Original Article

The effect of oral vitamin D on serum level of N-terminal pro-B-type natriuretic peptide

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Abstract

Background: The risk of cardiovascular disease in dialysis patients is higher than the general population. Vitamin D receptors exist in myocardium inhibit cardiac hypertrophy. N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) is a neurohormone secreted by the heart in response to ventricular mass increase. This study aimed to evaluate the effect of oral vitamin D on serum level of pro-B-type natriuretic peptide (pro-BNP) in peritoneal dialysis patients.

Materials and Methods: In a randomized clinical trial, 84 peritoneal dialysis patients (49 males and 35 females) were randomly divided into two groups. The intervention group received 50000 units oral vitamin D per week, for 12 weeks if 25-hydroxy-vitamin D level was <10 ng/ml and for 8 weeks if it was between 10 ng/ml and 30 ng/ml. The control group received placebo. Parathyroid hormone, calcium, phosphor, 25-hydroxy-vitamin D, albumin and NT-pro-BNP were evaluated before and after the study.

Results: The mean serum level of pro-BNP in patients receiving vitamin D and placebo group before the study was 875 pg/ml and 793 pg/ml, respectively. There was 895.9 pg/ml in the intervention group and 736.7 pg/ml in the control group ($P = 0.7$). Mean serum level of 25(OH) D in patients receiving oral vitamin D and placebo group before the study was 16.9 ng/ml and 31.9 ng/ml, respectively. There was 28.9 ng/ml in the intervention group and 12.9 ng/ml in the control group ($P = 0.001$). There were no significant differences regarding other indices (Alb, P, Ca, intact parathyroid hormone) between two groups.

Conclusion: Vitamin D did not significantly change the serum level of pro-BNP in peritoneal dialysis patients.

Key Words: N-terminal pro-B-type natriuretic peptide, peritoneal dialysis, vitamin D

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INTRODUCTION

Patients with chronic dialysis experience disorders that reduce their quality of life and life expectancy. Among these complications, the prevalence of cardiovascular problems is higher.[1] The prevalence of hypertension, left ventricular hypertrophy, ischemic heart disease and heart failure are higher in patients with chronic renal failure undergoing dialysis. Their cardiovascular mortality is about 10-30 times

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more than normal populations. Empirical evidence shows that reduction of vitamin D can cause cardiac structural and functional damage.[2]

Nutritional vitamin D deficiency is highly prevalent. Its prevalence among the general population is 30-50%,[3] which is enhanced in hospitalized patients up to 90%.[4] In patients with kidney failure undergoing dialysis, vitamin D level (25-hydroxy vitamin D) is also decreased.[5-7] Causes for vitamin D reduction include the loss of binding protein with vitamin D in urine, malnutrition, decreased reabsorption of filtered 25-hydroxy vitamin D in the proximal tubule and loss of vitamin D during dialysis (which is more common among peritoneal dialysis patients).[8]

Vitamin D receptors are present at myocardium[9] and their stimulation can prevent the growth of myocardium and hypertrophy and can decrease secretion of cardiac B-type natriuretic peptide (BNP) in the myocytes of the atria and ventricles.[9-14] The active vitamin D can act as a negative regulator of the renin angiotensin.[15] The reduction and cessation of vitamin D intake in rats caused cardiac hypertrophy by activating renin angiotensin system and cardiac natriuretic peptide. The treatment of these rats by angiotensin converting enzyme inhibitor (captopril) resulted in reduction of cardiac hypertrophy and normalization of atrial natriuretic peptide (ANP).[16]

In another study on rats, activation of vitamin D receptors suppressed the production and release of BNP and ANP in cardiomyocytes. It is more than a decade that BNP is used as a marker for cardiac failure.[17]

During the process of BNP secretion of cardiac myositis the pro-B-type natriuretic peptide (pro-BNP) precursor consisting of 108 amino acids splits into BNP peptide with 32 amino acids and N-terminal pro-BNP (NT-Pro-BNP) fragment with 76 amino acids.[18] It is a response to the increased stress in the ventricular wall caused by diastolic pressure and pressure overload. BNP and NT-pro-BNP are markers of severity and prognosis of acute coronary syndrome and heart failure.[19]

It seems that in the natriuretic peptide family the NT-pro-BNP is the best predictor of clinical outcome and the best marker for the increase of extracellular volume. This peptide is bigger considering its structure and it has longer half-life than BNP and it is easier to be measured.[20]

The most common cause of death in chronic dialysis patients is cardiovascular events. Identification and treatment of these complications significantly contributes to patients' health and reduces health care costs. Based on the effect of vitamin D on the function and structure of the heart, considering NT-pro-BNP as a cardiac diagnostic and prognostic marker and taking into account that no study has been conducted so far on evaluating the effect of vitamin D on NT-pro-BNP serum level, this study was conducted to investigate this relationship among the peritoneal dialysis patients.

MATERIALS AND METHODS

The present study was a double-blind clinical trial conducted at the Al-Zahra University Hospital in Isfahan, Iran. At first, information regarding age, gender, cause of primary renal failure, duration of dialysis and medications including calcium carbonate, sevelamer and calcitriol were collected. Inclusion criteria included peritoneal dialysis for at least 3 months, age over 18 years, not being treated with vitamin D during the last 3 months, absence of malignancy and patient satisfaction. Exclusion criteria included recent history of heart failure (past 3 months), vitamin D level more than 30 ng/ml, Ca × P product more than 55 and lack of patient consent. Sample size was calculated to 84 patients.

After obtaining informed consent from the patients, blood samples were taken during morning dialysis. Immediately after obtaining the samples they were sent to laboratory for intact parathyroid hormone (iPTH), Ca, P, 25(OH) vitamin D, albumin and pro-BNP measurement. Samples were immediately centrifuged at 4°C in the laboratory and were maintained at −20°C. 25(OH) vitamin D was considered insufficient if the level was 10-30 ng/ml; if lower than 10 ng/ml it was deemed deficient and values higher than 30 ng/ml was considered as sufficient.[9,22] In the intervention group, in case of being deficient, 50,000 unit vitamin D pearl manufactured by Zahravi Company, Tabriz, IRAN was given weekly for 12 weeks. For subjects with insufficient level, 50,000 unit vitamin D with a similar pattern was given for 8 weeks.[21] The control group was given placebo from Zahravi Company using similar manner. The level of 25(OH) vitamin D, pro-BNP, iPTH, Ca, P, Alb was assessed in the same laboratory after 12 weeks.[10] Calcium, phosphorus and albumin levels of patients were assessed in the middle of study for adjusting the dosage of medications. To measure the pro-BNP, Novogent kit (Made in UK) and to assess vitamin D, IDS kit which both use Elisa method was employed.

Statistical analysis

This study has approved by Isfahan Kidney Diseases Research Center (project No. 290369) and ethical committee of Isfahan University of Medical Sciences. This study was registered in Iranian registry of clinical trials with ID number: IRCT201212142417N10.

Kolmogorov-Smirnov test was used to evaluate data normality when the variable was continues. Chi-square test, Fisher's test and Student's *t*-test were used for analysis. Data were analyzed by SPSS 20 (SPSS, Inc., Chicago, IL, USA). The findings of this research were results of project number 290369, Isfahan University of Medical Sciences.

RESULTS

A total of 89 patients participated in the study. All candidates were randomized into either vitamin D therapy (n = 49) or placebo therapy (n = 40). During the study period, one patient died in both groups, modality of dialysis change in one patient in the placebo group and two patient in vitamin D group. A total of 84 patients completed the study [Figure 1].

Nearly 56.5% of the patients were entered in the intervention group receiving vitamin D and 60.5% were in the placebo group. This difference was not statistically significant. Some demographic data like mean age and frequency of dialysis are included in Table 1. The average calcium carbonate at baseline in patients treated with vitamin D was 1050 mg and in the placebo group it was 800 mg. After the study, this amount was 1025 and 750 mg respectively (P = 0.01). Changes in average calcitriol usage before and the end of study in patients treated with vitamin D and placebo group showed no significant changes like for sevelamer. Details of these data as shown in Table 2.

Mean pro-BNP before the study in patients receiving vitamin D and placebo group were 895.1 pg/ml and 793.3 pg/ml and after the study it was 895.9 and 736.7 pg/ml, respectively. The differences were statistically significant neither within group nor between groups comparison [Figure 2]. Mean vitamin D at baseline in patients receiving vitamin D and placebo group was 16.9 ng/ml and 19.5 ng/ml, respectively. After the study, it was 31.9 ng/ml in the intervention group and 12.9 ng/ml in the placebo group. The mean difference before and after the study in both groups was statistically significant (P = 0.001) [Figure 3]. There was no significant difference regarding other indices (P, Ca, Alb and iPTH) between the two groups [Tables 3 and 4]. In addition to the assessments in the beginning and the end of the study, the changes in calcium and phosphorus were also measured 1 month after the study [Table 5].

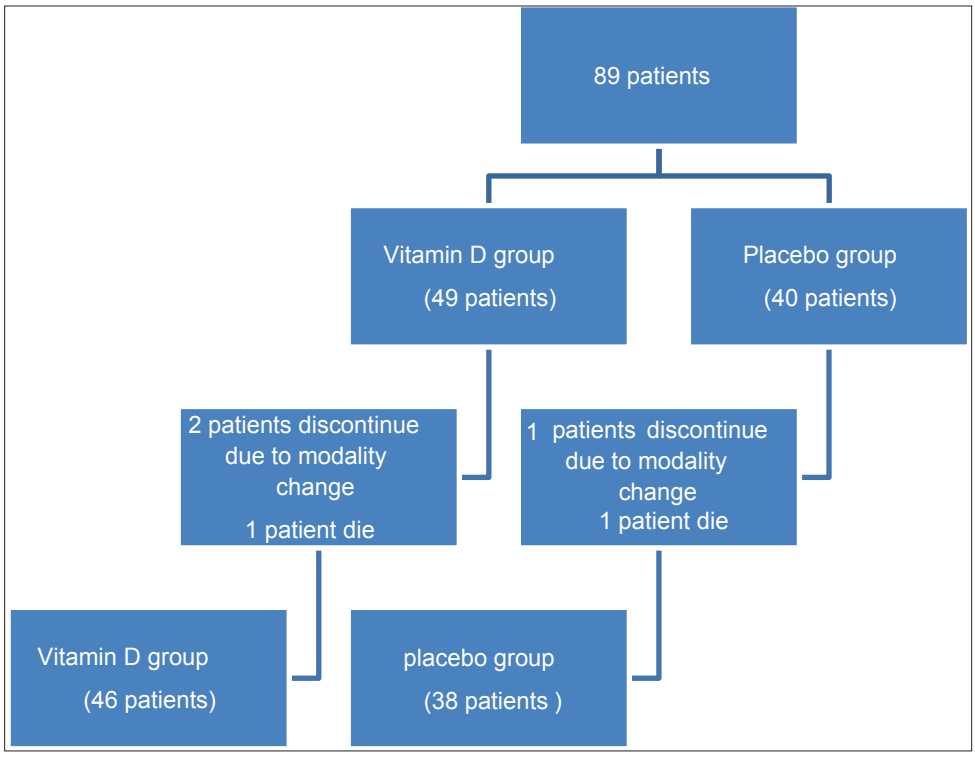

Figure 1: Flow diagram of the study process and patient selection

DISCUSSION

In patients with renal failure reduced level of vitamin D can be seen. Only 29% of patients with moderate renal failure, 17% with severe renal failure and 22% dialysis patients have sufficient vitamin D level.[23,24] With regard to the existing evidence about the role of vitamin D on the cardiovascular system, the present study evaluated the effect of vitamin D on serum level of NT-pro-BNP in peritoneal dialysis patients. The results indicated that there was no significant difference between the group receiving vitamin D and the placebo group regarding pro-BNP level.

Bozic *et al*.[25] chose 65 patients with low level of vitamin D (insufficient, <30 ng/ml) and New York Heart Association class I and II heart failure. They studied them regarding echocardiography, parathyroid hormone, 25(OH) vitamin D, NT-pro-BNP and adiponectin. Increase of heart failure class was associated with secondary hyperparathyroidism. Secondary hyperparathyroidism decreased left ventricular ejection fraction. Patients with congestive heart failure had higher levels of NT-pro-BNP, adiponectin and bone markers, while 25(OH) vitamin D level was decreased.[25]

Table 1: General characteristics of peritoneal dialysis in the study group

Characteristics	Vitamin D group (%)	Control group (%)
Gender		
Male	26 (56.5)	23 (60.5)
Female	20 (43.5)	15 (39.5)
Age (years)		
Mean±SD	55.1±17.4	54.6±13.5
The cause of renal failure		
Diabetes	11 (25)	18 (50)
Hypertension	20 (45.5)	13 (36.1)
Other causes	15 (29.5)	7 (13.9)
Frequency of dialysis during a week		
1-2	5 (10.9)	4 (10.52)
3-4	37 (80.4)	33 (86.85)
5-6	4 (8.7)	1 (2.63)
Kind of dialysate solution		
Dextrose 1.5%	35 (76.1)	28 (73.7)
Dextrose 2.5%	3 (6.5)	0
Both	8 (17.4)	10 (26.3)

SD: Standard deviation. $P<0.05$ is significant

Measuring 25(OH) vitamin D level and BNP plasma level of patients undergoing chronic hemodialysis in Japan showed a relationship between BNP, pro-BNP and 25(OH) vitamin D level. In these patients, the plasma level of cardiac natriuretic peptides (specially type B level) represents the structural and functional cardiac involvement and it also determines the cardiovascular mortality.[26,27]

Tamez *et al*.[28] study in America showed that treatment with 2 mg paricalcitol weekly for 48 weeks reduces cardiac hypertrophy indexes and BNP serum level.[28] Wetmore *et al*.[29] mentioned the relationship between nutritional deficiency of vitamin D with an increased

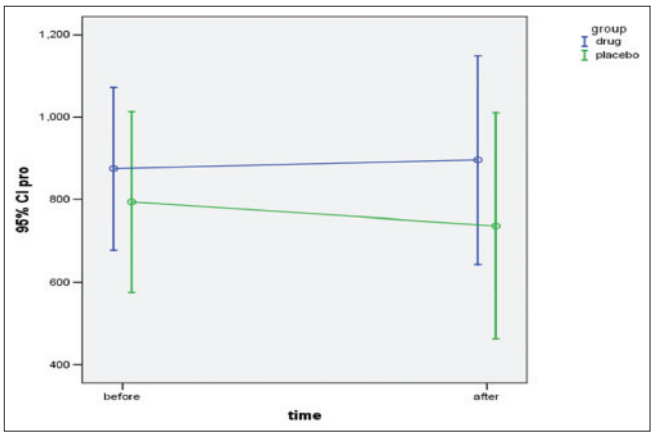

Figure 2: Changes of pro-B-type natriuretic peptide during the study in the control and intervention groups

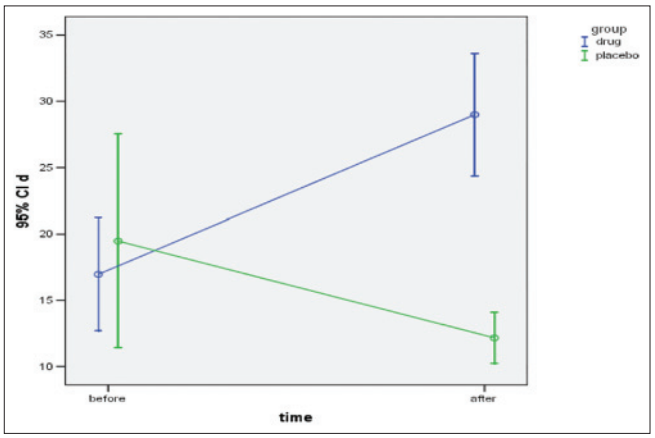

Figure 3: Changes of vitamin D during the study in the control and intervention groups

Table 2: Mean and SD of medications used for patients before and after the study

Time of the measurement	After the study (mean±SD)			Before the study (mean±SD)		
Medication (group)	Sevelamer (g/d)	Calcitriol (mg/d)	Calcium carbonate (g/d)	Sevelamer (g/d)	Calcitriol (mg/d)	Calcium carbonate (g/d)
Vitamin D	0	0.675±0.525	1025±475	0	0.7±0.52	1050±450
Placebo	800±800	1.35±0.875	750±425	800±800	0.87±0.64	800±430.5

SD: Standard deviation. $P<0.05$ is significant

level of NT-pro-BNP in dialysis patients with acute myocardial infarction.[29] Park *et al*.[30] in their study have reported that prescribed intravenous calcitriol 2 times a week for 15 weeks reduces the ventricular muscle loss and suppresses renin-angiotensin level II and ANP in chronic hemodialysis patients with secondary hyperparathyroidism.[30] The mentioned studies suggest a relationship between the decrease of vitamin D level and increase of BNP in patients with chronic renal failure and dialysis patients.

There are also other studies, which have not reached these findings. Hur *et al*.[21] examined the relationship between vitamin D level and cardiac biomarkers in dialysis patients. This study was conducted on 65 patients and the levels of 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D, cardiac troponin T and NT-pro-BNP were measured. There was a negative relationship between 25-hydroxy vitamin D level and cardiac troponin T (Spearman's rho = −0.44, $P < 0.01$) but there was no relationship between vitamin D level and BNP (Spearman's rho = −0.17, $P = 0.17$). There was no relationship between 1,25 dihydroxy vitamin D and both cardiac markers, cardiac troponin T and NT-pro-BNP.[31] In a study by Saadi *et al*.[31] there was no relationship between vitamin D level and NT-pro-BNP, which is the same as the present study.[31]

Therefore, there are inconsistent results regarding the relationship between vitamin D level and cardiac biomarkers which show that further researches are needed. One reason for these differences might be the racial differences and dialysis modality. It can be concluded from the present study that prescribing oral vitamin D has no significant effect on serum level of pro-BNP of peritoneal dialysis patients.

Limitations of this study were as follows: First, measuring pro-BNP one times in the study; this measurement needs to be done in other levels and also in greater time intervals. Second, the lack of investigating echocardiographic parameters during the study, such as ventricular mass index which indicates the heart's condition and the effect of vitamin D on this matter. Therefore, to have more accurate findings, it is suggested that further research with larger sample size and applying the above mentioned notes be conducted in Iran.

CONCLUSION

Serum BNP level did not show any changes during vitamin D supplementation in patients on peritoneal dialysis.

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Table 3: Mean and SD of albumin, Ca, P, iPTH and pro-BNP of the patients

Characteristic	Groups	Time of the study (mean±SD)		*P* value
		Before	After	
Pro-BNP (pg/ml)	Vitamin D	8951.±1631	895.9±779.6	0.50
	Placebo	7933.±1492	736.7±797.9	0.52
Albumin (g/dL)	Vitamin D	3.4±0.52	3.3±0.45	0.38
	Placebo	3.3±0.53	3.2±0.61	0.21
P (mg/dL)	Vitamin D	4.6±1.07	4.7±1.03	0.72
	Placebo	4.7±0.91	4.4±1.01	0.14
Ca (mg/dL)	Vitamin D	9.1±0.49	9.4±0.52	0.08
	Placebo	8.9±0.71	9.3±0.68	0.10
iPTH (pg/ml)	Vitamin D	196.5±162.8	273.6±257.5	0.019
	Placebo	392.6±553.1	370.2±443.1	0.71
Vitamin D (ng/ml)	Vitamin D	16.9±14.4	31.9±14.7	<0.001
	Placebo	19.5±24.5	12.2±5.6	0.06

BNP: B-type natriuretic peptide, SD: Standard deviation, iPTH: Intact parathyroid hormone. *P*<0.05 is significant

Table 5: Mean and SD of Ca and P in different measurement points

	Mean±SD		
	Beginning	After 1 month	End
P			
Vitamin D	4.6±1.07	4.5±1.10	4.7±1.03
Placebo	4.7±0.91	4.5±0.98	4.4±1.01
Ca			
Vitamin D	9.1±0.49	8.8±0.51	9.4±0.52
Placebo	8.9±0.71	8.8±0.58	9.3±0.68

SD: Standard deviation, Ca: mg/dL, P: mg/dL

Table 4: Statistical indicators of laboratory variables before the study

Laboratory variables	iPTH (pg/ml)	Albumin (g/dL)	P (mg/dL)	Ca (mg/dL)	Vitamin D (ng/ml)	Pro-BNP (pg/ml)
Vitamin D						
Mean±SD	196.5±162.8	3.3±0.52	4.6±1.07	9.1±0.49	16.9±14.3	8951.±1631
Placebo						
Mean±SD	392.6±553.1	3.2±0.53	4.7±0.91	8.9±0.71	19.4±24.5	7933.±1492
P value	0.02	0.36	0.78	0.35	0.56	0.62

BNP: B-type natriuretic peptide, SD: Standard deviation, iPTH: Intact parathyroid hormone. *P*<0.05 is significant

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