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Effect of vitamin D treatment on magnesium levels in chronic hemodialysis patient; a double blind controlled clinical trial

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ABSTRACT

Introduction: The homeostasis of magnesium (Mg) is impaired in chronic kidney disease (CKD) and it has been suggested that intestinal absorption of Mg may be affected by vitamin D status. 25-Hydroxy vitamin D or 25(OH)D deficiency is common in patients undergoing chronic hemodialysis; however the efficacy of nutritional vitamin D supplementation on Mg level in this population remains uncertain.

Objectives: The aim of this study was to evaluate the effect of vitamin D treatment on Mg levels in chronic hemodialysis patients.

Patients and Methods: This randomized clinical trial study was conducted on 69 chronic hemodialysis patients (mean age of 56.93 ± 12.26 years) with serum 25-hydroxy vitamin D levels <30 ng/mL. The patients were randomly assigned to one of treatment groups of oral vitamin D3-50 000 units per week (n=35; experimental group) or 500 mg calcium D3 tablets, every 12 hours (n=34; control group) for three months. At the beginning and end of the treatment period, the levels of serum 25-hydroxy vitamin D and the levels of Mg, calcium, phosphorus and intact parathyroid hormone (iPTH) were measured in two groups.

Results: In both groups, serum vitamin D levels increased significantly after treatment ($P<0.0001$ for both groups), however after three months of treatment, in the experimental group the levels of vitamin D were significantly higher than the patients in the control group (57 ng/mL versus 28 ng/mL; $P<0.0001$) and the median increase of vitamin D after treatment in the experimental group was significantly higher than the control group (40 ng/mL versus 10.5; $P<0.0001$). Serum Mg levels before and after treatment were not significantly different between two groups ($P=0.880$ and $P=0.434$). In this study, we found no significant correlation between serum vitamin D level with serum Mg, calcium, phosphate, and parathyroid Hormone levels ($P>0.05$).

Conclusion: Our study shows that oral vitamin D therapy can increase 25(OH)D levels in maintenance hemodialysis patients without significant alterations in serum calcium, phosphate, magnesium and parathyroid hormone during a 12-week period.

Trial Registration: Registration of trial protocol has been approved by the Iranian registry of clinical trial (#IRCT20210314050698N1; https://en.irct.ir/trial/55159, local ethical code# IR.SKUMS.REC.1397.181).

Implication for health policy/practice/research/medical education:
In a randomized clinical trial study conducted on 69 chronic hemodialysis patients, we found administration of oral vitamin D for 12 weeks may raise 25(OH)D levels in patients of chronic hemodialysis however, it has no significant effect on serum magnesium, calcium, phosphorus and parathyroid hormone levels. We concluded that other factors besides vitamin D are involved in magnesium regulation in hemodialysis patients.

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Original

Introduction

Magnesium (Mg) is known to be the fourth most frequently found cation in the body and the second most pivotal intracellular cation. Recently, with increasing awareness and recognition of Mg as an essential cofactor in several enzymatic reactions, more attention has been paid to this element (1,2). Mg is also involved in mineral metabolism, protein synthesis, adenosine triphosphate metabolism, release of neurotransmitters, vascular tone regulation, platelet thrombosis and cardiac rhythm (2-5). Mg homeostasis is impaired in patients with chronic and end-stage renal diseases (ESRD) (1,2), which is mostly due to reduced glomerular filtration and decreased renal excretion of Mg (4,6). Hemodialysis patients are also at risk for hypomagnesemia due to the administration of proton pump inhibitors (PPIs), calcineurin inhibitors, vitamin D status, diabetes, malnutrition, or other factors, including alcohol consumption (4,7,8). In ESRD, there is a direct correlation between serum levels of Mg and patient survival. Moreover, hypomagnesemia has been identified as a strong predictor of promoted risk of cardiovascular diseases in these patients (9,10). Mg has also been reported to be involved in altering bone metabolism in chronic renal failure patients (6).

In conditions of renal impairment, Mg uptake is likely to be associated with a deficiency in the synthesis of vitamin D active metabolite (2). Intestinal absorption of Mg may be affected by vitamin D state, though such hypothesis has not been accurately proven, while the available data are also inconsistent (7). High doses of vitamin D (1,25-dihydroxy vitamin D) increase Mg absorption, since Mg is also absorbed independent of vitamin D and its intestinal receptor (11).

In one study, administration of vitamin D receptor activators was reported to improve intestinal absorption of Mg in chronic kidney disease (CKD) patients (12). Furthermore, a significant direct correlation between serum Mg and vitamin D (25-OH-vitD) levels of ESRD patients undergoing hemodialysis has been observed (13-16). Several investigations have shown the active vitamin D (1,25 dihydroxy vitamin D) to stimulate and increase intestinal absorption of Mg (1,5), which may partly explain the reported decrease in Mg absorption in CKD patients with vitamin D deficiency (3).

Although several studies have been conducted on the role of Mg, its interaction with vitamin D has been less studied (14).

Objectives

Given the plausible role for vitamin D in intestinal absorption of Mg, and also the prevention and treatment of complications due to Mg deficiency in ESRD patients, no clinical study has been conducted to assess vitamin D treatment effect on serum Mg levels in renal disease patients and it is still to be known whether vitamin D treatment affects Mg levels. Therefore, this clinical trial was conducted to assess vitamin D treatment effect on Mg levels in patients with chronic hemodialysis.

Patients and Methods

Study design

The present study was a double-blind controlled clinical trial conducted on hemodialysis patients referred to the dialysis ward of Imam Khomeini hospital in Ahvaz in 2020.

Considering power of 80%, type I error of 5% (α=0.05), and mean and standard deviation of vitamin D (48.2 and 0.24 ng/mL in the experimental group and 78.2 and 0.46 in the control group), number of samples in each group was equal to 36 people. Hemodialysis patients over 18 years of age who had been undergoing dialysis for at least three months and whose vitamin D level was below 30 ng/mL met the inclusion criteria of this study. Subjects were excluded in case of presence of any active or chronic infection, Mg supplementation, chronic diarrhea and hyperparathyroidism. The diagram of the study process and participants' exclusion is shown in Figure 1.

Groups and intervention

At the beginning of the study, demographic and clinical characteristics of all individuals were extracted and recorded from patients' medical records. Blood samples were taken from every patient and calcium, phosphorus, intact parathyroid hormone (iPTH) and 25-hydroxy vitamin D serum levels in were measured using special standard kits. For patients with vitamin D deficiency (a serum level of below 30 ng/mL) (15), Mg levels were checked before treatment. Patients with vitamin D deficiency were randomly divided into two groups. The method of randomization was that individuals were divided into two groups completely randomly (by a person who was not involved in the study process) based on the first randomized quadruple. One group underwent oral vitamin D therapy (pearl vitamin D; Dana Pharmaceutical Company, Iran) 50 000 IU/ per week (experimental group) and the other (control group) received calcium D 500 mg tablets (Dineh Company, Iran) every 12 hours (control group)/daily for three months. Blinding was also conducted in such a way that the person who randomized and assigned people to the groups did not know the patients and had no information about the patients' condition. The patient and the physician had no information about how to place the groups. All patients were advised to continue a normal diet throughout the study period. None of the participants took Mg-lowering drugs. After the follow up period of three months, serum vitamin D treatment, Mg, vitamin D and also phosphorus, calcium and iPTH serum levels were measured again then, compared with baseline values. In this study, hypomagnesemia is a Mg level of below 1.7 mg/dL and a Mg level of above 1.7 mg/dL is referred to as normomagnesemia (16).

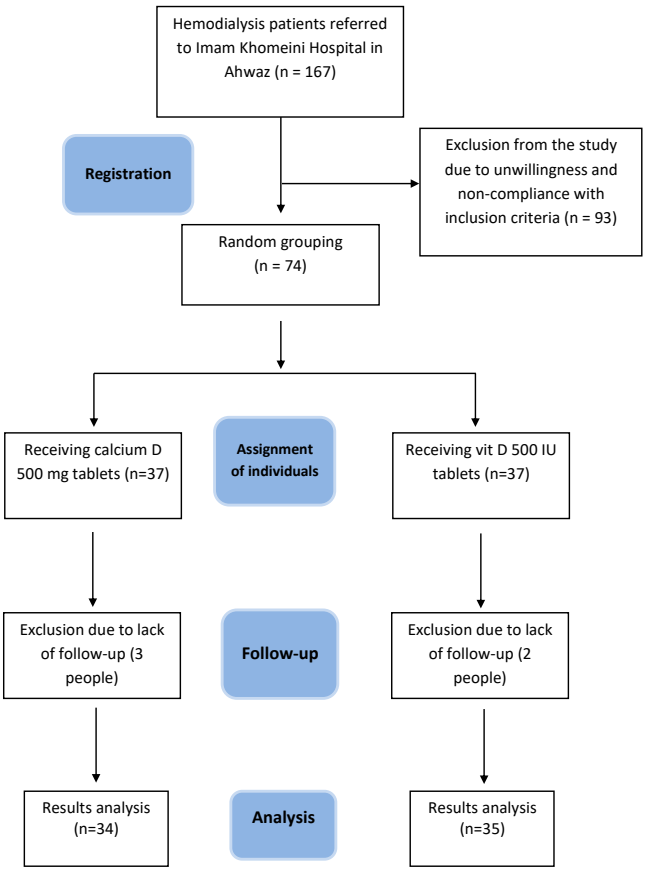

Figure 1. The study flowchart.

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, USA) version 22 was employed for statistical analysis. Mean quantification, standard deviation, median and interquartile range (IQR) were employed to data description for quantitative variables and frequencies and percentages were applied to describe data for qualitative variables. The normality of the data was checked by Kolmogorov-Smirnov test. Mann-Whitney U nonparametric test was conducted for comparing the means of variables between the two groups and Wilcoxon test was applied for comparing the results pre- and post-intervention. Pearson's and chi-square correlation tests were utilized to determine the relationship between quantitative and qualitative variables, respectively. The significance level in the tests was considered 0.05 and below.

Results

In this study, 69 hemodialysis patients aged 18 to 83 years (with the mean age 56.93 ± 12.26 years) including 45 men (65.2%) and 24 women (34.8%) participated. No significant difference was found in age and gender between the groups of vitamin D 50000 IU oral tablets (experimental group) and calcium D 500 mg (control group) ($P=0.267$ and $P=0.318$, respectively). Comparison of changes in serum levels of different parameters in the two groups is presented in Table 1. Serum vitamin D, Mg, phosphorus, calcium and iPTH serum levels before treatment had no significant difference ($P<0.05$). Levels of calcium, iPTH and phosphorus after treatment did not show a noticeable difference between the experimental and control groups ($P=0.194$, $P=0.178$ and $P=0.773$). After treatment for three months, the level of vitamin D in the experimental group (receiving oral vitamin D tablets) was noticeably higher compared to the control group (receiving calcium D tablets) ($P<0.0001$). In addition, in both experimental and control groups, serum vitamin D showed a remarkable increase after treatment ($P<0.0001$ for both groups). Vitamin D changes after treatment in the experimental group showed a noticeably higher rate compared to the control group (40 ng/mL versus 10.5; $P<0.0001$). Furthermore, after treatment, four patients (11.4%) in the experimental group and 22 patients (64.7%) in the control group had vitamin D deficiency ($P<0.0001$). In both the experimental and the control group, Mg levels increased significantly after three months of follow up ($P=0.002$ and $P<0.0001$, respectively). The amount of Mg changes after treatment was not remarkably different between the control and experimental groups (0.3 mg/dL versus 0.4; $P=0.228$).

The frequency of hypomagnesemia before and after treatment in the two groups is presented in Table 2. In this

Table 1. Comparison of changes in different parameters before and after treatment in the two groups

Variable	Experimental group (mg/dL)	Control group (mg/dL)	*P* value
Vitamin D- before	20 (23-14)	(14.75-23.25) 20.5	0.815
Vitamin D-after	57 (79-38)	28 (33 – 25)	<0.0001
P value**	<0.0001	<0.0001	
Mg- before	(1.8-2.5) 2.2	(1.77-2.52) 2.0	0.880
Mg- after	(2.1-2.9) 2.4	(2.1-3.02) 2.6	0.434
P value**	0.002	<0.0001	
Ca- before	(7.6-8.8) 8.0	(7.8-9.0) 8.05	0.420
Ca- after	(8.0-8.9) 8.5	(8.1-9.12) 8.7	0.194
P value**	0.044	0.002	
PTH- before	(456.6-999.0) 693	(359.0-740.0) 600	0.101
PTH- after	(410.5-999.0) 558	(383.6-609.75) 525	0.178
P value**	0.259	0.096	
P- before	(4.9-6.2) 5.5	(4.87-6.32) 5.6	0.665
P- after	(4.2-5.8) 5	(4.07-6.15) 5.05	0.773
P value**	0.009	0.008	

Numbers are frequency (percentage) or median (IQR).
* Difference between the two groups at the level of 0.05 (Mann-Whitney U test).
** Intragroup difference at level 0.05 (Wilcoxon test).

Table 2. Comparison of frequency and percentage of hypomagnesemia before and after treatment in the two groups

Variable	Test group (%) number	Control group (%) number	*P* value
Hypomagnesemia-before	(11.4) 4	(23.5) 8	0.218
Hypomagnesemia-after	(2.9) 1	(5.9) 2	0.489

Difference between the two groups at the level of 0.05 (Mann-Whitney test).

study, the frequency of hypomagnesemia (Mg level 0.7 mg/dL) before and after treatment showed no significant difference between the two groups. Serum Mg less than 0.7 was not observed in either group before or after treatment. The results related to the correlation between vitamin D and Mg, iPTH, calcium and phosphorus serum levels in the two groups are presented in Table 3. As evident, no significant relationship between the serum levels of vitamin D, Mg, calcium, phosphorus and iPTH among the groups($P<0.05$).

Discussion

Findings of the current study revealed that in both control and test groups, serum vitamin D levels increased significantly after three months of treatment. However, the increase rate in serum vitamin D following treatment in the experimental group (oral vitamin D tablets) was noticeably higher than that of the control group (calcium D tablets). Moreover, after treatment, only four patients (11.4%) of the experimental group and 22 patients (64.7%) of the control group were deficient in vitamin D. These results indicate the positive effect of oral consumption vitamin D in improving serum levels of vitamin D in hemodialysis patients.

Recently, the importance of vitamin D evaluation in different patients has become apparent. When

Table 3. Relationship between vitamin D and Mg, calcium, PTH and serum phosphorus in the two groups

Spearman's correlation		Test group (*P* Value)	Control group (*P* Value)
Vitamin D changes and Mg changes	Rho	0.019	0.176
	Significance	0.912	0.319
Vitamin D after and Mg after	Rho	0.133	0.116
	Significance	0.447	0.512
Vitamin D before and Mg before	Rho	-0.240	-0.120
	Significance	0.164	0.499
Vitamin D after and calcium after	Rho	0.022	0.102
	Significance	0.898	0.567
Vitamin D after and PTH after	Rho	-0.076	0.205
	Significance	0.713	0.314
Vitamin D after and Phosphorus after	Rho	-0.212	-0.121
	Significance	0.223	0.496

serum vitamin D level is below normal, vitamin D supplementation is recommended or the dose may be increased if supplementation is taken. Various studies have shown complex interactions between vitamin D and other nutrients, including Mg (17, 18). Based on a random trial (17), plasma Mg affects vitamin D levels. Mg had regulatory effects since Mg deficiency essentially stopped vitamin D synthesis and metabolism. The study by Dai et al, on patients with a risk of colorectal cancer, showed that Mg supplementation increased the level of 25-hydroxy vitamin D (17). When baseline levels were less than 30 ng/mL, no effect was observed on 1,25-dihydroxyvitamin D levels. However, in vitamin D levels of 30 to 50 ng/mL, Mg consumption increased the serum level of vitamin D dose-dependently. As a result, the optimal state of Mg is important and serves to optimize vitamin D level (17). In a descriptive study on 41 ESRD patients undergoing hemodialysis, a direct and noticeable correlation between serum Mg levels and 25-hydroxy vitamin D levels was reported (16). In addition, Schmulen et al conducted a study to investigate 1,25-dihydroxyvitamin D3 effect on intestinal absorption of Mg in chronic hemodialysis patients (12).

Patients were treated with 1,25-dihydroxyvitamin D3 (2 μg/d orally) for seven days. The results showed that the serum levels of vitamin D increased significantly after treatment. In addition, the amount of Mg absorption after treatment increased similar to the normal individuals. The results obtained in their study showed that the absorption of Mg in the jejunum depends on vitamin D (19). Treatment with 1,25-dihydroxyvitamin D3 in chronic renal failure patients improves intestinal absorption of Mg (19). Meintzer and Steenbock studied vitamin D effect on Mg uptake in mice with normal Mg uptake in an experimental study. They showed that the amount of Mg absorption in the absence of vitamin D decreased by 50 to 71% and increased by 53 to 77% if vitamin D was added to the diet (18).

Although several studies have been conducted on the role of Mg, its interaction with vitamin D has been less studied (14). Our clinical trial has been performed for the first time to assess vitamin D treatment effect on Mg serum levels in chronic hemodialysis patients. Our findings in the current study revealed that serum levels of Mg both before treatment and after treatment were not remarkably different between the control and experimental groups. Nevertheless, Mg levels increased significantly after treatment in both groups. The amount of Mg changes after treatment was not remarkably different between the groups either. Finally, no significant correlation between vitamin D and Mg levels was detected. These results indicate that treatment with vitamin D has no effect on serum Mg levels. However, in our study, most patients had normal serum Mg levels. In the study by Ortega et al, on 70 CKD patients in stages 4 and 5 without dialysis treatment, the mean Mg of all patients was in the normal range (1.2 mg/dL) and the mean vitamin D at the beginning of the study was 16 ng/mL. No significant relationship was observed between Mg and 25-hydroxy vitamin D levels either. In addition, Mg levels showed no significant difference between patients taking vitamin D supplements and non-vitamin D receiving patients (19). These results are in line with our study, although there are some methodological differences.

Previous experimental studies showed oral vitamin D in the treatment regimens had no significant effect on increasing serum Mg levels in laboratory samples (20-25). In an experimental study on vitamin D deficient mice, the mice were assigned to six groups, each group receiving one of the 1,25-dihydroxyvitamin D3, 1,24,25-trihydroxyvitamin D3, 24,25-dihydroxyvitamin D3, a combination of the last two regimens, or vehicle (-D) for six days. Their results showed that none of the above treatment regimens had exerted any noticeable effect on increasing serum Mg levels (20). In another in vivo study, vitamin D effects on Mg uptake in pigs receiving Mg and vitamin D were investigated. The effect of three levels of vitamin D (500, 1500 and 3000 IU/kg) in the diet for two months on Mg metabolism was investigated. The results showed that Mg uptake increased linearly from 28% to 39% with increasing vitamin D intake, but urinary Mg did not change. Plasma Mg and calcium were also unaffected by vitamin D intake (25). Therefore, the results of these two experimental studies also showed that the consumption of vitamin D has no effect on serum Mg levels in laboratory samples. In our study, serum phosphorus, calcium and iPTH levels, before and after treatment showed no noticeable difference among the groups. However, in both groups, calcium demonstrated a significant rise after three months of treatment. In addition, no remarkable relationship was observed between vitamin D level and plasma calcium, phosphorus and iPTH. These results suggest that vitamin D treatment has no impact on serum phosphorus, calcium and iPTH levels. Moreover, increased calcium levels after treatment in both groups can indicate calcium normalization during the process of dialysis, while consumption of active vitamin D, stimulates calcium absorption, and increased dietary intake following uremic correction.

The controlled randomized trial by Bhan et al (21) conducted on the impact of vitamin D supplementation in hemodialysis patients suffering from vitamin D deficiency, who were randomly assigned to two treatment groups of 50,000 IU oral ergocalciferol weekly (36 patients) or monthly (n=33) and placebo (36 patients) for 12 weeks. The mean vitamin D serum level in the two groups of weekly and monthly vitamin D was higher than placebo (49.8 ng, 38.3 and 27.4 ng/mL, respectively). However, the levels of calcium, phosphate and parathyroid hormone did not reveal any remarkable difference between the

three groups. As a result, treatment with oral vitamin D increases serum levels of 25-hydroxyvitamin D3 in patients undergoing hemodialysis and has no significant effect on phosphate, calcium and parathyroid hormone levels. These results are in line with the findings of our study. In the present study, after 12 weeks of treatment, only 11.4% of the patients in the oral vitamin D treatment group and 64.7% of those in the control group demonstrated vitamin D deficiency. Our study showed no correlation between serum vitamin D concentration with calcium, phosphorus or iPTH levels. In another study with a relatively small sample size (42 patients), 15 weeks of cholecalciferol treatment did not have a significant effect on calcium, phosphate and iPTH levels in hemodialysis patients (22).

Although vitamin D may affect the intestinal absorption of Mg, the available data are inconsistent. High doses of 25-hydroxyvitamin D increase Mg absorption; however, Mg is also absorbed regardless of vitamin D and its intestinal receptor (11). According to previous studies, several factors such as diabetes, certain medications, PPIs, thiazide diuretics, cisplatin, aminoglycoside antibiotics and calcineurin inhibitors (4,7,8), tubular defects (1) and type of dialysis (23) affect changes in Mg levels and the incidence of hypomagnesemia.

Consequently, in dialysis patients, even with limited renal Mg excretion, total Mg levels may be high, normal, or low. This is due to the complex interactions of Mg with other nutrients, some drugs and the effect of the amount of Mg on dialysis on the Mg and Mg balance of the whole body (4,7,8). Deficiency of active vitamin D is only one of the reasons for the decrease in intestinal absorption of Mg in chronic kidney patients (1). In fact, various factors can play a role in the results of studies and vitamin D supplementation effect on Mg serum levels. Therefore, it is important to consider other factors in the correlation between vitamin D and Mg.

Conclusion

The findings of the current study revealed that administration of oral vitamin D for 12 weeks may raise 25 (OH) D levels in patients of chronic hemodialysis however, it has no significant effect on serum Mg, calcium and phosphorus and also iPTH levels. Moreover, we found, high dose vitamin D treatment did not cause hypermagnesemia. In other words, although serum Mg levels were not observed to be significantly different between the two groups, they did not cause side effects such as hypermagnesemia either. Therefore, it seems that other factors besides vitamin D are involved in Mg regulation in hemodialysis patients.

Limitations of the study

It is worth mentioning that the number of patients studied herein is considered to be a limitation for this study and larger scale sample size can provide more solid findings in future investigations.

Our study also faced some limitations as follows: lack of evaluation of people with normal and insufficient vitamin D levels, lack of subjects with insufficient Mg levels, lack of accurate monitoring and recording of information about the nutritional status of patients during the study, failure to evaluate factors related to changes in Mg levels and hypomagnesemia including underlying diseases such as diabetes, and consumption of PPIs. Moreover, due to ethical issues, it was not possible to have a control group without vitamin D treatment. Therefore, further studies with a more accurate multicenter design and a large-scale sample size are crucial to affirm the findings of the present study.

Authors' contribution

Conceptualization: SAH. Methodology: AG. Validation: EA. Formal Analysis: LS, FH. Investigation: KH. Resources: AG, EH. Data Curation: SAH, EH. Writing—Original Draft Preparation: EH. Writing—Review and Editing: KH. Visualization: SAH. Supervision: KH, EH. Project Administration: LS. Funding Acquisition: AJUMS.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was performed after approval in Ahvaz Jundishapur University of Medical Sciences ethics committee (ethics number: IR.AJUMS.HGOLESTAN.REC.1399.172) and receiving the IRCT code from the Iranian Clinical Trial Registration Center (identifier: IRCT20210314050698N1). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of internal medicine residency thesis of Ebrahim Hamreh at this university. This study was also conducted in accordance with the tents of the Declaration of Helsinki. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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