spearman's rank correlation tests.

Results: In our study, two groups of control and intervention were similar in terms of patients' demographic and hemodialysis characteristics. After the intervention, compared to the control group, the serum uric acid levels were significantly lower in the intervention group, while the level of 25-hydroxyvitamin D showed no significant difference between the two groups.

Conclusion: In this study, no significant effect of uric acid lowering therapy with vitamin D elevation in hemodialysis patients was detected.

Keywords: Vitamin D, 25-hydroxyvitamin D, Uric acid, Hemodialysis, End-stage renal disease, Clinical trial

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT2015041721803N1; <https://en.irct.ir/trial/18996>, ethical code#IR.SKUMS.1395.231).

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Introduction

The significant role of vitamin D in most diseases makes it a start point for many researchers to study vitamin-D-deficiency-related diseases. As in chronic renal failure, insufficient levels of 25-hydroxyvitamin D cause a wide range of diseases from osteodystrophy to cardiovascular and immunologic issues (1). Nevertheless, higher than normal levels of vitamin D can cause serious damage such as dynamic bone disease or extra-osseous calcification (2). Keeping vitamin D between the safe edges in hemodialysis patients is an everyday challenge for nephrologists (3).

It was detected that uremic condition perturbs the production and bioavailability of vitamin D. Furthermore, purine derivations hypothetically reduce the pre-active form of vitamin D like 25-hydroxy vitamin D (4). The study by Vanholder et al is one of the few studies conducted to support the idea that reducing uric acid levels can raise the vitamin D levels in renal failure patients (5). Another study by Takir et al on middle-aged to elderly population

of the middle east supported the idea that people with higher levels of uric acid had lower levels of vitamin D (6).

Objectives

The aim of this study is to assess the effect of reducing serum uric acid levels on serum 25-hydroxy vitamin D levels as the precursor for active vitamin D.

Patients and Methods

Study design

This study is a triple-blind clinical trial, conducted in university hospitals of Chaharmahal and Bakhtiari province, Iran. In this study, the sample volume was by far greater than the one in the study by Vanholder et al (5). We attempted to reduce the cofounder factors by including a control group and to choose our sample population from the hemodialysis patients who had the same care. Ninety-two patients, who met the inclusion criteria, entered the study. The inclusion criteria were specified as follows:

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■ Implication for health policy/practice/research/medical education

To find the effect of uric acid level reduction on serum 25-hydroxy vitamin D levels in hemodialysis patients, we conducted a randomized triple-blind clinical trial study on 81 patients. Results showed that after the intervention, compared to the control group, the serum uric acid levels were significantly lower in the intervention group while the level of 25-hydroxyvitamin D showed no significant difference between the two groups. Therefore, we conclude that no significant effect of uric acid lowering therapy with vitamin D elevation in hemodialysis patients was detected.

- Known cases of end-stage renal disease (ESRD)
- Regular hemodialysis
- Hyperuricemia (serum uric acid >5.5 mg/dL)

The exclusion criteria were specified as follows:

- Taking uric acid-reducing medications
- Taking vitamin D supplements at the beginning of the study
- Suffering gout arthritis
- Hypertension due to high levels of uric acid

As for stopping the study, the following criteria were set:

- Showing any reverse effect or allergy symptoms linked to allopurinol
- Hospitalization in intensive care unit
- Any pause or change of method in the hemodialysis routine
- Immigration out of the province or changing health care provider unit
- Patient who will not continue taking medication

Sample volume in each control and intervention group was determined according to prior studies in this field with the following equation (5):

$$n = \frac{2 \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 SD^2}{d^2} = 46$$

Patients then were randomly divided into two groups with 46 patients for each as control and intervention groups, using computerized random numbers. The control and intervention groups were labeled by a confidential third party as group "A" and group "B". All patients' blood samples were obtained prior to the study and the serum level of uric acid was measured. Then, the intervention group received 100 mg of allopurinol (made by Hakim Company) for 60 days. At the same time, the control group received placebo tablets (made in Isfahan University of Medical Sciences, Pharmacology Department) for the same duration of 60 days. The pills administered in this study shared the same appearance and were packed in "A" and "B" packages by a confidential third party. After the time mentioned, both groups' blood samples were obtained and the level of uric acid and 25-hydroxyvitamin D were measured. Uric acid level was measured using a BT1300 spectrophotometer and 25-hydroxyvitamin D

was measured using electrochemiluminescence with Cobas e411.

At the beginning of the study, there were 92 participants. After two months of intervention, 81 patients were referred for the post-intervention sampling, and 11 patients were excluded from the study due to the following reasons; three patients left for kidney transplantation, two immigrated, two shifted from hemodialysis to peritoneal dialysis, and one patient stopped hemodialysis due to a fall in creatinine and three patients passed away before the end of the study (Figure 1).

Statistical analysis

Data were analyzed by SPSS version 26. Data normality was analyzed by Kolmogorov–Smirnov test. Meanwhile, chi-square, independent *t* test, Mann–Whitney U, and Spearman's rank correlation coefficient were employed to compare demographic characteristics between two control and intervention groups and explore the correlation between uric acid and 25-hydroxyvitamin D levels. *P* values less than 0.05 were considered significant.

Results

In our study, 54 of all participants (66.7%) were men and 27 (33.3%) were women. In the control and intervention groups, the frequency of men was 73.8% with a mean age of 60.17 ± 15.13 years old. The mean hemodialysis duration was 25.26 ± 24.5 months in the control group and 22.31 ± 22.17 months in the intervention group, ranging from one to 108 months. Serum uric acid level in the control group was 7.3 ± 0.88 mg/dL and in the intervention group was 7.42 ± 0.97 mg/dL. Results demonstrated that the two groups of control and intervention were similar in terms of patients' demographic and hemodialysis characteristics, since there were no statistically significant differences between the two groups regarding age, gender, site of hemodialysis, hemodialysis duration, uric acid level, and the number of hemodialysis sessions per week (Table 1).

Results showed that after the intervention, serum 25-hydroxyvitamin D level in the control group was 45.12 ± 33.02 ng/dL and in the intervention group was 61.28 ± 50.05 ng/dL ($P=0.261$). After the intervention, serum uric acid level in the control group was 7.29 ± 2 mg/dL and in the intervention group was 5.53 ± 1.41 mg/dL. Compared to the control group, the serum uric acid levels were significantly lower in the intervention group ($P<0.001$), while the level of 25-hydroxyvitamin D showed no significant difference between two groups ($P = 0.261$; Table 2).

Results demonstrated no statistically significant correlation between serum uric acid level and 25-hydroxyvitamin D levels in all patients after the intervention. In addition, no statistically significant correlation was found between serum uric acid level and 25-hydroxyvitamin D levels considering the two groups of

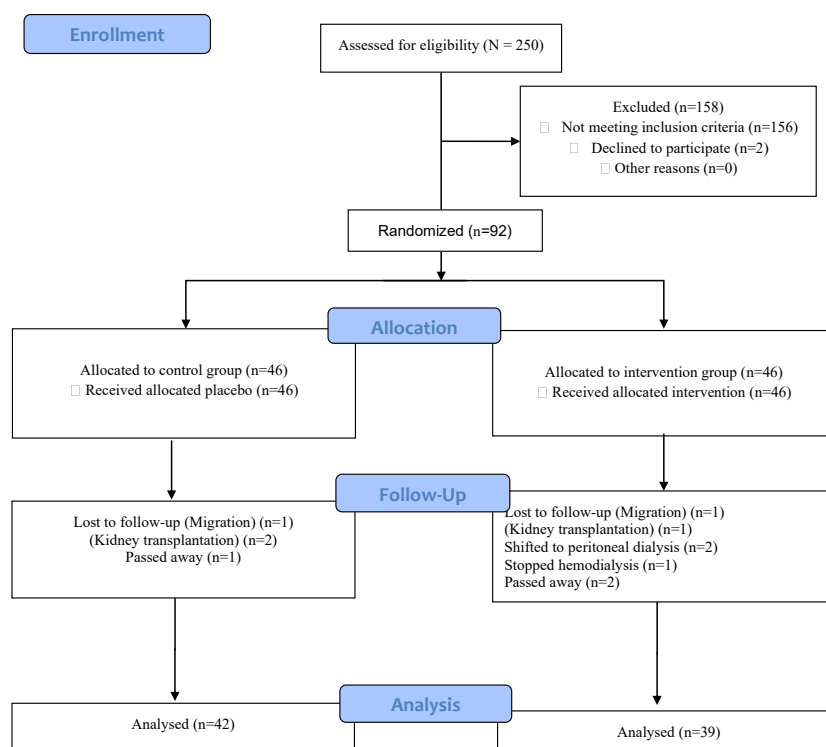


Figure 1. CONSORT flowchart of the study.

control and intervention separately (Table 3).

In Table 4, results showed that following the comparing of serum uric acid level and vitamin D levels after the intervention, the uric acid levels were significantly reduced in the females of intervention group in comparison to the male intervention group. Nonetheless, no significant difference in vitamin D level changes between females and males in both groups of control and intervention was found.

Discussion

The present study aimed to analyze the effect of uric acid serum level reduction on 25-hydroxy vitamin D serum levels in hemodialysis patients. This study, which was conducted on 81 hemodialysis patients, failed to show any significant effect.

Few human studies have been conducted to evaluate the direct effects of uric acid levels on vitamin D levels. The most important of all is the study by Vanholder et

Table 1. Demographic characteristics of participating patients in the control and intervention groups in this study

Variable	Group		P value
	Control No. (%)	Intervention No. (%)	
Gender			
Male	31 (73.8)	23 (59)	0.157 ^a
Female	11 (26.2)	16 (41)	
Hemodialysis session/week			
Twice/week	10 (23.8)	10 (25.6)	0.849 ^a
Three times/week	32 (76.2)	29 (74.4)	
Site of hemodialysis			
Hajar	20 (47.6)	23 (59)	0.200 ^a
Day	6 (14.3)	7 (17.9)	
Farsan	7 (16.7)	7 (17.9)	
Farokhshahr	9 (21.4)	2 (5.1)	
Age (y), Mean ± SD	60.17 ± 15.13	61.26 ± 15.96	0.753 ^b
Hemodialysis duration (months), Mean ± SD	25.26 ± 24.51	22.31 ± 22.17	0.791 ^c
Uric acid (mg/dL), Mean ± SD	7.3 ± 0.88	7.42 ± 0.97	0.467 ^{**}

^a Chi-square test, ^b Independent *t* test, ^c Mann-Whitney U test.

Table 2. Comparison of uric acid and 25-hydroxyvitamin D levels between two groups of control and intervention after the intervention

Variables	Group		P value
	Control Mean ± SD	Intervention Mean ± SD	
Uric acid (mg/dL)	7.29 ± 2	5.53 ± 1.41	< 0.001 ^a
25-Hydroxyvitamin D (ng/dL)	45.12 ± 33.02	61.28 ± 50.05	0.261 ^b

^aIndependent t test, ^bMann-Whitney U test.

Table 3. Correlation of serum uric acid and 25-hydroxyvitamin D levels in all patients and also in control and intervention groups following the intervention

Variables	Group		P value
	Uric acid (mg/dL) Mean ± SD	25-hydroxyvitamin D (ng/dL) Mean ± SD	
Control	7.29 ± 2	45.12 ± 33.02	<0.061*
Intervention	5.53 ± 1.41	61.28 ± 50.05	0.278*
Total patients	6.44 ± 1.94	52.9 ± 42.6	0.090*

* Spearman's correlation.

Table 4. Comparison of serum uric acid and 25-hydroxyvitamin D levels based on gender following the intervention in two groups of control and intervention

Variable	Group	Gender		P value
		Male Mean ± SD	Female Mean ± SD	
Uric acid	Control	7.51 ± 1.85	6.66 ± 2.35	0.229 ^a
	Intervention	6.06 ± 1.17	4.78 ± 1.42	0.004 ^a
25-Hydroxyvitamin D	Control	49.88 ± 34.36	31.71 ± 25.73	0.098 ^b
	Intervention	48.32 ± 42.15	79.19 ± 55.79	0.095 ^b

^aIndependent t test, ^bMann-Whitney U test.

al conducted on nine renal failure patients in a 7-day period (5). Patients received 300 mg of allopurinol while at the end of the seventh day, 25-hydroxy vitamin D and 1,25(OH)D levels were evaluated. The level of 1,25(OH)D had increased by 20%; however, the levels of 25-hydroxy vitamin D showed no significant change.

Increased levels of 1,25(OH)D in the study by Vanholder et al were probably not because of the direct effect of allopurinol since later in the same study it is mentioned that the effect of allopurinol on 1,25(OH)D was assessed in rats and had no meaningful impact.

Furthermore, as was mentioned in the study by Vanholder et al, allopurinol causes a rise in xanthine levels through inhibiting xanthine oxidase activity, which in term reduces the level of 25-hydroxy vitamin D (5). Therefore, in our study, no increase in 25-hydroxy vitamin D levels resulted from neutralized effects of allopurinol by the xanthine level rise caused by allopurinol during the course of the study; an effect that was not noted in the study by Vanholder et al due to the short period of the study.

In a cell study by Thakkinstian et al, the cause-and-effect correlation of vitamin D and uric acid was assessed by studying genes and additionally the alleles responsible for their production. Results showed a rise in 25(OH)D caused a rise in uric acid levels and a reduction in 25(OH)D levels caused a reduction in uric acid levels (7).

In a previous study, high uric acid levels caused a

reduction in the conversion of 25(OH)D to 1, 25(OH)D (8). It could thus be concluded that a rise in uric acid levels could cause a rise in 25-hydroxy vitamin D by preventing from conversion of 25-hydroxy vitamin D to 1,25(OH)D.

In a study on middle-aged and elderly women, low levels of vitamin D were observed in women with hyperuricemia (9). This correlation was more prominent in women affected by menopause. This study considered the estradiol effect as the cofounder and concluded that the lack of correlation between uric acid and vitamin D in women of childbearing age was due to the estradiol effect. In our study, no age limitation for participating women was considered, which could be a reason why no meaningful correlation was found in this study.

In our study, the intervention group had a higher mean level of vitamin D after the intervention in comparison to the control group. Although this difference was not significant, it may show a meaningful difference in a larger sample.

Meanwhile in the study by Brazier et al, patients who took calcium and vitamin D supplements for one year had a high level of uric acid at the end of the study (10). It can be therefore concluded that uric acid levels change in concordance with vitamin D levels. In our study, the difference in vitamin D levels in both control and intervention groups was not significant after the intervention, independent of the uric acid level changes. It is possible that the duration of the study was not long

enough to find the correlation between these two factors.

Conclusion

Results showed that after the intervention, compared to the control group, the serum uric acid levels were significantly lower in the intervention group while the level of 25-hydroxyvitamin D showed no significant difference between the two groups. Therefore, we conclude that no significant effect of uric acid lowering therapy with vitamin D elevation in hemodialysis patients was detected.

Limitations of the study

This study is a single-center investigation, requires further consideration by larger population.

Authors' contribution

Conceptualization: NK, SK, and SM.

Methodology: NK and MGh.

Validation: MGh and MSG.

Formal analysis: MGh.

Investigation: NK and SM.

Resources: SM, and NK.

Data Curation: NK and SM.

Writing—original draft preparation: HM, MSG, and SK.

Writing—review and editing: HM, SM, and MGh.

Visualization: HM and SK.

Supervision: NK.

Project administration: NK and SM.

Funding acquisition: SM.

Conflicts of interest

The authors declare that they have no conflict of interest. Medications administered in this study were free of charge. The drug was purchased from the market without any relation with the Hakim Company, which manufactured this drug.

Ethical issues

The research was conducted in accordance with the tents of the Declaration of Helsinki. The Ethics Committee of Shahrekord University of Medical Sciences approved this study. The institutional ethical committee at Shahrekord University of Medical Sciences accepted all study protocols (Ethical code #IR. SKUMS.1395.231). Accordingly, written informed consent was taken from all participants before any intervention. This study was part

of the MD, thesis of Negar Karevan at this university (Thesis #1417). The trial protocol was approved in the Iranian registry of the clinical trial (identifier: IRCT2015041721803N1; <https://en.irct.ir/trial/18996>).

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