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An Investigation of Vitamin D Effect on Alterations of Glomerular Filtration Rate (GFR) in Patients with Chronic Renal Failure

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ABSTRACT

Vitamin D deficiency is highly prevalent in general population and patients with Chronic Kidney Disease [1]. The deficiency of nutritional form of vitamin D including 25OH Vit D and its hormonal form (1,25OHVit D), is common in patients with CKD. Vitamin D deficiency is traditionally associated with hyperparathyroidism and renal bone disease; however, we all know that besides being a calcium hormone, Vit D plays a crucial role in preventing cardiovascular disease, infectious disease, autoimmune disease, glucose control, and protecting kidneys.

Key words: Vitamin D, Chronic Kidney Disease, Glomerular Filtration Rate

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INTRODUCTION

Vitamin D deficiency is highly prevalent in general population and patients with Chronic Kidney Disease [1]. The deficiency of nutritional form of vitamin D including 25OH Vit D and its hormonal form (1,25OHVit D), is common in patients with CKD. Vitamin D deficiency is traditionally associated with hyperparathyroidism and renal bone disease; however, we all know that besides being a calcium hormone, Vit D plays a crucial role in preventing cardiovascular disease, infectious disease, autoimmune disease, glucose control, and protecting kidneys. Most of human body cells are equipped with Vit D Receptor and can convert it into the active form of 1.25 using enzymes [2, 3]. Despite the definite target organs for Vit D like Kidneys, bones and intestines, Vit D Receptors can also be found in other cells like cardiomyocytes, vascular smooth muscles and macrophages. Vit D functions via nuclear receptors and as a translation factor [2, 3]. Various evidence from experiments conducted through laboratory and animal based models [4, 5] as well as clinical and epidemiological studies [6-8] reflect the protective effect of Vit D on cardiovascular system. Additionally, there is ample debatable evidence concerning the influence of Vit D in slowing down the progress of kidney failure disease which needs further studies.

Once a noticeable impairment occurs in kidneys performance, CKD often progresses towards ESRD. The speed of this progression depends upon the underlying disease causing CKD. There is abundant clinical evidence indicating that Proteinuria and hypertension are two influential factors in pathophysiological progression of CKD [10]. Renin - angiotensin - aldosterone system (RAAS) is influential in CKD in terms of hypertension and exacerbates renal damages in a condition of hypertension and proteinuria. Angiotensin II as a renal growth factor stimulates cell proliferation and hypertrophy. It is also a proinflammatory and fibrotic factor [10]. Angiotensin II activates tubular and mesenchymal cells and interstitial fibroblasts [11]. VDR activation reduces the activity of the renin gene [12]. Several studies have demonstrated that Vit D reduces hypertension and cardiovascular events through inhibition of vascular RAAS system, even in healthy people population [12]. Limited number of studies has also been carried out on the effects of Vit D on Proteinuria. These studies discuss that in spite of ACEi consumption; Using Vit D either

improves proteinuria or slows down proteinuria progression [13]. VITAL and et al, in a study conducted on 281 patients with diabetes type 2 and albuminuria, showed that in patients who were taking 2 mg Paricalcitol per day, Albuminuria rate decreased by 20% in comparison with control group [14]. Two clinical trials have also shown that increased vascular stiffness and Calcification in dialysis patients are more prevalent in the presence of Vit D deficiency ([15, 16]. Vit D deficiency and secondary hyperparathyroidism directly cause vascular stiffness and cardiac hypertrophy [17]. Chronic kidney disease is recognized as a chronic inflammatory. Inflammatory markers such as CRP and IL-6 are among the predictors of disease outcome. Two main reasons for death in patients with CKD (cardiovascular, infection) are associated with low levels of Vit D and poor immune responses [18]. Through a study on hemodialysis patients with insulin deficiency, it was observable that Vit D would improve insulin secretion and increase cells sensitivity to insulin, although other studies on diabetic patients with appropriate renal function, revealed different results [13]. It is acknowledged that in diabetic patients, the active form of Vit D can inhibit the activities associated with hyperglycemia TGF-B in juxtaglomerular and mesenchyme cells [19] and this can prevent tubulointerstitial fibrosis from taking place. Not so many studies have been done on Vit D effect on CKD progression so far in Iran. Therefore, the present study is going to identify the effect of vit D on renal performance alterations in adult patients suffering from chronic renal deficiency.

MATERIALS AND METHODS

Study framework and participants:

This study was carried out as a double blind clinical trial in 2014 in educational-medical center of Al-Zarahra, Isfahan. The studied population included CKD patients referring to nephrology clinic. The criteria for being engaged in the study comprised of aging over 18 years, having CKD stage 3 and 4 (glomerular filtration at 15 to 95 mL per minute per 1/73 m^2), having no plan for pregnancy or breastfeeding, not receiving organ transparent, no recent Vit D products intake (less than 3 months), not taking anticonvulsants, improved calcium, serum leveling less than 10 mg/dl or phosphorus less than 5.2 mg/dl, vit D less than 30 ng/mL and the patient's consent to take part in the study. It was also agreed upon that those patients not referring for further examinations and not easy to follow up, be excluded.

The study-required sample size was estimated 28 people and finally 30 people were assigned to each group to be studied. The sample size was calculated through sample mass formula in order to compare two mean scores, regarding the significance level of 5%, statistical power of 80%, and standard deviation of 25 hydroxy vitamin D was estimated as 1.1 through pilot test and the significance of the least difference between the two groups which was considered 0.8.

Methodology

After approval of the proposal and obtaining permission from the university ethics committee, patient who met inclusion criteria, were assigned to two groups via blocked randomization of size 2.

Firstly, Patients' demographic data were cumulated and recorded in the study specific check list. In both groups, GFR was estimated with MDRD formula and through (*) software, then, at the beginning of the study, levels of calcium, phosphorus and 25(OH) Vit D were checked in reference laboratory. 25 (OH) Vit D level below 30 ng/mL was considered insufficient, below 10 ng/mL, Deficient and above 30 ng/mL, Sufficient [29].

The first group called treatment group, being in the Deficient range, received Pearl vitD50000IU per week and for 12 weeks, the insufficient group also received weekly vitD50000IU for an 8 week period of time. The control group got placebo and the level of 25 (OH Vit D was repeated at the end of 12^{th} and 20^{th} weeks at the same reference laboratory. Vitamin D pearls and placebo were collected from Zahravi pharmaceutical company. In terms of 25 (OH) VIT D level above 30 ng/mL, the maintenance treatment was continued as taking one 50000 IU pearl per month; patients were observed for 3 months. After this period of time, the treatment would be replicated if 25 (OH) VIT D become below 30 ng/mL [31].

Patients' compliance was assessed by the number of tablets returned; all adverse events were also analyzed and recorded during the study. In case of any side effect or increase of 25 Vit D level above the normal level, the drug consumption would be discontinued.

During the study patients were visited every one month and the levels of calcium, phosphorus, albumin, were checked at the end of the three months. Patients' weights BUN, Creatinine and GFR were also checked at the end of per month.

Data analysis:
After cumulating process, the data were analyzed through computer by using SPSS software version 22. Data normality was measured by Kolmogorov - Smirnov and QQ charts. The quantitative and qualitative data between the two groups were compared through T-test and chi-square test respectively. The intergroup comparison, in terms of numerical variables, was performed through T-test, the intragroup comparison through ANOVA and repeating observations, and the mauchly's test of sphericity.

RESULTS

In the present study, 60 patients suffering from renal failure were studied in two groups, 30 people assigned to each group. The average age of treatment and control group participants was 56.2±12.1 and 51±9.8 respectively. According to T-test no significant difference was observed between these two groups (P=0.07). There were assigned 22 and 17 male participants to treatment and control groups respectively (73.3% vs. 56.7%), other participants were all female. According to Chi-square test the difference was not significant (P= 0.18). The average weight rates for two groups were 73.55±10.6 and 75.39±9.9 kg respectively and according to T-test the difference between the two was not significant (P=0.5). The prevalent reason for renal failure in both groups was Diabetes, i.e. in nine patients of treatment group and 12 patients of control group, the main reason for renal failure was diabetes (30% vs. 40%). According to Fisher's exact test, the causes for renal failure on both groups were not significantly different (P= 0.99).

The pre-treatment mean score for serum level of vitamin D was estimated 18.46±6.36 and 20.14±5.08 in treatment and control groups respectively and according to T-test, the difference between the two groups was not significant (P=0.28). the post-treatment level of 25 (OH) VIT D was reported 43.33±19.59 and 19.07±3.74 in two groups respectively and according to T-test this difference was significant (P<0.001), i.e. the level of 25 (OH) VIT D significantly increased in treatment group but decreased in control group.

Table 1 demonstrates the frequency distribution of 25 (OH) VIT D before and after the treatment in both treatment and control groups. According to the same table, the pre-treatment level of vit D was not normal at all in any patient in both groups and according to Fisher's exact test the difference was not significant (P=1). However, in the next 12 weeks following the treatment, 25 (OH) VIT D level reached the normal level in 20 patients of treatment group and 2 patients of control groups (66.7% vs. 6.7%) and according to Chi-square test the difference was significant (P<0.001). The 25 (OH) Vit D treatment was carried on 10 patients with still inadequate level of 25 (OH) VIT D. At the end of the 20th week, 25 (OH) VIT D level was at a normal level in 23 patients of treatment group and five patients of control group (76.7% vs. 16.7) and according to Chi-square test the difference between the two groups was significant (p<0.001).

Table 1: The frequency distribution level of 25 (OH) VIT D before and after the treatment in both groups

Time	Group Level	Treatment Number (%)	Control Number (%)	P
Before treatment	abnormal	30(100)	30(100)	1
	Normal	0(0)	0(0)	
12weeks after treatment	abnormal	10(33/3)	28(93/3)	<0.001
	Normal	20(66/7)	2(6/7)	
20weeks after treatment	abnormal	7(23/3)	25(83/3)	<0.001
	Normal	23(76/7)	5(16/7)	

Figure 1 depicts the level of GFR during the study for both groups distinctively. It should be mentioned that according to the same test, time variable exerted no significant effect on GFR alterations (P=0.11) but the effect of time-group was significant (P<0.001).

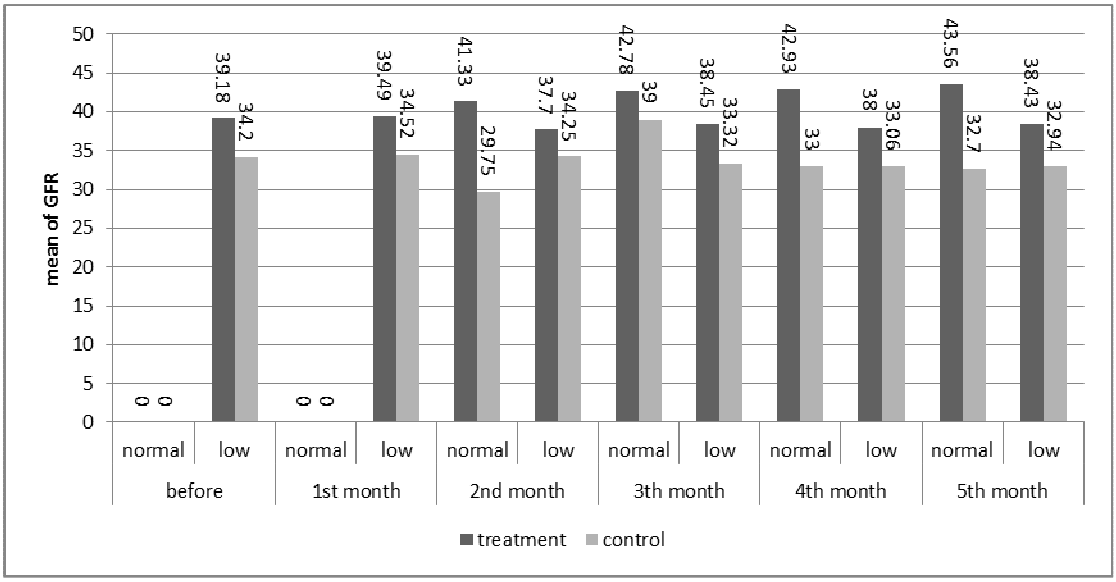

Figure 2: the mean score for GFR level in treatment and control groups in terms of vitamin D level

According to T-test, the average weight, the improved calcium level, and phosphorus level were not significantly different before and after treatment in both groups (P>0.05). But the serum level of Albumin after the treatment and serum level of calcium before and after the treatment were significantly different in both groups (P<0.05). Table 2 represents the mean score and standard deviation for the levels of biochemical parameters before and after treatment in both treatment and control groups.

The observation of BUN and Creatinine levels before the treatment up to 5 months after the treatment revealed that BUN and Creatinine levels were not different before the treatment up to two months after the treatment in both groups. However after the 3rd month the difference was significant. The ANOVA test along with the replication of observations also indicated the alteration process of BUN and Creatinine was significantly different for the two groups during the treatment (figure 1 and 2).

Table 2: the mean score and standard deviation for biochemical parameters before and after the treatment in both groups

Factor	Group Time	Treatment		P
Weight	Before treatment	73/55±10/6	75/39±9/9	0.5
	After treatment	74/69±10/8	73/78±10/3	0.75
Calcium Serum level	Before treatment	8/83±0/52	8/56±0/47	0.035
	After treatment	8/89±0/54	8/53±0/43	0.006
Corrected Calcium Level	Before treatment	8/81±0/45	9/37±3	0.34
	After treatment	8/8±0/47	8/78±0/31	0.82
phosphorus serum level	Before treatment	4/09±0/43	4/14±0/49	0.73
	After treatment	4/08±0/45	4/09±0/42	0.93
Albumin	Before treatment	3/93±0/31	3/88±1/06	0.82
	After treatment	4/02±0/38	3/64±0/4	<0.001
BUN	Before treatment	34/5±20/8	31/9±9/6	0.54
	1 month after	29±7/2	31/9±6	0.1
	2 months after	28/3±6/3	31±4/4	0.06
	3 months after	28/8±6/8	32/2±4/3	0.022
	4 months after	24/5±5/3	31/8±5/1	<0.001
	5 months after	24/5±5/3	31/8±5/1	<0.001
Creatinine	Before treatment	2/25±1/4	2/11±0/44	0.59
	1 month after	1/89±0/63	2/14±0/48	0.08
	2 months after	1/83±0/56	2/16±0/47	0.017
	3 months after	1/8±0/53	2/22±0/5	0.003
	4 months after	1/62±0/47	2/26±0/53	<0.001
	5 months after	1/46±0/46	2/28±0/59	<0.001

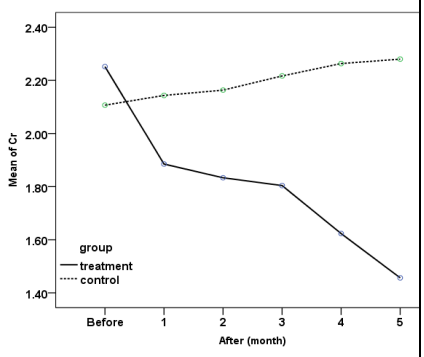

Figure 1: the mean score for GFR indicator prior to the treatment up to 5 months after applying treatment in both groups

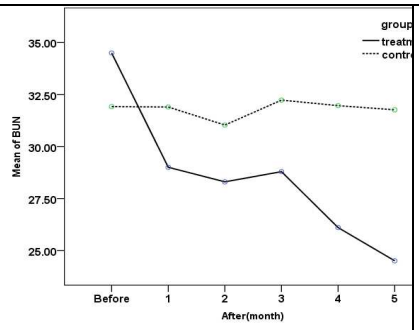

Figure 2: the mean score for BUN indicator prior to the treatment up to 5 months after applying treatment in both groups (P=0.032)

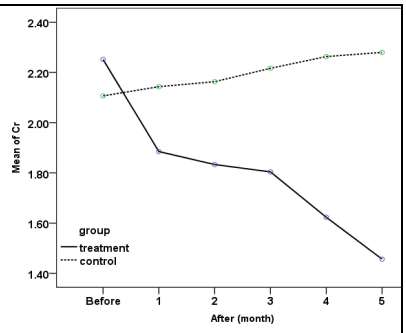

Figure 3: the mean score for Cr indicator prior to the treatment up to 5 months after applying treatment in both groups (P=0.004)

Figure 2 Alterations process of BUN and Creatinine for the two groups during the treatment

DISCUSSION AND CONCLUSION

The overall purpose of conducting this study was to determine the effect of 25 (OH) VIT D on GFR indicator in patients with renal failure. Based on the findings of the study, both treatment and control groups were not significantly different in terms of baseline and demographic variables and according to covariance analysis, variables of age, gender and the cause of renal failure had no significant effect on the alterations of GFR level. Therefore, 25(OH) VIT D level is likely to be at least one of the factors that would affect the remaining kidney function.

Based on the findings of our research, improving the level of vit D would result in the significant improvement of GFR, i.e. the mean score for this indicator in 12 and 20 weeks after the treatment was significantly different in the 2 treatment groups which received vit D treatment and the control group that got no vit D. on the other hand, besides the applied treatment, 25 (OH) VIT D and GFR indicator were significantly related. Generally speaking, patients with low levels of 25 (OH) VIT D, showed levels of GFR. This relation was observable at the end of both 12^{th} and 20^{th} weeks. Previous studies mostly indicated that there was a direct relation between serum level of 25 (OH) VIT D and remaining kidney function. Rothenbacher et al., in a prospective study in 2014, examined 1385 people aging 65 years or above in terms of 25 (OH) VIT D and kidney function, falls and fractures. Based on their findings there was significant relation between kidney function and serum level of 25 (OH) VIT D (24). Oh et al. also found out in a research in 2008 that there is a direct relation between the remaining kidney function and serum level of 25 (OH) VIT D [25]. Michel and et al also evidenced the relation between 25 (OH) VIT D and GFR through a study conducted in 2012 [12]. Lan et al. examined the relation between GFR and serum level of 25(OH) VIT D in 1705 people, which also concluded that GFR and the level of 25 (OH) VIT D are significantly related. Based on the same study findings, in patients whose level of 25 (OH) VIT D was less than 10 Nano grams per milliliter, GFR rate was reduced by 25 % (26). There is also some other controversial evidence on the role of Vit D in reducing the speed of kidney failure progress that requires further studies [9]. Self-care education is emphasized because it leads in active role in treatment process and accepting responsibility for individual health [27]. Social networks are used for behavior improvement, educational performance and other self-care education [28].Thus, regarding the findings of the present study and the result of comparing them to other studies findings, the overall conclusion would put that GFR is related to 25 (OH) VIT D level and the inadequacy of 25 (OH) VIT D in CKD patients can fasten the disease progress. Therefore, it is essential the renal failure patients be examined in terms of 25 (OH) VIT D level and necessary actions be taken to maintain their Vit D level. Additionally, regarding the results of the study, vitamin D deficiency sounded to be prevalent among renal failure patients. So, it is urgent for these patients to examine their Vit D level, at least every 6 months regularly.

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