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Peritoneal and hemodialysis patients: The relationship between serum 25-Hydroxy vitamin D and nuclear Factor-$_K$B levels and fatigue syndrome

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Abstract

Chronic inflammation and vitamin D deficiency are hallmarks of end-stage renal disease (ESRD), with potential links to fatigue through NF-κB-mediated pathways. However, the interrelationships among these factors in different dialysis modalities remain unclear. In this cross-sectional study, we enrolled 29 peritoneal dialysis (PD) and 29 hemodialysis (HD) patients, alongside 20 healthy controls. Measurements included serum 25-hydroxyvitamin D (25[OH]D), Nuclear Factor-kappa B (NF-κB), pro-inflammatory cytokines (IL-1β, IL-6, sIL-6R, IL-8, TNF-α), anti-inflammatory cytokines (IL-4, IL-10), and Short Form 36 (SF-36) quality of life assessments. Dialysis patients exhibited a pro-inflammatory state, characterized by significantly elevated levels of IL-6 ($p=0.007$), sIL-6R ($p<0.001$), and TNF-α ($p=0.002$) compared to controls. Conversely, IL-1β and IL-8 levels were lower, and anti-inflammatory IL-10 levels also tended to be lower in dialysis patients. NF-κB showed a positive correlation with TNF-α exclusively in HD patients ($r=0.476$, $p=0.009$). Vitamin D deficiency was profound in both groups (HD: 9.6±5.9 ng/mL; PD: 15.8±12.1 ng/mL). Despite these biochemical disturbances, no significant associations emerged between 25(OH)D, NF-κB levels, and fatigue scores. While PD patients reported better physical functioning (51.5±29.8 vs 33.6±30.2, $p=0.027$), both modalities showed marked vitality impairments (42.0±23.9 PD, 32.8±18.9 HD) compared to population norms (60.9±20.9). The study confirms a predominance of pro-inflammatory over anti-inflammatory cytokines in dialysis patients, accompanied by severe vitamin D deficiency in both groups, particularly in HD patients. The absence of a clear vitamin D-NF-κB-fatigue relationship may reflect the widespread deficiency observed, potentially obscuring biological effects. These findings highlight the need for interventional trials to evaluate whether vitamin D repletion to achieve sufficient levels can modify inflammatory profiles and alleviate fatigue symptoms in this patient population.

Keywords: NF-κB, 25-OH vitamin D, cytokines, inflammation, fatigue, dialysis

Introduction

Chronic kidney disease (CKD) is a complex pathophysiological process characterized by the progressive and irreversible loss of nephron function. This gradual decline in glomerular filtration rate (GFR) over months or years impairs the kidney's ability to maintain fluid, solute, and metabolic-endocrine balances [1-5]. Patients with CKD often progress to end-stage renal disease (ESRD), requiring renal replacement therapy such as hemodialysis (HD) or peritoneal dialysis (PD).

A significant complication of CKD is the disruption of vitamin D metabolism. Reduced residual renal mass, hyperphosphatemia, metabolic acidosis, and uremic toxins suppress 1-α hydroxylase activity, leading to decreased production of calcitriol ($1.25(OH)_2D_3$) and elevated parathyroid hormone levels [6]. Consequently, vitamin D deficiency is highly prevalent in CKD patients. This deficiency can lead to non-specific symptoms, notably fatigue and functional disturbances, mirroring symptoms found in conditions like thyroid disease or vitamin B_{12} deficiency [7]. The striking similarity between symptoms such as pain, sleep disturbances, and mood changes in chronic fatigue syndrome and those associated with vitamin D insufficiency highlights a potential link between vitamin D status and fatigue [8].

Chronic inflammation is another pervasive issue in patients with

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CKD and ESRD. Impaired renal function promotes uremia, increasing susceptibility to infections and immune system dysregulation. Furthermore, repeated dialysis treatments can activate leukocytes, leading to sustained cytokine production [9]. Pro-inflammatory cytokines and a reduced adenosine triphosphate (ATP) pool (energy loss) are recognized contributors to fatigue symptoms. Persistent activation of Nuclear Factor-kappa B (NF-κB), a key pro-inflammatory transcription factor, has been implicated in chronic fatigue syndrome [10]. Conversely, adequate levels of 25-hydroxyvitamin D (25[OH]D) can lead to the local production of $1,25(OH)_2D_3$, which has been shown to suppress NF-κB activation by interfering with its DNA binding [11]. NF-κB itself is a crucial regulator of the immune system, playing an important role in inflammatory and fibrogenic processes within the kidney [12].

Given the high prevalence of both vitamin D deficiency and chronic inflammation in dialysis patients, alongside frequent reports of fatigue, understanding the complex interplay between these factors is critical. While existing literature suggests connections between vitamin D, inflammation, NF-κB, and fatigue in various contexts, the specific relationships in the context of ESRD patients undergoing different dialysis modalities remain less thoroughly elucidated. Therefore, this study aimed to compare inflammatory cytokine profiles, quality of life, and fatigue symptoms between peritoneal dialysis and hemodialysis patients, and to investigate the relationship of serum 25(OH)D and NF-κB levels with fatigue symptoms in these populations.

Material and Methods

The present prospective study was conducted at the Nephrology Department of Inönü University Faculty of Medicine, utilizing patients from both its Peritoneal Dialysis and Hemodialysis units. The study cohort comprised 58 individuals undergoing regular dialysis treatment, with 29 patients receiving Continuous Ambulatory Peritoneal Dialysis (CAPD) (16 males, 13 females) and another 29 patients on hemodialysis (HD) (15 males, 14 females). For comparative analysis, a control group consisting of 20 healthy adults (10 males, 10 females) was also enrolled. Patients were carefully selected, with exclusion criteria encompassing any clinical signs of infection, including hepatitis B and C, as well as individuals with active immunological diseases or those currently prescribed immunosuppressive, immunomodulatory, or anti-inflammatory medications. Ethical approval for this study was obtained from the Inonu University Faculty of Medicine Clinical Research Ethics Committee on November 5, 2014 (Protocol No: 2014/168). Prior to participation, all individuals were thoroughly briefed on the study's objectives and procedures, and written informed consent was subsequently obtained from every willing participant. Sample size was estimated a priori using GPower 3.1 software. Based on pilot data (IL-6 effect size 0.65, α=0.05, 80% power), 23 participants per group were calculated as sufficient. To account for potential attrition and specific group comparisons, we recruited 29 patients per dialysis group (HD/PD) and 20 controls. The achieved sample size yielded a post-hoc power of 0.81, enabling the detection of clinically meaningful SF-36 vitality differences (Minimally Clinically Important Difference (MCID) = 5 points), moderate cytokine correlations ($r \geq 0.4$), and vitamin D effect sizes (Cohen's d=0.6) comparable to prior renal studies.

Detailed demographic and clinical data were systematically collected for each patient, encompassing age, gender, the established duration of their Chronic Kidney Disease (CKD) (measured from diagnosis to the study date), the specific type of dialysis they were receiving, and whether they were currently undergoing active vitamin D supplementation. Hemodialysis patients adhered to a standard regimen of three dialysis sessions per week, each lasting 4 hours. These sessions employed lactate-containing solutions and polysulfone membrane dialyzers (Polysulfon UF 4.0; Hemoflow F5, Fresenius, Germany) with a surface area ranging from 1.6 to 1.8 m^2. Conversely, CAPD patients performed daily peritoneal dialysis four times, utilizing solutions containing either 1.36% glucose or, when clinically deemed necessary, 3.86% glucose or icodextrin (Maltose-containing) solutions.

Blood samples were diligently collected from all enrolled participants. For hemodialysis patients, these samples were specifically drawn immediately preceding their scheduled dialysis session. Samples designated for the measurement of NF-κB, Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-4 (IL-4), Interleukin-6 (IL-6), soluble Interleukin-6 Receptor (sIL-6R), Interleukin-8 (IL-8), Interleukin-10 (IL-10), and 25(OH)D vitamin levels were promptly centrifuged and archived at -20°C until the time of laboratory analysis. In addition to these specific markers, routine biochemical parameters were assessed, including serum corrected calcium, phosphorus, albumin, intact parathyroid hormone (iPTH), creatinine, and a complete blood count. Laboratory analyses were performed using specific methodologies: 25(OH)D levels were quantified using High Performance Liquid Chromatography (HPLC) with a Vitamin D3 ImmunoChrom GmbH kit on an HPLC device (Heppenheim, Germany). Concentrations of TNF-α, IL-1β, IL-6, IL-8, and IL-10 were determined via Enzyme-Linked Immunosorbent Assay (ELISA) using a DIAsource kit (DIAsource ImmunoAssays S.A., Louvain-la-Neuve, Belgium). Similarly, IL-4 and sIL-6R levels were measured by ELISA with a Sunred kit (Sunred Biological Technology, Shanghai, PRC). NF-κB levels were assessed using an ELISA kit from Uscn Life Science Inc. (Wuhan, PRC). Intact PTH was measured using a Siemens Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Calcium, phosphorus, albumin, and creatinine levels were analyzed via an Abbott Architect c 16000 device (Abbott Diagnostics).

To evaluate the impact of CKD and vitamin D deficiency on patients' quality of life and the presence of fatigue, the widely recognized Short Form 36 (SF-36) questionnaire was administered specifically to the dialysis patient groups. The vitality subscale of the SF-36 was employed as a key indicator

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for assessing fatigue, with higher scores being indicative of greater vitality and, consequently, less fatigue. Statistical analyses were meticulously conducted using Statistical Package for Social Sciences (SPSS) for Windows 15.0. Comparisons of variables among the hemodialysis, peritoneal dialysis, and healthy control groups were performed using the Kruskal-Wallis H test, Mann-Whitney U test, or One-Way Analysis of Variance (ANOVA) test, selected based on the specific data distribution and suitability for each parameter. The strength and direction of relationships between variables were determined using either Pearson or Spearman correlation coefficients. All reported probability values were two-tailed, and a p-value of less than 0.05 was pre-established as the threshold for statistical significance. Categorical variables were expressed as percentages (%), and their comparisons between groups were carried out using Chi-square or Wilcoxon tests. All findings were critically evaluated within a 95% confidence interval.

Result

The demographic and baseline characteristics of the study participants indicated a comparable distribution across the groups. The mean age for HD patients was 53.6 ± 12.5 years, while PD patients had a mean age of 50.6 ± 13.1 years. The healthy control group exhibited a mean age of 47.2 ± 11.0 years. No statistically significant difference in age was detected among the three cohorts (p>0.05). Similarly, gender distribution did not vary significantly, with 51.7% (15 patients) of HD patients, 55.2% (16 patients) of PD patients, and 50% (10 patients) of the healthy controls being male (p=0.934). Furthermore, the duration of dialysis treatment showed no statistically significant difference between the HD and PD groups (p=0.434), nor was there a significant difference in the reported use of active vitamin D between these two patient groups (p=0.773).

Analysis of biochemical parameters, as detailed in Table 1, revealed no significant differences between HD and PD patients in terms of hemoglobin, serum creatinine, albumin, phosphorus, and parathyroid hormone levels (p>0.05 for all). However, a statistically significant distinction was observed for serum calcium levels, which were notably higher in PD patients compared to HD patients (p=0.005).

Table 1. Comparison of biochemical values of hemodialysis and peritoneal dialysis patients

	Peritoneal Dialysis N:29	Hemodialysis N:29	p
Hgb (g/dL)	11.2±1.8	10.6±1.7	0.308
Creatinine (mg/dL)	9.6±3.1	8.4±2.4	0.120
Albumin (gr/dL)	2.9±0.4	3.1±0.4	0.072
Calcium (mg/dL)	9.2±0.1	8.5±0.7	0.005
Phosphorus (mg/dL)	4.8±1.6	4.9±1.5	0.630
PTH (pg/mL)	353.4±251.7	530.7±503.5	0.253

The comparison of cytokine and vitamin D levels across the HD, PD, and control groups is presented in Table 2. Pro-inflammatory cytokines, specifically IL-6, sIL-6R, and TNF-α, were found to be statistically significantly higher in both HD and PD patients when compared to the healthy control group (p=0.002, p=0.007, and p=0.000, respectively, demonstrating significance for both HD-Control and PD-Control comparisons). Conversely, IL-1β (p=0.000) and IL-8 (p=0.001) levels were lower in dialysis patients compared to the control group, with specific significant differences noted across PD-HD, PD-Control, and HD-Control comparisons for IL-1β, and PD-HD and PD-Control comparisons for IL-8. Among anti-inflammatory cytokines, IL-4 levels were higher in both dialysis groups compared to controls (p=0.004, significant for HD-Control and PD-Control comparisons), while IL-10 levels did not show a statistically significant difference across the three groups (p=0.085). Importantly, there was no significant difference observed in NF-κB values when comparing HD, PD patients, and the control group (p=0.870). Regarding 25(OH)D levels, significant differences were identified across the groups (p=0.002), with PD patients having mean levels of 15.8±12.1 ng/mL, HD patients at 9.6±5.9 ng/mL, and control participants at 7.4±4.5 ng/mL, indicating significant distinctions between PD and HD groups, as well as between HD and control groups.

Evaluation of Quality of Life utilizing the SF-36 questionnaire, as summarized in Table 3, indicated that PD patients generally reported higher scores across most subscales compared to HD patients. Statistically significant advantages for PD patients were specifically observed in physical functioning (51.5±29.8 vs. 33.6±30.2, p=0.027), role limitations due to physical problems (37.9±49.3 vs. 5.7±21.5, p=0.006), and the physical component summary (11.9±2.7 vs. 10.0±3.1, p=0.018).

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Table 2. Comparison of cytokine and vitamin D values of hemodialysis, peritoneal dialysis patients and healthy controls

	Peritoneal Dialysis 29 patient	Hemodialysis 29 patient	Control group 20 patient	p
Gender (male)	%55.2 (16)	%51.7 (15)	%50(10)	0.932
Age (years)	50.6±13.1	53-6±12.5	47.2±11.0	0.245
NF-κB (ng/mL)	0.4±0.2	0.4±0.3	0.4±0.2	0.870
sIL6r (ng/mL)	52.3±43.9	61.4±54.7	29.5±35.3	0.007[b,c]
IL4(pg/mL)	646.0±501.1	726.9±526.3	382.0±424.2	0.004[b,c]
IL8 (pg/mL)	42.0±39.2	64.5±33.4	83.8±80.5	0.001[a,b]
TNFalfa (pg/mL)	18.6±7.7	22.1±29.2	3.1±2.8	0.000[b,c]
IL1beta (pg/mL)	249.3±64.9	281.2±56.1	381.6±111.3	0.000[a,b,c]
IL6 (pg/mL)	14.6±6.3	44.0±115.1	9.2±7.8	0.002[b,c]
IL10 (pg/mL)	7.2±9.3	4.8±3.0	9.8±13.1	0.085
25 (OH)D (ng/mL)	15.8±12.1	9.6±5.9	7.4±4.5	0.002[a,c]

a: PD-HD, b: PD-control group, c: HD-control group comparison

Table 3. Calculation of scores of SF-36 quality of life scale subgroups

	Peritoneal Dialysis 29 patient	Hemodialysis 29 patient	p
Physical Function	51.5±29.8	33.6±30.2	**0.027**
Physical Limitation	37.9±49.3	5.7±21.5	**0.006**
Bodily Pain	54.8±29.4	44.2±28.7	0.165
General Health	66.3±12.4	60.3±13.6	0.158
Vitality/Fatigue	42.0±23.9	32.8±18.9	0.144
Social Health	61.1±33.9	48.5±41.1	0.196
Mental Health	68.2±17.9	62.1±21.5	0.327
Emotional Restriction	25.2±43.3	14.1±32.8	0.400
Physical Dimension	11.9±2.7	10.0±3.1	**0.018**
Mental Dimension	12.1±2.3	10.9±2.1	0.090

Correlation analyses revealed distinct patterns between the two dialysis groups. In PD patients (Table 4), no significant correlations were established between serum 25(OH)D levels, NF-κB levels, or SF-36 vitality/fatigue scores with age, dialysis duration, hemoglobin, creatinine, calcium, phosphorus, PTH, or any of the measured cytokines (IL-1β, IL-4, IL-6, sIL-6R, IL-8, IL-10, and TNF-α). In contrast, for HD patients (Table 4), serum 25(OH)D levels demonstrated a negative correlation with age (r=-0.473, p=0.01) and with the pro-inflammatory cytokine IL-8 (r=-0.386, p=0.038). A significant positive correlation was also identified between NF-κB levels and TNF-α (r=0.476, p=0.009). Furthermore, SF-36 Vitality/Fatigue scores in HD patients also showed a positive correlation with serum albumin levels (r=0.460, p=0.018).

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Table 4. Correlation results of serum 25(OH)D, NF-κB levels, and SF-36 vitality/fatigue scores with demographic, biochemical parameters, and cytokines in peritoneal dialysis and hemodialysis patients

		Peritoneal Dialysis			Hemodialysis		
		25(OH)D	**NF-κB**	**Vitality/Fatigue Score**	**25(OH)D**	**NF-κB**	**Vitality/Fatigue Score**
Age	r	-0.096	0.08	-0.354	-0.473	-0.132	-0.226
	p	0.619	0.682	0.060	0.01	0.494	0.266
Dialysis Duration	r	-0.102	-0.05	-0.281	-0.033	-0.11	0.025
	p	0.598	0.797	0.140	0.866	0.572	0.904
25(OH)D	r	1	-0.321	-0.152	1	0.319	0.138
	p	.	0.09	0.431	.	0.091	0.502
NF-κB	r	-0.321	1	-0.190	0.319	1	0.287
	p	0.09	.	0.324	0.091	.	0.155
Hgb	r	0.02	0.205	0.015	0.361	0.044	0.023
	p	0.918	0.287	0.937	0.055	0.822	0.910
Creatinine (mg/dL) Albumin (gr/dL)	r	-0.047	-0.204	0.089	0.443	0.171	0.035
	p	0.809	0.288	0.652	0.016	0.375	0.386
Calcium (mg/dL)	r	0.34	0.163	0.067	0.153	-0.344	0.251
	p	0.071	0.398	0.732	0.428	0.068	0.215
Creatinine (mg/dL) Albumin (gr/dL)	r	0.162	0.272	-0.163	0.209	0.032	0.460
	p	0.4	0.154	0.398	0.277	0.869	0.018
Calcium (mg/dL)	r	0.094	-0.155	-0.391	-0.044	0.161	0.139
	p	0.626	0.421	0.036	0.822	0.405	0.497
PTH	r	-0.154	0.007	0.137	-0.165	0.013	-0.186
	p	0.424	0.97	0.477	0.392	0.948	0.363
sIL6r	r	-0.197	0.169	-0.057	0.036	-0.061	0.011
	p	0.305	0.382	0.768	0.855	0.753	0.959
IL-4	r	-0.057	0.136	0.035	0.233	0.028	0.191
	p	0.768	0.48	0.857	0.224	0.886	0.351
IL-8	r	0.035	-0.141	-0.058	-0.386	0.071	-0.198
	p	0.858	0.465	0.765	0.038	0.713	0.331
TNF-alfa	r	-0.074	-0.366	0.118	-0.071	0.476	0.016
	p	0.704	0.051	0.541	0.716	0.009	0.940
IL-1beta	r	-0.224	0.307	0.084	-0.25	0.134	0.028
	p	0.242	0.105	0.663	0.191	0.489	0.892
IL-6	r	0.08	-0.262	0.315	-0.018	0.19	-0.117
	p	0.68	0.17	0.096	0.927	0.322	0.568
IL-10	r	0.017	-0.174	-0.093	-0.425	0.07	0.088
		0.932	0.366	0.632	0.021	0.717	0.668

Values are presented as n (%). ASD: autism spectrum disorder; ADHD: Attention-deficit/hyperactivity disorder; ID: intellectual disability; OCD: Obsessive–compulsive disorder. Chi-square (χ^2) and p values indicate comparisons between single- and multi-center follow-up groups

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Further correlation analyses examining the relationship between serum 25(OH)D, NF-κB levels, and SF-36 vitality/fatigue scores with the various SF-36 subscales are detailed in Table 5. In PD patients, no significant associations were found between vitamin D or NF-κB levels and any of the SF-36 subscales. However, SF-36 vitality/fatigue scores in this group were strongly and positively correlated with numerous other SF-36 subscales, including physical function (r=0.677, p=0.000), physical limitation (r=0.421, p=0.023), bodily pain (r=0.531, p=0.003), social health (r=0.510, p=0.005), mental health (r=0.407, p=0.029), emotional restriction (r=0.490, p=0.007), physical dimension (r=0.796, p=0.000), and mental dimension (r=0.785, p=0.000), confirming their interrelationship. Similarly, in HD patients, no significant relationships were observed between serum 25(OH)D or NF-κB levels and the SF-36 subscale scores. Nevertheless, SF-36 vitality/fatigue scores in this group also exhibited significant positive correlations with physical function (r=0.589, p=0.001), bodily pain (r=0.457, p=0.019), general health (r=0.501, p=0.008), social health (r=0.503, p=0.007), mental health (r=0.612, p=0.000), emotional restriction (r=0.467, p=0.015), physical dimension (r=0.679, p=0.000), and mental dimension (r=0.795, p=0.000).

Table 5. Correlation results of serum 25(OH)D, NF-κB levels and SF-36 vitality/fatigue scores with SF-36 subscales in peritoneal dialysis and hemodialysis patients

		Peritoneal Dialysis			Hemodialysis		
		25(OH)D	**NF-κB**	**Vitality/Fatigue Score**	**25(OH)D**	**NF-κB**	**Vitality/Fatigue Score**
Physical Function	r	-0.08	0.091	0.677	0.21	-0.021	0.596
	p	0.679	0.638	0.000	0.275	0.912	0.001
Physical Limitation	r	0.004	0.077	0.421	0.243	0.017	0.424
	p	0.983	0.693	0.023	0.232	0.934	0.031
Bodily Pain	r	0.11	-0.058	0.531	0.95	0.224	0.596
	p	0.571	0.766	0.003	0.645	0.272	0.001
General Health	r	0	0.13	0.070	-0.071	0.049	0.055
	p	0.998	0.571	0.719	0.73	0.812	0.788
Vitality/Fatigue	r	-0.152	-0.19	1.000	0.138	0.287	1.000
	p	0.431	0.324	0.529	0.502	0.155	.
Social Health	r	0.38	-0.016	0.510	-0.336	0.103	0.365
	p	0.847	0.936	0.005	0.093	0.617	0.067
Mental Health	r	-0.066	0.22	0.407	-0.1	0.406	.652
	p	0.734	0.908	0.029	0.627	0.04	0.000
Emotional Restriction	r	-0.178	0.065	0.490	-0.183	0.053	0.053
	p	0.356	0.739	0.007	0.37	0.796	0.798
Physical Dimension	r	-0.085	0.018	0.796	0.138	0.109	0.741
	p	0.661	0.928	0.000	0.493	0.589	0.000
Mental Dimension	r	-0.111	-0.058	0.785	-0.056	0.325	0.796
	p	0.565	0.764	0.000	0.785	0.105	0.000

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Discussion

Chronic kidney disease (CKD) places a profound physiological burden on patients, consistently leading to a state of chronic inflammation and often culminating in debilitating fatigue. Our study sought to unravel the complex interplay of inflammatory markers, vitamin D status, and fatigue symptoms in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD), while also comparing their quality of life.

Our findings unequivocally demonstrate a marked inflammatory imbalance in both HD and PD patients. Serum levels of pro-inflammatory cytokines such as IL-6, sIL-6R, and TNF-α were significantly elevated in dialysis patients compared to healthy controls. This aligns with well-established literature highlighting chronic inflammation as a hallmark of uremia, driven by factors like impaired renal function, accumulation of uremic toxins, and repeated exposure to dialysis membranes [9,13]. The observed increase in IL-4, an anti-inflammatory cytokine, in our dialysis patients compared to controls is an intriguing finding that suggests a potential compensatory mechanism, though insufficient to counteract the overall pro-inflammatory state. However, the anti-inflammatory cytokine IL-10, crucial for tempering inflammatory responses [14], was either lower in HD patients or similar to controls in PD patients, indicating a relative deficiency of anti-inflammatory mediators. The peculiar observation that IL-1β and IL-8 levels were lower in dialysis patients compared to healthy controls, while still being higher in HD compared to PD, warrants further investigation. This might reflect different inflammatory pathways activated or suppressed in end-stage renal disease, or variations in the assay's ability to detect certain active forms of these cytokines. Despite these nuances, the overall cytokine profile strongly supports a persistent pro-inflammatory milieu in both HD and PD populations, emphasizing the systemic inflammatory stress experienced by these patients.

Nuclear Factor-kappa B (NF-κB) serves as a pivotal regulator of genes involved in immune and inflammatory responses [15,16]. While we found no statistically significant difference in overall serum NF-κB levels among dialysis patients and controls, a notable positive correlation between NF-κB levels and TNF-α was observed specifically in hemodialysis patients. This suggests that even if the baseline total NF-κB levels are not elevated, its activity or its interaction with certain pro-inflammatory pathways, particularly those involving TNF-α, might be heightened in the demanding environment of HD. This finding underscores NF-κB's central role in driving inflammation and warrants further research, perhaps focusing on NF-κB activation pathways rather than just total protein levels.

Fatigue is a pervasive and profoundly impactful symptom in CKD, affecting a vast majority of dialysis patients—reported in 60-97% of this population [17,18]. Our study corroborates this high prevalence, with average SF-36 vitality scores in both PD (42.0±23.9) and HD (32.8±18.9) patients falling significantly below community averages (60.9±20.9) [19], clearly indicating substantial fatigue. This pervasive fatigue is widely recognized as a major contributor to reduced quality of life and increased morbidity [20]. When comparing the two dialysis modalities, our results consistently showed that peritoneal dialysis patients reported significantly better quality of life scores across several critical domains of the SF-36, including physical functioning, role limitations due to physical problems, and the physical component summary, compared to hemodialysis patients. PD patients' superior physical function scores may stem from preserved residual renal function (RRF), which enhances middle-molecule clearance and reduces inflammatory burden [10]. Notably, RRF correlates with better phosphate control and reduced protein-bound uremic toxins—factors independently linked to fatigue [21]. This observation could be attributed to several factors inherent to PD, such as greater patient autonomy, a more continuous and gentle form of ultrafiltration, and the absence of rapid fluid shifts and hemodynamic instability often associated with HD treatments, which can collectively contribute to a better overall sense of well-being [22]. Fatigue's multifactorial nature—encompassing anemia, sleep disorders, and depression [22]—likely obscured cytokine-specific effects. Multivariate analyses adjusting for these confounders could isolate inflammatory contributions, as demonstrated in cancer-related fatigue studies [23,24].

A central aim of this study was to investigate the hypothesized relationships between serum 25(OH)D, NF-κB levels, and fatigue symptoms. Despite the theoretical basis for these connections—namely, vitamin D's known role in modulating immune responses and suppressing NF-κB activation [11,25-33], and NF-κB's link to chronic fatigue [10]—our study did not find a direct association between serum 25(OH)D or NF-κB levels and SF-36 vitality (fatigue) scores in either HD or PD patients. This presents a critical interpretative challenge. The most plausible explanation for this null finding lies in the profound and widespread vitamin D deficiency prevalent within our study cohort. The mean 25(OH)D levels were strikingly low in both PD (15.8±12.1 ng/mL) and HD (9.6±5.9 ng/mL) patients, well below widely accepted sufficiency thresholds.The lack of 25(OH) D-fatigue correlation may also reflect threshold effects, as levels <12 ng/mL (severe deficiency) are likely insufficient for NF-κB modulation [34,25]. This aligns with Hoeck's observations (8) where fatigue improved only after achieving 25(OH)D >30 ng/mL. Additionally, our ELISA measured total NF-κB, whereas phosphorylated NF-κB (p65) or DNA-binding activity might better reflect pro-inflammatory signaling [16]. When a significant majority of a study population is profoundly vitamin D deficient, the range of vitamin D levels within that group is often too narrow and too low to demonstrate a gradient effect or a protective association with clinical outcomes like fatigue. In essence, if nearly everyone is deficient, it becomes challenging to identify a subgroup with "sufficient" levels whose vitamin D status might differentiate their fatigue experience or inflammatory response. This limitation obscures the potential benefits of vitamin D on NF-κB modulation and fatigue, which have been suggested by

other studies where vitamin D status spanned a wider, healthier range [7,8,25-33]. Our results, therefore, do not refute the biological plausibility of such a relationship but rather highlight a methodological and population-specific constraint.

It is important to acknowledge certain limitations of our study. Firstly, its cross-sectional design precludes inferring causality between the measured variables. Longitudinal studies would be necessary to establish cause-and-effect relationships. Secondly, while the sample size allowed for meaningful comparisons between dialysis modalities and controls, a larger cohort might have provided greater statistical power to detect more subtle associations, particularly if participants exhibited a broader range of vitamin D levels. The primary limitation, as discussed, is the pervasive vitamin D deficiency, which likely confounded our ability to observe a statistically significant correlation between vitamin D status, NF-κB, and fatigue, despite the strong theoretical underpinnings. Additionally, measuring serum NF-κB levels may not fully reflect its active state, which is often a more critical indicator of its biological effect on inflammation.

Conclusion

In conclusion, While our study confirms significant inflammation and fatigue burdens in dialysis patients, the interplay between vitamin D, NF-κB, and fatigue remains unresolved, likely due to near-universal vitamin D deficiency in our cohort. Future investigations should adopt a three-pronged approach: [1] rigorous vitamin D repletion protocols (targeting 25(OH)D >30 ng/mL) to ensure biological activity; [2] phospho-specific NF-κB assays (e.g., p65 subunit quantification) to evaluate pathway activation rather than total protein levels; and [3] multidimensional fatigue assessments incorporating tools like the FACIT-F scale to differentiate inflammatory contributions from anemia, depression, and uremia-related factors.

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Conflict of Interests

The authors declare that there is no conflict of interest in the study.

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Ethical Approval

The study received ethical approval from the İnönü University Clinical Research Ethics Committee with protocol number (2014/168) on (05.11.2014).

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