ORIGINAL ARTICLE

The effect of vitamin D administration on serum leptin and adiponectin levels in end-stage renal disease patients on hemodialysis with vitamin D deficiency: A placebo-controlled double-blind clinical trial

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Background: The prevalence of vitamin D deficiency is higher in end-stage renal disease (ESRD) patients compared to healthy populations. This deficiency could lead to several complications with different mechanisms and might result in reduced survival in patients. Leptin and adiponectin are messenger proteins with endocrine secretion from adipocytes and various effects in cellular mechanisms. The goal of this study was to find the effect of vitamin D administration on serum levels of leptin and adiponectin in ESRD patients. **Materials and Methods:** This double-blind randomized placebo-controlled clinical trial was carried out on 64 ESRD patients on hemodialysis in the Amin and Noor hospitals of Isfahan, Iran. Patients were categorized into two groups, on control and intervention; serum levels of vitamin D, leptin, and adiponectin were measured in both groups before and after the study. The intervention group was treated with vitamin D pearls, while the control group received placebo in the same manner. **Results:** The mean [standard deviation (SD)] ages of the patients were 62 (21) years and 60 (19) years in the control and treated groups, respectively. **Conclusion:** The change in serum level of vitamin D was statistically significant in the treatment group but not in the control group. The serum level of leptin was reduced in the treatment group, while the serum level of adiponectin increased significantly, but none of these changes were statistically significant in the control group. This study showed that vitamin D administration is associated with an increase in adiponectin and a decrease in leptin level in ESRD patients.

Key words: Adiponectin, chronic kidney disease (CKD), end-stage renal disease (ESRD), leptin, vitamin D deficiency

How to cite this article: Naini AE, Vahdat S, Hedaiati ZP, Shahzeidi S, Pezeshki AH, Nasri H. The effect of vitamin D administration on serum leptin and adiponectin levels in end-stage renal disease patients on hemodialysis with vitamin D deficiency: A placebo-controlled double-blind clinical trial. J Res Med Sci 2016;21:1.

INTRODUCTION

Adipocytes as a part of the endocrine system secrete several proteins called adipokines into the bloodstream. Adipokines consist of leptin, adiponectin, interleukin (IL)-ß6, tumor necrosis factor (TNF)α, resistin, and visfatin.[1,2] These proteins play roles in different processes such as food intake, insulin-related functions, energy balance, the coagulation process, angiogenesis, glucose and lipid metabolism, and vascular remodeling. They are also known as a part of pathogenesis for some diseases, vascular atherosclerosis, insulin resistance, and dyslipidemia.[3-11] The concentration of adipokines is related to body fat mass, i.e., their levels in the body increase with body fat mass, except for adiponectin, which is reduced.[5,12,13]

Adiponectin is a 244-amino acid protein with protective action against atherosclerosis and other cardiovascular diseases and also an antiinflammatory effect.[14] Leptin

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/1735-1995.175144

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Received: 24-10-2015; **Revised:** 13-11-2015; **Accepted:** 30-11-2015

is a 167-amino acid protein with a role in energy balance and nutrition, immune system balance, and inflammatory effect.[4]

Serum levels of adipokines increase in end-stage renal disease (ESRD) patients due to decreased clearance result in increased blood levels.[5,13] Another factor contributing to the serum level of adipokines is the level of vitamin D in patients. Elevation in vitamin D level is related to increased adipokine serum level and could limit leptin production in adipocytes.[15-17] Increased vitamin D level could also regulate the level of TNFα.[18]

Vitamin D deficiency is more prevalent in ESRD patients on dialysis than in the normal population. This in turn leads to increased morbidity and mortality in these patients. Several studies have been carried out that suggest that vitamin D prescription could lead to enhanced life expectancy, better quality of life, and improvement of other complications in these patients.[19]

The goal to this study was to find the effect of cholecalciferol prescription on leptin and adiponectin levels in ESRD patients.

MATERIALS AND METHODS

Participants

This study is a double-blind placebo-controlled randomized clinical trial on ESRD patients on dialysis. The study was carried out in the Amin and Noor Hospitals of Isfahan, Iran between July 2013 and August 2014. Hemodialysis patients aged 18-80 years old with vitamin D deficiency were entered in the study. At the beginning, the complete process was explained to the patients and if they volunteered to participate, a consent form was signed. As the level of vitamin D was measured in all ESRD patients as part of a routine protocol in the Noor and Amin hospitals of Isfahan, the patients with vitamin D levels less than 30 ng/mL were selected as vitamin D deficiency cases and were entered in the study. The patients were categorized into two groups of treatment and control using simple randomization method. The number of patients in both groups was 32 patients.

Study design

Patients in the treatment group were prescribed 50000 IU vitamin D pearls according to the KDOQI protocol. One 50000-IU weekly dose of vitamin D pearl was given to this group for 12 weeks and the regimen was continued with 50000 IU every 3 weeks.[20] Control group patients were given placebo pearls (product of Zahravi Pharmaceutical Co., Iran) with exactly the same sequence. Neither the patients nor the nurses knew which patients received placebo or vitamin D pearls. Patients were followed for 6 months. Serum levels of vitamin D, leptin, and adiponectin were measured for all patients at the beginning of the study and 4 months after that. Leptin and adiponectin levels were evaluated from venous bloods samples using LDN kit (LDN, Nordhorn, Germany) and Boster kit (Boster Bio, USA) respectively by the enzyme-linked immunosorbent assay (ELISA) method at Baradaran Lab., Isfahan.

Criteria for patient inclusion:

- Age >18 years.
- ESRD patients undergoing hemodialysis for at least 3 months.
- Patients with vitamin D deficiency (serum level <30 ng/mL).
- Consent for entering the study.

Criteria for patient exclusion:

- Obesity [body mass index (BMI) >40 based on body weight after dialysis].
- Low compliance.
- History of malignancy or chemotherapy.
- Inflammatory or infectious diseases.
- Patients taking antiseizure medications.

Statistical analysis

Average levels of vitamin D, leptin, and adiponectin for patients in the control and treatment groups before and after the study were analyzed by gender using paired *t*-test and two-way repeated measured analysis of variance (ANOVA) on IBM SPSS Statistics for Windows, Version 20.0., Armonk, NY: IBM Corp.

Ethical considerations

The current study was approved ethically by the Research Ethics Committee of the Research Department at Isfahan University of Medical Sciences. All patients were fully informed about the course of the study, potential side effects, and other such considerations. The research followed the tenets of the Declaration of Helsinki. The authors made certain that all participants made an informed decision to enter the study. The specific questionnaire for clinical trials was filled by the Research Department. The project also registered at the Iranian Registry of Clinical Trials (IRCT): IRCT201505152417.

RESULTS

Characteristic and demographic data of patients

Demographic parameters were similar between the two groups, with ages ranging 20-78 years, with 24 patients (37.5%) aged 51-60 years of age. The participants consisted of 32 male (50%) and 32 female (50 %) patients [Figure 1 and Table 1].

The effect of vitamin D administration on serum levels of leptin and adiponectin

Serum levels of vitamin D, leptin, and adiponectin were measured in all patients before and after the study [Table 2]. As is seen in Table 2, the level of vitamin D in the treatment group was significantly increased ($P = 0.001$), while these changes were not statistically significant in the control group ($P \geq 0.05$). Before the study, 7 patients in the control group and 5 patients in the treatment group suffered from vitamin D deficiency (serum level ≤10 ng/dL), whereas after the study, all of these patients had a vitamin D level of over 10 ng/dL. None of the patients had hypervitaminosis D during the course of the study.

Average serum levels of leptin in the control group before and after treatment were 35.020 ng/mL and 34.042 ng/mL, respectively ($P \geq 0.05$), while in the treatment group these levels were 37.052 ng/mL and 32.676 ng/mL, respectively ($P = 0.001$). In other words, the decline in the serum level of leptin was statistically significant in the treatment group but not in the control group.

In addition, the average level of adiponectin in the control group before and after treatment were 4.01 ng/mL and 4.07 ng/mL, respectively ($P \geq 0.05$), while in the treatment group, these levels were 4.35 ng/mL and 4.92 ng/mL in that order ($P = 0.001$). This shows a significant elevation in adiponectin level in the treatment group.

Table 1: Basic characteristics of the study population

Character	Mean/(SD)		Min		Max	
	Control	Treated	Control	Treated	Control	Treated
Age (years)	62/21	60/19	21	18	78	76
BMI (kg/m^2)	26.2/6	27.4/8	18.1	17.2	35.1	34.8
Hb (mg/dL)	9.19/1.42	9.93/1.65	7.2	7.4	11.2	12.2
DM	14	10				
HTN	12	17				

*Min = Minimum; Max = Maximum; BMI = Body mass index; SD = Standard Deviation; DM = Diabetes mellitus; HTN = Hypertension

Table 2: Serum 25 (OH) vitamin D levels of the patients before and after the study in both groups

Group	Sex	Before study				After study				*N*	*P*
		Mean	SD	Confidence interval		Mean	SD	Confidence interval			
				Lower bound	Upper bound			Lower bound	Upper bound		
Control	M	20.9	6.53	17.22	24.58	21.74	5.98	18.06	25.41	16	>0.05
	F	21.64	6.5	17.96	25.31	23.06	6.49	19.39	26.74	16	
Treated	M	22.12	7.72	18.45	25.80	79.24	7.59	75.57	82.92	16	<.0001
	F	20.04	8.52	16.36	23.71	79	9.41	75.32	82.68	16	

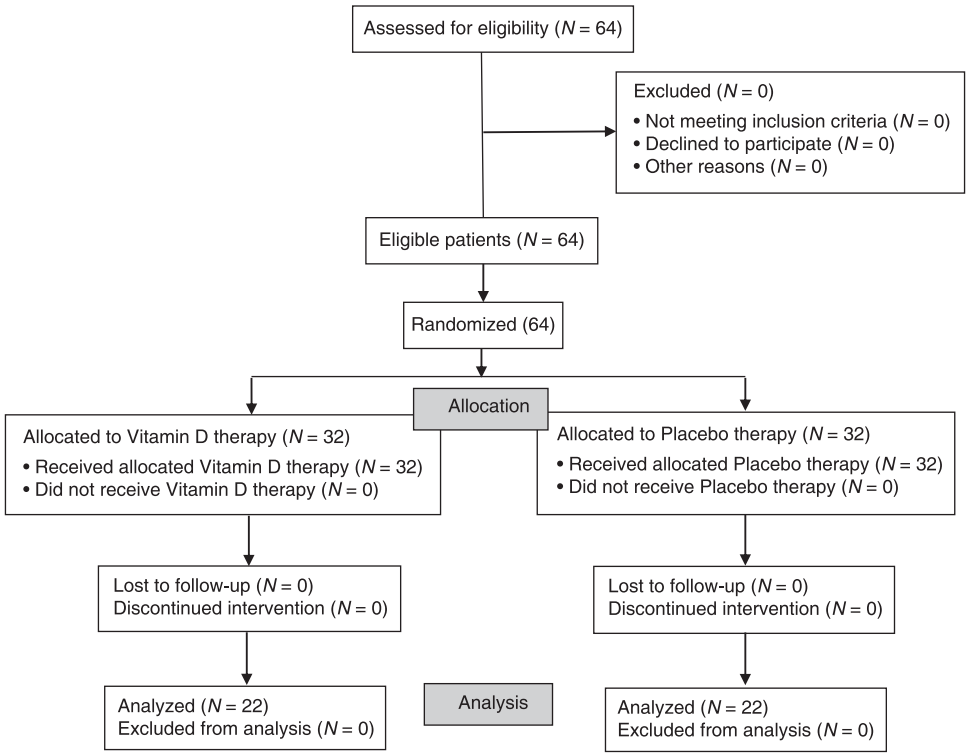

Figure 1: Clinical trial diagram

Table 3: Adiponectin and leptin serum levels before and after the study in both groups (mean ± standard deviation)

Group	Adiponectin			Leptin		
	Before study	After study	*P* value	Before study	After study	*P* value
Control	4.01±1.23	4.07±1.14	>0.05	35.020±5.23	34.042±5.07	>0.05
Treated	4.35±1.02	4.92±0.96	0.001	37.052±3.76	32.676±4.48	0.001
P value	0.001	0.001		0.001	0.001	

On statistical analysis, the average change in serum levels of leptin and adiponectin based on gender in the two groups demonstrate that sex has no significant effect on these levels. Apart from vitamin D administration, all other factors have a *P* value of over 0.05. The fact that the difference between means in two groups has a *P* value of below 0.05 shows that the difference in the average change of leptin and adiponectin levels in the two groups is statistically significant [Table 3]. Furthermore, the effects of age, BMI, and underlying factors for ESRD on changes in serum levels of these two markers were not statistically significant.

DISCUSSION

The goal of this study was to determine the effect of vitamin D administration on serum levels of leptin and adiponectin. It has been show that administration of vitamin D leads to decline in serum leptin level and rise in serum adiponectin level.

Administration of 650000 IU vitamin D *per os* in the treatment group resulted in an increase in serum level of vitamin D to 79 ng/dL, whereas administration of the placebo resulted in no significant change in vitamin D level in the control group. This study also showed that other factors such as gender, BMI, age, and underlying cause of ESRD have no effect in determining serum leptin and adiponectin levels.

Leptin and adiponectin are hormones that are secreted in blood by adipocytes, influencing various tissues and resulting in several different outcomes in the human body.[1,2] Leptin plays a role in nutrition, energy balance, triggering inflammation, and immune modulation. Adiponectin has antiatherogenic and antiinflammatory characteristics, and also increases response to insulin.[5,7-9] Various factors could change the levels of these hormones in serum. One of the most substantial ones is body fat mass. Generally, all adipokines are increased with an increase in body fat mass except for adiponectin. Other factors influencing the level of these hormones are age, sex hormone levels, and inflammatory process.[5,12,13]

The level of adipokines are generally increased in ESRD patients due to their reduced renal clearance while body fat mass still plays a significant role in adipokine levels in these patients too. The level of adipokines is further increased in ESRD patients and this could in part result in changes in the metabolism of patients.[21-24]

Several studies have been carried out on the effect of various factors on leptin and adiponectin and other adipokines in ESRD patients. Aguilera *et al*. demonstrated the association between triglyceride (TG), cholesterol, and serum level of adiponectin.[25] Malyszko *et al*. showed that leptin levels could also be related to platelet aggregation and hemostatic parameters.[26] Several other studies have shown the association between the rise of vitamin D levels with an increase in adiponectin levels and a decrease in leptin levels.[27-30]

The current study has established that vitamin D administration in ESRD patients leads to a rise in adiponectin level and reduction of leptin level.

As adiponectin results in protective effects against atherosclerosis, cerebrovascular accident (CVA), chronic inflammation, and increased sensitivity to insulin, a decrease in its serum level could improve prognosis in ESRD patients.[31] Moreover, due to the effects of leptin in increasing appetite, weight gain, triggering of inflammation, rising heart rate and blood pressure and hence increasing the risk of myocardial infarction (MI) and CVA, a reduction in serum level of this marker could improve survival in ESRD patients.

Oral antidiabetes medications such as metformin could affect serum levels of leptin and adiponectin; however, in the present study, due to their chronic kidney disease (CKD), all subjects were only on treatment with Insulin and therefore were not excluded from the study.

Some of the downsides to this study include it being undertaken in a hemodialysis center that omits subjects on peritoneal dialysis. The small sample size is another shortcoming, and we suggest further studies be carried out with larger sample sizes of ESRD patients.

CONCLUSION

As a conclusion, it could be stated that the administration of vitamin D supplements in ESRD patients could result in an increase in adiponectin and a decrease in leptin level. This could in turn reduce the risk of other ESRD complications. Due to the very few side effects and the various benefits,

vitamin D administration in these patients could lead to enhanced survival overtime.

Financial support and sponsorship

This study was funded by Isfahan University of Medical Sciences (Research project number: 293286).

Conflicts of interest

The authors have no conflicts of interest.

AUTHOR'S CONTRIBUTION

AHP contributed in conception of the work, study design, writing the article, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SV contributed in conception of the work, study design, samples and data collection, data analysis, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AE contributed in conception of the work, study design, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SSh contributed in conception of the work, sample collecting, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HN contributed in study design, article writing, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. ZPH contributed in Conception of the work, study design, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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