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Evaluation of the causes affecting the development of pruritus in patients with peritoneal dialysis

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Abstract

Background Several factors play a role in the pathogenesis of pruritus in uremic patients. The pathophysiology is complex and many factors have been identified in these patients. The aim of this study was to investigate the presence, severity, and possible causes of pruritus in patients with peritoneal dialysis (PD) .

Methods Eighty patients, who received continuous ambulatory peritoneal dialysis (CAPD) treatment, were included in this study. Biochemical measurements, parathormone, C-reactive protein (CRP), and vitamin B12 levels of all the patients were recorded. Furthermore, substance P (SP) levels were measured by ELISA methods. Patients were examined by a dermatologist and pruritus degrees were queried using the visual analog score (VAS) with skin dryness.

Results In generalized linear model analysis, total urea clearance and SP independently predicted VAS scores. SP was significantly predictive in ROC analysis in identifying the VAS score in patients with peritoneal dialysis. The sensitivity and specificity of SP were 80% and 67% (cut-off > 364), respectively, with an area under the ROC curve of 0.757 (95% CI 0.650–0.865, $p < 0.001$). SP also was significantly predictive in ROC analysis in identifying xerosis in PD patients.

Conclusion Pruritus was proportional to the amount of substance P and total urea clearance was another reason affecting pruritus in peritoneal dialysis patients.

Keywords Evaluation · Pruritus · Peritoneal dialysis

Introduction

Several changes in the skin begin to appear with advanced chronic renal disease. The most common of these is pruritus and its prevalence has been reported as 10–30%. In patients, who undergo dialysis for end-stage renal disease (ESRD), this rate reaches from 50 to 90% [1–3]. Xerosis (dry skin) is also very common in patients with ESRD. Older people are more likely to be affected by xerosis and uremic pruritus [4, 5]. Several factors play a role in the pathogenesis of pruritus in uremic patients. The pathophysiology is complex and many factors have been identified, including dryness of the skin, hyperparathyroidism, calcium and phosphate accumulation, anemia, inadequate dialysis, magnesium and aluminum levels, imbalances between the opioid receptors mu and kappa, and systemic inflammation [6–9].

There are important studies in favor of the concept that the uremic state is a chronic inflammatory condition in which several pro-inflammatory cytokines are activated. Accordingly, uremic pruritus may be the skin counterpart of the chronic inflammatory condition. It has been shown that in severely itchy patients, albumin levels are lower and ferritin levels are higher than those without this symptom [10, 11].

Neuropeptides, including substance P (SP), calcitonin gene-related protein, beta-nerve growth factor, vasoactive intestinal peptide, and bradykinin, appear to play an important role in the pathogenesis of pruritus. Increased pruritus after SP agonist administration has been reported in an animal model of atopic dermatitis and administration of SP antagonist resulted in relief from the pruritus. It can transmit

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pain and some pruritus sensations from the periphery to the central nervous system [12].

Recently, several studies focused on the understanding of pruritus pathways, including the neuropeptides and nerve fibers involved in pruritus perception. The histaminergic pathway is primarily mediated by a subpopulation of unmyelinated, mechano-insensitive C-fibers that respond to histamine. In addition to their afferent function of transmitting sensory information to the spinal cord, these cutaneous nerve fibers are also involved in peripheral sensitization as they release neuropeptides, such as SP and CGRP upon neural activation in response to pruritus mediators [13–16].

SP, which is produced and secreted by nerve fibers, binds to NK1R and another class of receptors, which are involved in itch signaling, the mas-related G protein-coupled receptors [17].

While some studies showed that the effect of duration and type of renal replacement therapy on the intensity of pruritus constituted a positive correlation, other studies in the literature showed them to be ineffective [18–23]. Several studies have investigated pruritus in peritoneal dialysis (PD) and hemodialysis (HD). Authors showed that a lower severity of uremic pruritus among PD patients was attributed to better preservation of residual kidney function through PD therapy [24–27].

In this study, we planned to research the presence, severity, and possible causes of pruritus in patients with PD.

Materials and methods

Eighty patients, who received peritoneal dialysis treatment between 01.02.2020 and 01.09.2020, were included in this study, which was conducted in the outpatient PD unit after the approval of the Erciyes University Faculty of Medicine Ethics Committee (No:2020/151). An informed consent form was received from all participants. 11 of the patients were receiving automated peritoneal dialysis (APD) and 69 were receiving CAPD treatment.

In this study, inclusion criteria were: age > 18 years; chronic kidney disease stage—G5D, and peritoneal dialysis at the time of the study. Exclusion criteria were: past renal transplantation; skin diseases other than uremic pruritus, such as atopic dermatitis, allergic dermatitis, chronic urticaria, and collagen disease at the time of study. In addition, patients, who had dialysis inadequacy, who were not regularly followed up and were incompatible with treatment were not included in this study.

Laboratory measurements, such as hemoglobin (Hb), leukocyte, ferritin, transferrin saturation, blood urea nitrogen, creatinine (Cr), uric acid, calcium (Ca), phosphorus (P), alkaline phosphatase, parathormone (PTH), total cholesterol, triglyceride, high- and low-density lipoprotein, albumin, C-reactive protein (CRP), vitamin B12, and folic acid levels of all the patients, were performed and recorded. Additionally, information about medication used by the patients was recorded. All patients enrolled in the study were on a standard PD treatment schedule (4 or 5 times a day, 2000 or 2500 mL volume change). Demographic and clinical information, such as 4-h peritoneal equalization test (D/P Cr), renal, peritoneal, and weekly Kt/V, normalized protein catabolic rate (nPCR), peritoneal UF, and residual urine volume were recorded for each patient.

The patients were examined by a dermatologist in the Erciyes University, Department of Dermatology. Pruritus degrees were queried using the visual analog score (VAS). VAS is a scale instrument with a horizontal line numbered from 0 (no pruritus) to 10 (the most severe pruritus). Patients were asked to draw a vertical line on the number they thought corresponded to the intensity of their symptoms. The evaluation was as follows: 0 points: no pruritus, > 0– < 4 points mild pruritus, ≥ 4– < 7 moderate pruritus, ≥ 7– < 9 severe pruritus, and ≥ 9 very severe pruritus [28]. In addition, skin dryness was evaluated as dry or absent in the dermatological examinations of the patients and was recorded by the same dermatologist. There was no additional dermatological disease in the patients.

Blood samples were drawn into a gel-barrier tube and subsequently centrifuged for 5 min at approximately 2500×*g*, and serum samples were stored at − 80 °C until analysis. The serum concentrations of SP were determined by an enzyme-linked immunoassay (ELISA) kit according to the manufacturer's guidelines (USCN Cloud-Clone Corp., Houston TX, USA). Concentrations were reported as ng/L.

Statistical analysis

Histogram and *q*–*q* plots were examined and the Shapiro–Wilk's test was performed to assess data normality. The Levene test was used to test variance homogeneity. A two-sided independent samples *t* test or Mann–Whitney *U* tests were applied to compare the distributions of continuous variables between patient subgroups (i.e., the presence of pruritus and gender). The Pearson chi-square test was conducted to compare the distributions of categorical variables. Generalized linear models were built to assess the risk factors of VAS scores and sclerosis in peritoneal dialysis patients. A Poisson family and log link function was used in estimating the VAS scores, while Binomial family and logit link function were used in estimating the sclerosis of the patients. Significant variables at $p < 0.25$ were included in multiple model and forward elimination was performed using Wald chi-square test statistics to determine the independent risk factors. The estimated coefficients and odds ratios were calculated with 95% confidence intervals. A receiver-operating characteristic curve (ROC) analysis was

used to assess the diagnostic effect of urine volume on both high pain and sclerosis. Moreover, the area under the ROC curve was calculated with 95% confidence interval. The Youden index was used to identify the optimal cut-off value. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratio statistics were calculated with 95% confidence intervals based on the identified cut-off values. Analyses were performed using R 4.0.1 (www.r-project.org). A p value less than 5% was considered as statistically significant.

Results

Patient characteristics are shown in Table 1. The mean age of the patients was 53.30 ± 15.12 and the duration of dialysis was 54 ± 22 months. The major reason for end-stage renal disease was diabetes mellitus. 69 patients were on CAPD; 11 patients were on automated PD (APD). A total of 51 patients had pruritus. 29 of the patients with pruritus were male and 22 were female. 23 had mild, 22 had moderate, 5 had severe, and 1 had very severe pruritis. The pruritis of all patients was generalized, persistent, and daytime. The proportions of patients using icodextrin solution, lactate-buffered solution, and bicarbonate-buffered solution were 75.0%, 20.0%, and 80%, respectively (the solutions are Physioneal and CAPD/DPCA). The proportions of patients with medication use were: calcium-containing phosphate binders (45%), calcium-free phosphate binders (60%), vitamin D analogs (70%), cinacalcet (20%), and erythropoiesis-stimulating agents (80%).

We compared peritoneal dialysis patients, who had pruritus with those that did not. There were statistical differences between the two groups in terms of renal urea clearance, total urea clearance, vas score, and substance P, while 69% of patients with pruritus and 60% of those without pruritus were using icodextrin. The relationship of the patients with Ca, P, and PTH, and DM and other parameters are shown in Table 2. In addition, we compared peritoneal dialysis patients. There was a higher rate of eosinophilia and total urea clearance in male patients (Table 3).

Generalized linear models were conducted to determine the risk factors of pruritus in patients with peritoneal dialysis. In univariate analysis, SP, total kt/V, renal kt/V, total urea clearance, and renal urea clearance were all found to be associated with the presence of VAS score in PD patients. These variables were then used to construct a multivariate model. Moreover, the elimination procedure was forward

Table 1 Patient characteristics

Variable	Statistics
Age	53.30 ± 15.12
Gender (male)	36 (43.4)
Cause of chronic renal failure	
Diabetes mellitus	34 (42)
Hypertension	25 (31)
Glomerulonephritis	8 (10)
Pyelonephritis	5 (6)
Polycystic kidney disease	3 (4)
Amyloidosis	2 (3)
Unknown	3 (4)
Body mass index (kg/m^2)	25.77 ± 5.47
Duration of peritoneal dialysis (months)	54 ± 22
Hemoglobin (g/dl)	10.8 ± 2.4
Albumin (g/dl)	3.85 ± 0.5
D/P creatinine	0.72 ± 0.09
Kt/V	
Dialytic	1.74 (1.29–2.00)
Renal	0.30 (0.00–1.08)
Total	2.05 (1.90–2.48)
Residual urine volume (ml/day)	400 (0–1700)
Urea clearance	
Renal urea clearance	15 (0–48.4)
Dialysis urea clearance	48.5 (39–54)
Total urea clearance	69.5 (53–93.75)

Values are expressed as n (%), mean ± SD, or median (1st–3rd quartiles)

Table 2 Comparison of several parameters in peritoneal dialysis patients with and without pruritus

Variables	Pruritus		p
	Absent (n = 29)	Present (n = 51)	
Age (years)	51.24 ± 12.11	54.27 ± 16.95	0.357
Gender (male)	11 (37.9)	22 (43.1)	0.649
Icodexp (present)	20 (69.0)	31 (60.8)	0.464
Eop (present)	13 (44.8)	24 (47.1)	0.847
Dialytic kt/V	1.75 (1.21–2.00)	1.73 (1.49–1.98)	0.738
Renal kt/V	0.75 (0.14–1.32)	0.25 (0.00–0.89)	0.059
Total kt/V	2.15 (2.02–2.71)	2.03 (1.90–2.42)	0.126
Residual urine volume	850 (250–1450)	300 (0–1000)	0.066
Renal urea clearance	36.0 (7.0–66.0)	10.5 (0.0–38.0)	**0.027**
Dialysis urea clearance	50.0 (39.0–56.0)	49.0 (39.0–54.0)	0.909
Total urea clearance	77.0 (60.0–109.0)	64.0 (50.8–80.0)	**0.026**
VAS score	0.00 (0.00–0.00)	4.00 (2.00–5.00)	**< 0.001**
Substance P	314 (120–601)	476 (181–834)	**0.041**
PTH	403 (291–496)	345 (184–628)	0.518
DM	9 (31.0)	11 (21.6)	0.347
Ca	9.00 (8.50–9.30)	9.00 (8.50–9.40)	0.952
P	4.10 (3.90–4.65)	4.50 (3.80–5.40)	0.266
Ca × P	36.0 (31.2–44.2)	40.0 (32.2–48.2)	0.300

Values are expressed as n (%), mean ± SD, or median (1st–3rd quartiles) and significant values are indicated in bold

Table 3 Between gender comparison of several parameters in peritoneal dialysis patients

Variables	Gender		*p*
	Female (*n* = 47)	Male (*n* = 36)	
Age (years)	51.89 ± 17.17	55.14 ± 11.91	0.313
Pruritus (present)	22 (66.7)	29 (61.7)	0.649
Usage icodextrin (present)	31 (66.0)	23 (63.9)	0.845
Eosinophilia (present)	15 (31.9)	23 (63.9)	**0.004**
Dialytic kt/V	1.76 (1.62–1.98)	1.52 (1.20–2.00)	0.085
Renal kt/V	0.25 (0.00–0.90)	0.63 (0.00–1.12)	0.246
Total kt/V	2.07 (1.92–2.45)	2.04 (1.90–2.53)	0.722
Residual urine volume	300 (0–1000)	825 (0–1225)	0.307
Renal urea clearance	13.0 (0.0–38.0)	32.0 (0.0–66.0)	0.138
Dialysis urea clearance	49.5 (40.5–52.5)	47.0 (36.0–56.8)	0.978
Total urea clearance	61.0 (50.9–79.0)	75.0 (60.0–96.0)	**0.024**
VAS score	2.00 (0.00–4.00)	2.00 (0.00–6.00)	0.417
Substance P	259 (148–679)	464 (197–1172)	0.091
PTH	367 (155–535)	372 (271–627)	0.252
DM (present)	10 (21.3)	10 (27.8)	0.492
Ca	9.00 (8.60–9.30)	8.85 (8.30–9.35)	0.433
P	4.30 (3.60–5.30)	4.45 (4.00–4.95)	0.505
Ca × P	36.0 (30.7–45.5)	38.3 (34.0–44.8)	0.676

Values are expressed as *n* (%), mean ± SD or median (1st–3rd quartiles) and significant values are indicated in bold

and there were only two independent variables in the final model. In the final model, total urea clearance and SP independently predicted VAS scores (Table 4).

SP was significantly predictive in ROC analysis in identifying the VAS score in patients with peritoneal dialysis (Fig. 1A). The sensitivity and specificity of SP were 80% and 67% (cut-off > 364) with an area under the ROC curve of 0.757 (95% CI 0.650–0.865, $p < 0.001$). SP also was significantly predictive in ROC analysis in identifying xerosis in PD patients (Fig. 1B). The sensitivity and specificity of SP were 52% and 79% (cut-off > 608) with an area under the ROC curve of 0.667 (95% CI 0.545–0.788, $p = 0.007$) (Table 5).

Discussion

In this study, in which we investigated the etiology of pruritus in patients receiving PD treatment, we found three major factors associated with pruritus. First, pruritus was proportional to the residual urine amount. Second, total urea clearance was another reason affecting pruritus, and finally, as the amount of SP increased, the pruritus score increased.

In some studies, about pruritus, which causes serious discomfort in the social life of ESRD patients, its relationship with dialysis modalities has been examined and it was shown that PD patients have a higher prevalence of uremic pruritus compared to HD patients [27]. Another interesting finding of the same study was the difference between the intensity of uremic pruritus and clinical parameters according to dialysis modality. In one study, the intensity of uremic pruritus was negatively associated with serum albumin levels in HD patients, suggesting the effect of serum albumin as a negative acute-phase protein in uremic pruritus in HD patients [29].

Other studies examined the relationship between pruritus and ferritin levels and albumin [30, 31]. We could not find a correlation in our study, which is consistent with many studies in the literature. Furthermore, many studies evaluated the relationship between mineral metabolism disorders

Table 4 Generalized linear models of VAS scores and other parameters in peritoneal dialysis patients

Variables	Univariate		Multiple	
	Beta (95% CI)	*p*	Beta (95% CI)	*p*
Age (years)	0.001 (− 0.009/0.009)	0.969	–	–
Gender (male/female)	− 0.199 (− 0.472/0.073)	0.151	–	–
Usage icodextrin (present)	0.054 (− 0.227/0.334)	0.708	–	–
Eosinophilia (present)	− 0.150 (− 0.422/0.122)	0.278	–	–
Dialytic kt/V	0.176 (− 0.117/0.468)	0.239	–	–
Renal kt/V	− 0.412 (− 0.650/− 0.174)	< 0.001	–	–
Total kt/V	− 0.462 (− 0.758/− 0.167)	0.002	–	–
Residual urine volume	− 0.030 (− 0.051/− 0.009)	0.006	–	–
Renal urea clearance	− 0.009 (− 0.015/− 0.004)	< 0.001	–	–
Dialysis urea clearance	0.006 (− 0.002/0.015)	0.127	–	–
Total urea clearance	− 0.007 (− 0.013/− 0.002)	0.008	− 0.016 (− 0.023/− 0.009)	**< 0.001**
Substance P	0.024 (0.003/0.045)	0.023	0.021 (0.001/0.044)	**0.045**

Coefficients and 95% confidence intervals are calculated for 100 unit increase

CI confidence interval and significant values are indicated in bold

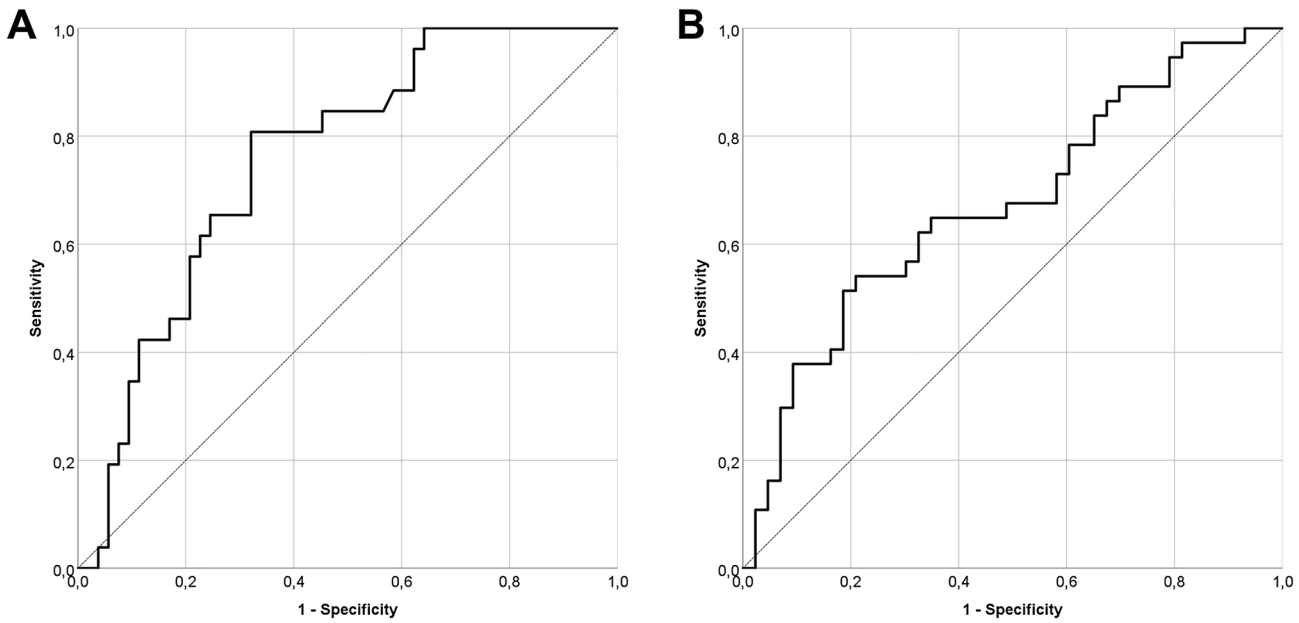

Fig. 1 ROC curves of substance P in predicting **A** high VAS score and **B** xerosis in peritoneal dialysis patients

Table 5 Statistical diagnostic measures calculated for substance-p to identify the high VAS score and xerosis in peritoneal dialysis patients

Substance P	ROC curve statistics		Diagnostic statistics					
	AUC (95% CI)	*p*	SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
> 364 for VAS	0.757 (0.650–0.865)	< 0.001	0.808 (0.606–0.934)	0.679 (0.537–0.801)	0.553 (0.403–0.807)	0.878 (0.725–0.932)	2.518 (1.631–3.888)	0.283 (0.126–0.636)
> 608 for xerosis	0.667 (0.545–0.788)	0.007	0.528 (0.355–0.696)	0.791 (0.640–0.900)	0.679 (0.498–0.812)	0.667 (0.496–0.826)	2.522 (1.306–4.869)	0.597 (0.409–0.872)

ROC receiver-operating characteristics, *AUC* area under the curve, *SEN* sensitivity, *SPE* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio, *CI* confidence interval

such as Ca, P, and PTH levels and pruritus [32, 33]. Similar to most studies in the literature, we found no correlation among them.

In a study by Wu. et al., it was found that a weekly total Kt/V of less than 1.88, longer dialysis duration, higher dietary protein intake, higher PTH, and high sensitivity in CRP levels were independent determinants of higher VAS scores [34]. The opinions explaining why PD patients have a higher prevalence of uremic pruritus compared to HD patients associated uremic pruritus with the accumulation of medium molecular weight uremic toxins such as beta 2-microglobulin [35]. It was reported that dialysis clearance of beta 2-microglobulin with HD treatment using a high-flow membrane is much higher than with PD treatment [36].

In concordance with this idea, PD patients had significantly higher serum beta 2-microglobulin levels than HD patients in this study. Therefore, increased uremic toxin accumulation in PD patients is likely to contribute to a higher prevalence and intensity of uremic pruritus compared to HD patients [28].

In a questionnaire-based study conducted in our clinic with 52 PD and 289 HD patients, the rate of uremic pruritus was found to be 50.2%, and in PD patients, it was found to be 61.5%. In addition, uremic pruritus was observed more in men than in women [37]. In another cohort study evaluating the role of uremic pruritus in patients receiving maintenance PD, they also found that patients with higher pruritus intensity were significantly associated with greater technical failure and poorer patient survival [34].

In the opioid hypothesis regarding pruritus, it is suggested that imbalances in the expression of mu and kappa opioid receptors cause pruritus [38]. Thus, pruritus increases with mu-receptor activation and kappa-receptor blockage and decreases with kappa-receptor activation and mu-receptor blockage [32]. This hypothesis is supported by the observation that the ratio of mu-receptor agonist (beta-endorphin)

to kappa-receptor agonist (dynorphin-A) in HD patients increased compared to healthy controls, and this ratio increased with the severity.

It was reported that there is an important role of the expression of neuropeptides and their receptors in the development of pruritus in several chronic skin disorders. The disturbance in number and structure of nerve fibers and of neuropeptide expression may result in pruritus. Especially, substance P may affect pruritus via mast cells and keratinocytes [39–41]. Nakamura et al. found the increased number of fibers with substance P surrounding vessels and diminished activity of SP degrading enzymes in keratinocytes in the skin of patients, who had skin disorders [39, 42]. Hon et al. concluded that there was a positive correlation between serum SP and nocturnal motor activity in patients with atopic dermatitis [43]. In addition, it was shown that there are an increased number of SP-reactive fibers in patients with psoriasis in skin compared to healthy volunteers [44].

Few studies have been published on the role of neuropeptides in chronic kidney disease. SP, one of the neuropeptides, may be one of the main mediators of uremic pruritus. Recently, it has been reported that the expressions of neuropeptides and their receptors play an important role in the development of pruritus in various chronic skin disorders. Impairment in the number and structure of nerve fibers and neuropeptide expression may affect the pathogenesis of pruritus. SP can affect pruritus via mast cells and keratinocytes [45].

Mast cells release a variety of substances, such as histamine, proteases, interleukin-2, and tumor necrosis factor. SP is a potent agent to stimulate mast cell degranulation. In a study by Snit et al., they showed that SP did not play an important role in pruritus in patients receiving HD and PD, and they did not find any correlation between the duration of dialysis treatment, but the duration of chronic kidney disease was positively correlated with the occurrence of pruritus in both of the studied groups [46]. We found a correlation between SP and VAS scores in our study.

In other studies, conducted with PD patients, the relationship with Kt/V was examined and showed that pruritus was more in patients with low Kt/V [47]; however, there are also other studies showing the opposite. In a cohort study of 105 patients, the mean Kt/V was 1.7 in non-pruritic and 1.82 in pruritic patients [8]. One explanation for this observation is that patients with higher Kt/V values had longer contact with dialyzer membranes or silicone tubes and this causes pruritus [48]. We did not find a relationship with Kt/V in our study. However, this may be because the Kt/V values of all our patients were above 1.7.

This study had some limitations. First, we did not collect data on uremic pruritus before the participants started dialysis treatment. Second, all participants were patients from a single center, which may limit the generalizability of our findings. Third, as this is a cross-sectional study, we were unable to establish causality and transience between dialysis and uremic pruritus. Therefore, larger, multi-center, multi-ethnic studies are needed to confirm our findings.

In conclusion, pruritus was proportional to residual renal function and total urea clearance was another reason affecting pruritus. Additionally, we found that SP levels contribute to pruritus score in these patients.

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