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THE EFFECT OF VITAMIN D LEVELS ON INFLAMMATION IN PATIENTS WITH CHRONIC RENAL FAILURE

ABSTRACT

It is suggested that a number of environmental and genetic factors trigger the formation of progressive kidney damage and complications. One of these factors is inflammation, it occurs as a result of a series of mechanisms included within a number of cytokines. Vitamin-D, IL-6, PCT and hs-CRP are also valuable biomarkers in terms of mortality in dialysis patients in this sense. Vitamin D deficiency is common in patients with chronic kidney disease (CKD) and is associated with inflammation. In recent years, some randomized controlled trials have revealed the effect of Vitamin D on inflammation in CKD patients, but the results are conflicting. The aim of this study is to investigate the relationship between Vitamin D, high-sensitivity C Reactive Protein (hs-CRP), procalcitonin and IL-6, and to evaluate the relation of Vitamin D levels with inflammation in PD patients, HD patients and controls. This study was carried on with 40 patients receiving on hemodialysis treatment, 40 patients receiving peritoneal treatment with renal failure disease and with a control group consisting of 40 healthy individuals. Vitamin D levels were measured by HPLC, PCT and IL-6 levels were measured by chemiluminescent method, hs-CRP is measured by nephelometric method. For Vitamin D, there was no differences between the groups. For PCT, there was a significant difference between all groups. For IL-6, while there was no difference between peritoneal and hemodialysis groups, a significant difference was determined between the peritoneal dialysis and control groups. For hs-CRP, there was a significant difference among all groups. While correlation was found between serum PCT levels with IL-6 and hs-CRP, no correlations were found between serum PCT with Vitamin D levels. Although a correlation was found between serum IL-6 levels and hs-CRP, no correlation was detected between serum IL-6 and Vitamin D levels. No correlations were detected between Vitamin D andPCT, IL-6 and hs-CRP.

Keywords: Hemodialysis, High Sensitivity C-Reactive Protein, Interleukin-6, Peritoneal Dialysis, Procalcitonin, Vitamin D

1. INTRODUCTION

Hypovitaminosis D and Vitamin D metabolism disorders are common in patients with Chronic Kidney Disease (CKD) [1 and 2]. In addition, renal inflammation is also faced in CKD patients as a pathological process during the disease [3]. Approximately 30-50% of dialysis patients show symptoms that indicate active inflammatory response [4]. Although multiple causes include the increased inflammatory response in such

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patients, there are several studies showing that the low serum concentration of Vitamin D is associated with elevated inflammation markers. Previous studies have shown that the glomerular infiltration of inflammatory cells decreases with Vitamin D administration in animal models with primary glomerular diseases [5, 6, 7, 8, 9 and 10]. Although the molecular mechanism by which Vitamin D inhibits inflammation in CKD remains unclear, there are some opinions about it. Some studies indicate that Vitamin D may have an anti-inflammatory effect with an inhibitory effect on the NF-κB pathway, which is a key transcription factor thought to mediate inflammation by regulating the gene expression of cytokines, chemokines and adhesion molecules [11]. Another view is that Vitamin D may affect inflammation mediated by TLRs, which are trans-membrane receptors on monocytes and macrophages that play a role in the innate immune response against pathogens [12 and 13]. With the introduction of using Procalcitonin (PCT) in inflammation for diagnostic purposes, it has started to be employed as an important diagnostic parameter to show serious bacterial infections and complications that are secondary to systemic inflammation [14]. It is known that PCT has high specificity and sensitivity for early diagnosis of systemic bacterial infections in patients who have Chronic Renal Failure or SDBY and who are treated with hemodialysis [15]. For today, it is widely accepted that this molecule is one of the earliest inflammatory markers of sepsis [16].It has been reported that the cytokine level increases with inflammation in chronic kidney patients; however, the etiology of this increase has not yet been fully elucidated [17]. It has also been reported previously that especially in hemodialysis patients, Interlokin-6 (IL-6) is an important risk factor for mortality because of its roles in inflammation cascade [18]. IL-6 also serves as the major inducer for hepatic protein synthesis, and depending on this, C-Reactive Protein (CRP) [19]. CRP is also a major acute phase reactant which is elevated as a response to tissue damage and is considered as an important indicator of systemic inflammation [20]. Some studies have shown that elevated CRP levels in dialysis patients may be the cause of inflammation-induced mortality [21].

Studies have strengthened the assumption that mortality due to cardiovascular problems in kidney patients has a direct relation with increased plasma concentrations of CRP. Chronic inflammation is related directly to cardiovascular problems and the course of the disease in End-Stage Renal Disease (ESRD) patients, and is elevated with the level of acute phase reactants like CRP [22]. In addition to studies showing that Vitamin D has an effect on this inflammation [23, 24, 25 and 26], there are also studies showing that it has no role [27, 28, 29, 30, 31 and 32]. Therefore, the question "Does Vitamin D level have an effect on the inflammation status in CRF patients?" has not yet found the answer. Both animal models and the results obtained in cellular studies show that, whether Vitamin D actually plays a role in the modulation of immune function and inflammatory processes remains to be elucidated. The fact that this uncertainty becomes as clear as possible is the driving factor that led us to this study.

2. RESEARCH SIGNIFICANCE

The aim of our study, which we planned considering the literature with inconsistent results on the subject, was to investigate the relation between $25(OH)D_3$, high-sensitive C Reactive Protein (hs-CRP), procalcitonin and IL-6 levels in dialysis patients and to evaluate the relation between Vitamin D levels and inflammation in PD (Peritoneal Dialysis), HD (Hemodialysis) and healthy control groups (CG).

3. EXPERIMENTAL STUDY PRINCIPLES

3.1. Study Design and Participants

For the study, the CG consisting of healthy volunteers, the PD Patient Group, and the HD Patient Group in which the patients were followed-up at Inonu University Turgut Özal Medical Center Nephrology Clinic were formed. All participants who met the inclusion criteria were informed about the study procedure with the "Minimum Informed Volunteer Consent Form" in written and verbal form, and their signatures and permits were received. A total of 40 PD patients (20F-20M), who received dialysis for more than 3 months, 40 HD patients (22F-18M), and 40 healthy controls (25F-15M) were included in the analyses. Demographic characteristics and medical history were obtained by examining the records and through interviews. The sample collection was performed in 4 months' time. The samples to be studied IL-6, PCT and hs-CRP were transferred into routine biochemistry tubes, and the samples to be tested Vitamin D were taken to EDTA tubes. After the blood samples were centrifuged, the sera that were separated were stored in Eppendorf tubes, and were stored at -80°C until analyses. In the CG, IL-6, PCT, hs-CRP and Vitamin D levels of 40 healthy individuals, who had similar mean age, who did not have any known renal disease, and who did not have any active disease, were measured. Prior to the study, the approval for the study was received from Inonu University, Faculty of Medicine, Ethics Committee. The present study was supported by Inonu University, Scientific Research Projects Unit with the project number 2015/25.

3.2. Procedures

3.2.1. Procedure of Vitamin D

The samples that were taken for examining Vitamin D were studied with the ImmuChrom-brand kit with High-Performance Liquid Chromatography (HPLC) method in Shimadzu-brand 10 AVP model device in the Biochemistry Laboratory of Turgut Özal Medical Center of Inonu University. The samples were allowed to thaw at room temperature prior to the analyses. The analyses were made according to the procedure in the kit prospectus. Firstly, 400 µL of the samples were taken into 1.5 mL Eppendorf tubes, and 400 µL IS (Internal Standard) was added to them. After vortexing the mixture for 3 minutes, 500 µL of PREC (Precipitation Reagent) solution was added. After vortexing for 2 minutes again, the samples were kept at 4°C for 15 minutes. After 15 minutes, the solution was centrifuged at 10000 rpm for 5 minutes; and 50 µL of the supernatant was transferred to the HPLC system. HPLC separation was carried out with an "inverse phase" column at 30°C with the Isocratic Method. The chromatograms were created by UV-detector; and the separation was taken as 15 minutes for each flow depending on the column used.

3.2.2. Procedure of PCT

The samples were studied by electrochemiluminescence method in Roche branded Cobas-e 411 model (Roche Diagnostics GmbH D-68298 Mannheim/Germany). Centrifugal sera were stored at -80°C. The samples were allowed to thaw at room temperature before the study. The results of the study that was conducted in the fully-automated device, which was checked and calibrated, were evaluated as ng/mL. The measurement range was defined as 0.02-100 ng/mL.

3.2.3. Procedure of IL-6

The samples were examined with the Electrochemiluminescence Method in Roche-brand Cobas e-411 model device (Roche Diagnostics GmbH D-68298 Mannheim/Germany). The centrifuged sera were stored at -80°C. The samples were allowed to thaw at room temperature before the study. The results of the study conducted in the fully-automated device, which was checked

and calibrated, were evaluated as pg/mL. The measuring range was defined as 1.5-5000 pg/mL.

3.2.4. Procedure of Hs-CRP

The serum hs-CRP levels were examined by using the Nephelometric Method with Siemens-brand Dade Behring Nephelometer 100 model analyzer device (Siemens Healthcare Diagnostic Products GmBH, Emil-von-Behring-Str. 76, 35041 Marburg/Germany). According to the hs-CRP results that were obtained from the measurements, the values less than 3.13 mg/L were considered normal.

3.3. Statistical Analysis

The SPSS 20.1 (Chicago, the USA) package program was employed when the data obtained from the study were evaluated. The qualitative data were tested with the Chi-Square Analysis. The Shapiro Wilk Test was used to determine whether or not the quantitative variables matched normal distribution. When the groups with quantitative variables were compared, the Mann-Whitney U-test, which is one of the nonparametric tests, was used; and since there were more than two groups, the Kruskal-Wallis Test and the Conover Paired Comparison Test were used. The data are shown as mean±standard deviation. When the p value was less than 0.05, the results were considered to be statistically significant. Since the data were not parametric, the Spearman's Rho Rank Correlation Coefficient was also used for correlation coefficients.

4. RESULTS

The mean age values were 51.72±14.04 for PD Group, 57.10±15.8 for HD Group, and 33.8±11.58 for CG. No differences were detected between the PD and HD patients in terms of gender ($p>0.05$), duration of dialysis, weight and height (all p values were >0.05 and 0.296, 0.257, and 0.734, respectively). The demographic and biochemical characteristics of the patients and control groups are given in Table 1.

Table 1. The demographic and biochemical characteristics of the PD Group, HD Group and Control Group

	PD Group	HD Group	Control Group
VD (ng/mL)	9.71±9.14	11.45±9.49	10.61±6.19
PCT (ng/mL)	0.25±0.11	0.52±0.73	0.04±0.05
IL-6 (pg/mL)	11.92±7.55	18.67±15.59	2.99±3.00
hs-CRP (mg/L)	10.10±14.95	23.51±37.30	5.32±5.90
Age (Year)	51.73±14.04	57.10±15.80	33.80±11.59
Height (m)	1.64±0.09	1.63±0.07	-
Weight (kg)	62.25±11.58	67.40±18.70	-
Dialysis Duration (Year)	3.9±2.85	5.33±5.14	-
VD: Vitamin D PCT: Procalcitonin IL-6: Interlokin-6 hs-CRP: Highly sensitive C-Reactive protein			

According to 25(OH)D, there were no differences between PD, HD and control groups (9.71±9.14 ng/mL, 11.45±9.49 ng/mL, 10.61±6.19 ng/mL; $p=0.384>0.05$, respectively). The World Health Organization (WHO) has defined Vitamin D deficiency as a serum level of 25(OH)D below 20 ng/mL [33]. In 92.5% of the PD patients, in 85% of the HD patients, and in 95% of the participant in the CG, there was Vitamin D deficiency (less than 20 ng/mL). There was no difference among groups according the serum 25(OH)D levels ($p>0.05$). For PCT, there were differences between PD, HD and control groups (0.25±0.11 ng/mL, 0.52±0.73 ng/mL, 0.04±0.05 ng/mL; $p=0.000<0.05$, respectively). All groups were different from each other ($p<0.05$).

For IL-6, there were differences between PD, HD and control groups (11.92±7.55 pg/mL, 18.67±15.59 pg/mL, 2.99±3.00 pg/mL; p=0.000<0.05, respectively). PD and control groups, and HD and control groups were different from each other. However, there were no differences between PD and HD groups (p<0.05). For hs-CRP, there were differences between PD, HD and control groups (10.10±14.95 mg/L, 23.51±37.30 mg/L, 5.32±5.90 mg/L; p=0.000<0.05, respectively). All groups were different from each other (p<0.05). In both dialysis groups hs-CRP levels were higher thanin the controls. In HD patients hs-CRP levels were higher than those of PD patients. All groups were different from each other (p<0.05) and boxplot graphics for all parameters at all group levels are given in Figure 1-4.

The correlation coefficients and significance levels of the analysis results are given in Table 2.

Table 2. Demographic and biochemical characteristics of all groups

		VD (ng/mL)	PCT (ng/mL)	IL-6 (pg/mL)	hs-CRP (mg/L)
VD (ng/mL)	r	1.000	0.041	-0.016	-0.048
	p		0.654	0.859	0.605
PCT (ng/mL)	r	0.041	1.000	0.641*	0.498*
	p	0.654		0.000	0.000
IL-6 (pg/mL)	r	-0.016	0.641*	1.000	0.652*
	p	0.859	0.000		0.000
hs-CRP (mg/L)	r	-0.048	0.498*	0.652*	1.000
	p	0.605	0.000	0.000	
Age (Year)	r	-0.045	0.363*	0.428*	0.281*
	p	0.628	0.000	0.000	0.002
Dialysis Duration (Year)	r	-0.111	0.034	-0.150	-0.171
	p	0.325	0.762	0.184	0.130
Weight (kg)	r	-0.031	0.017	0.132	0.215
	p	0.796	0.884	0.270	0.070
Height (m)	r	0.087	0.160	-0.062	0.104
	p	0.468	0.179	0.607	0.386

Correlations between the variables examined were calculated in the entire data set.
VD: Vitamin D PCT: Procalcitonin
IL-6: Interlokin-6 hs-CRP: Highly sensitive C-Reactive protein
* Indicates the statistically significant relationship.

In the entire data set, Serum 25(OH)D levels were not correlated with age, PCT, IL-6, hs-CRP, dialysis duration, weight and height were not correlated (p>0.05). Serum PCT levels were were not correlated with 25(OH)D levels, dialysis duration weight and height (p>0.05). The serum IL-6 levels were positively correlated with age (r=0.428, p=0.000), PCT (r=0.641, p=0.000) and hs-CRP (r=0.652, p=0.000). The serum IL-6 levels and 25(OH)D, dialysis duration, weight and height were not correlated (p>0.05). The serum hs-CRP levels were positively correlated with age (r=0.281, p=0.002), PCT (r=0.498, p=0.000) and IL-6 (r=0.652, p=0.000). The serum hs-CRP levels and Vitamin D, dialysis duration, weight and height were not correlated (p>0.05). In addition, there were a positive correlation (r=0.664; p<0.01) between hs-cRP and IL-6 in the PD group; a positive correlation (r=0.433; p<0.01) between hs-cRP and PCT, and a positive correlation (r=0.621; p<0.01) between hs-cRP and IL-6 in the HD group; and a positive correlation (r=0.503; p<0.01) between hs-cRP and PCT in the CG.

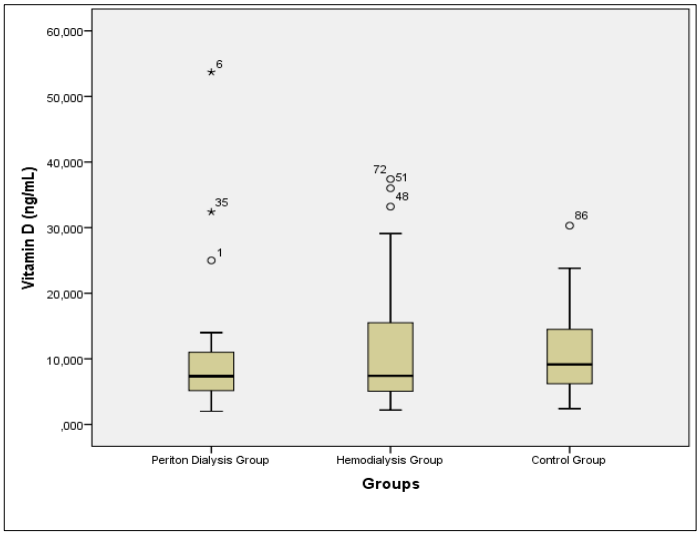

Figure 1. Comparison of the Vitamin D levels in PD, HD and control groups

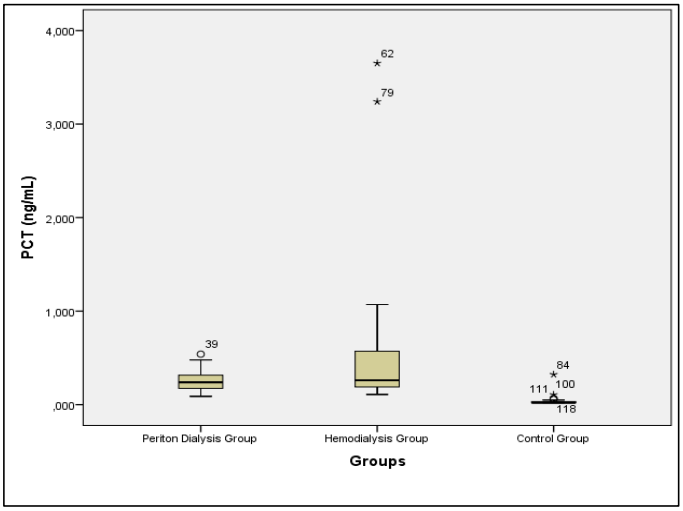

Figure 2. Comparison of PCT levels in PD, HD and control groups

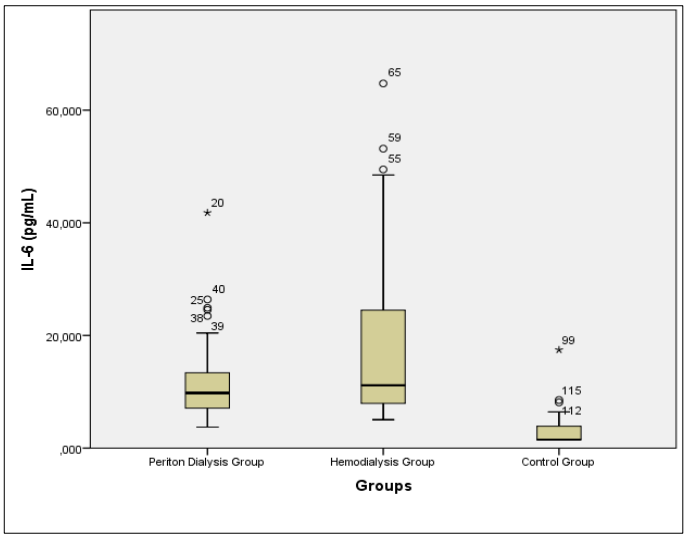

Figure 3. Comparison of the IL-6 levels in PD, HD and control groups

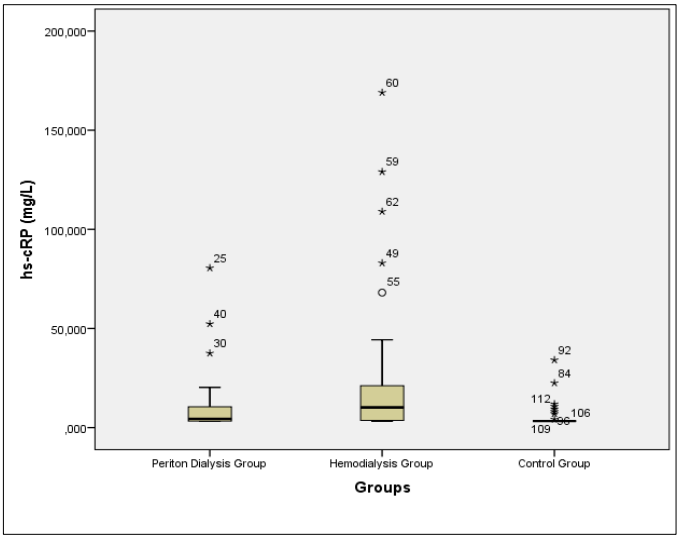

Figure 4. Comparison of hs-CRP levels in PD, HD and control groups

5. DISCUSSION

Previous studies show that Vitamin D deficiency is increasing more and more worldwide with each passing day [34 and 35]. Vitamin D deficiency is known in patients who have CKD, and Vitamin D levels show an inverse correlation with renal function [36]. While Vitamin D deficiency is detected in 86% of CRF patients, who do not receive dialysis, this rate increases to 93% in hemodialysis patients [37]. The exact reason of Vitamin D deficiency is not known in the patient group. However, it is considered that Vitamin D-binding protein loss and proteinuria at nephrotic level may be effective in Vitamin D deficiency [38]. Loss of functional kidney mass also leads to a Vitamin D deficiency. In addition, hyperphosphatemia, hyperuricemia, metabolic acidosis and other uremic toxins suppress 1-α hydroxylase enzyme in a functional manner [39 and 40].

Renal inflammation, as well as Vitamin D deficiency, is an important pathological process in the evolution of CKD [3] and CRP is a good marker for inflammation [15]. The importance of CRP stems from the fact that it increases to high values in a very short time after acute phase response, and it can decrease to normal values right away when the stimulation ends [41]. In our study, the levels obtained for HD, PD and control groups show that CRP may be a good marker for inflammation. Stenvinkel et al. conducted another study and showed that elevated CRP levels might be the cause of inflammation-induced mortality in dialysis patients [22]. Honda et al. conducted a study in patients with ESRF, they reported that IL-6 and hs-CRP were the most reliable parameters for bacterial infection, and IL-6 level was the most reliable parameter for CVD and mortality [42]. Zhang et al. examined the prognostic role of IL-6 and CRP in dialysis patients and showed that CRP and IL-6 are important for the mortality due to all reasons. For this reason, it was reported that the critical role of CRP and IL-6 may contribute clinically to the prognosis of dialysis [43]. In our study, the levels obtained for HD, PD and control groups indicate that IL-6 and CRP can be a good marker of inflammation. hs-CRP and IL-6 levels were higher than CG, and a significant positive correlation was found between IL-6 and hs-CRP ($p<0.05$). This result is compatible with the literature and shows that IL-6 may also be a marker of inflammation like hs-CRP.

Although many parameters that may affect the inflammation status in CRF patients have been investigated, there are not many studies that have examined the effect of Vitamin D.

In addition to a small number of studies showing the role of active Vitamin D in the modulation of renal inflammation [23, 24, 25 and 26] there are also studies showing that Vitamin D does not play a role in this modulation [27, 28, 29, 30, 31 and 32]. In these studies performed in CRF patients, various levels of inflammation markers were evaluated after Vitamin D supplementation. No significant difference in inflammation levels despite Vitamin D supplementation was generally attributed to insufficient intervention time, insufficient dose, and inter-population differences.

In our study, a positive correlation was detected between hs-CRP, PCT, and IL-6; and no significant correlation was determined between hs-CRP and Vitamin D. In our study, the serum PCT, IL-6 and hs-CRP levels were higher at a significant level than the healthy CG ($p<0.05$). No significant relations were detected between the serum Vitamin D, serum PCT, serum IL-6 and serum hs-CRP ($p>0.05$). Many factors can be effective in achieving such a result. Studies on Vitamin D levels among people living in Turkey are rare, and many of these studies are conducted on a certain age group or in a gender-specific manner and because of this, they are far from reflecting the general population [44, 45, 46 and 47].

It was shown in a study that was conducted in Western Anatolia in our country, 70-75% of individuals, especially the elderly and women, have Vitamin D deficiency particularly in autumn and winter periods. Vitamin D deficiency was found in 25% of adolescents in summer, and in 59% in winter in Turkey [48]. Again, Uçar et al., who are from our country, conducted a recent study in Ankara region, and reported that Vitamin D deficiency was 51.8%, which is a very high rate, and Vitamin D insufficiency was detected as 20.7% [49]. In a study conducted by Binnetoğlu to examine the relation between Vitamin D levels and proteinuria in CKD, a moderate but not statistically significant relation was found between the levels of 1.25 $(OH)_2D_3$ and CRP. This was associated with the increase in CRP levels with total and mortality related with Cardiovascular Disease (CVD) [50].

In our study, the reason why Vitamin D levels were found to be low in the patient and control groups, and the lack of significant differences between groups may be that the study was conducted in winter and that Vitamin D deficiency appears before us as a public health problem in Turkey. In our study, parallel to the findings of Binnetoğlu, no statistically significant relationship was found between Vitamin D and CRP. Opatrna et al. investigated the high incidence of infection and inflammation in PD patients who did not have PCT infection and in healthy volunteers, and determined that PCT blood levels were higher at a significant level in PD patients. It was reported that the reason for this was that the microinflammation, which is a condition that is specific to uremic patients, might increase the PCT levels in CRF patients who received PD treatment. In this study, in addition to these findings, a positive correlation was detected between serum CRP and plasma PCT, which is a marker of inflammation [51].

In our study, consistent with the findings of Opartna et al., the PCT level was found to be higher in the HD and PD patient group, and a statistically significant positive correlation was found between PCT and CRP. Sitter et al. conducted a study and showed that loss of renal function did not affect the serum PCT value. For this reason, it was reported that procalcitonin had high specificity and sensitivity for early diagnosis of systemic bacterial infections in patients who had CKD or ESRD and who were treated with HD [15]. Herget et al. investigated the PCT elevation in patients who had CRF and who received HD treatment, in PD patients, and in healthy controls, and detected that the PCT levels increased in direct proportion with the level of the renal failure. They interpreted that this increase was because of decreased renal clearance,

and increased synthesis from mononuclear cells [52]. In our study, no staging was made according to the renal failure level of the patients. However, consistent with the literature, higher PCT values were observed in both HD and PD groups compared to CG. In addition, when a comparison was made between HD and PD patients, it was observed that HD patients had slightly higher hs-CRP, IL-6 and PCT levels compared to PD patients, but the inflammation severity of PD patients was similar to HD patients.

Visvardis et al. investigated the correlation between the PCT levels and the known parameters of inflammation in hemodialysis patients, and determined that the PCT levels were above normal in 38% of the patients. In addition, in this study, significant relations were detected between CRP, PCT and IL-6 markers. In all patients who had increased CRP, the PCT concentration was found to be above the normal limits; and it was reported that the co-increase of the PCT and CRP levels was a reliable marker for chronic inflammation in HD patients. In addition, it was also considered that the increase in CRP, PCT and IL-6 levels together would be more sensitive in evaluating the inflammation compared to the evaluation of each marker separately [53]. In our study, the PCT levels were found to be normal in the patient groups, and there was a significant relation between the PCT, IL-6 and hs-CRP markers.

Mori et al. conducted a study with HD patients with and without bacterial infection and examined PCT, CRP, and IL-6 levels. As a conclusion, they reported that the PCT was a good marker for bacterial infection in patients who received HD treatment. Because the PCT levels may be affected by hemodialysis membrane, it is emphasized that PCT is a good marker of bacterial infection, and must be determined before HD; and the cut-off levels, which are indicative of bacterial infection in HD patients, must be determined as 0.5 ng/mL [54]. In our study, the samples were taken before the hemodialysis by considering that the PCT levels could be affected by hemodialysis membrane; and based on the findings, it was concluded the PCT level could be a good marker for bacterial infection in patients receiving HD and PD treatment. Level et al. conducted a study, and showed that the PCT, which was an inflammation marker in HD patients, increased with inflammation, and that PCT and CRP concentrations were correlated. In addition, it was also found that PCT was a better marker than CRP. Furthermore, it was also reported that the co-evaluation of the increase of PCT and CRP together was more sensitive than evaluating each marker separately [55]. In our study, the PCT level was found to be elevated in HD and PD patient groups, and a positive correlation was determined between the PCT and CRP. In our study, it was also concluded that PCT, which is a marker of inflammation, increased with inflammation, and the PCT and CRP concentration was correlated. Based on the findings obtained from the study, we believe that the combined evaluation of PCT and CRP is more sensitive than the evaluation of each marker separately.

6. CONCLUSION AND RECOMMENDATIONS

In our study, there may be several reasons why Vitamin D levels were low in both the patient and control groups and there was no significant difference between the groups.The sampling of our study concentrated in the winter months as it wasconducted in winter, the lack of extensivestudies of population and Vitamin D deficiency as a public health problem in Turkey may come up.By keeping the sampling of the study larger, additional groups in which Vitamin D is given at certain doses can be created to expand the study in a more comprehensive manner.Consequently, although there may be a mechanical link between Vitamin D signaling pathways and inflammatory markers, the available data are insufficient to uncover this link. Our study suggests that factors other than Vitamin D may be effective on IL-6, PCT, hs-CRP,

which are indicators of inflammation in chronic kidney disease. Based on our study, we believe that studies with larger populations will be planned and initiated in which dose, treatment duration, side effects, and supplementary therapeutic potentials are better designed.

ETHICS COMMITTEE APPROVAL

Ethics committee approval was received for this study from Clinical Research Ethics Committee of University of İnönü Training and Research (Decision No:2015/24; Date:11/02/2015).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

NOTICE

This article is derived from the master thesis of Nilüfer Bulut, supported by the 2015/25 project number of İnönü University BAP unit, at the Institute of Health Sciences.

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