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Substance P and intensity of pruritus in hemodialysis and peritoneal dialysis patients

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Background: Uremic pruritus is a common complication in patients undergoing dialysis. The pathophysiological mechanisms of pruritus in patients with end-stage renal disease remain unknown. Neuropeptides, including substance P, are postulated to play an important role in the pathogenesis of pruritus. The aim of this study was to evaluate the role of substance P in uremic pruritus in patients on hemodialysis and peritoneal dialysis.

Material/Methods: We included 197 patients with end-stage renal disease: 54 on continuous ambulatory peritoneal dialysis and 143 on hemodialysis. Substance P, calcium, phosphorus, iron, ferritin, CRP, albumin, hemoglobin, Ca × P product, and iPTH level were determined in all participants. The correlation between these parameters and self-reported itching was evaluated in patients on hemodialysis in comparison with peritoneal dialysis patients.

Results: The incidence of itching was similar in hemodialysis and peritoneal dialysis patients. No differences in substance P level between the 2 groups were found. There was no correlation between substance P level and the incidence or intensity of pruritus in dialyzed patients.

Conclusions: This study demonstrates that substance P does not play any important role in pruritus in hemodialysed and peritoneal dialyzed patients. However, further studies are necessary to assess the exact role of neuropeptides in uremic pruritus.

Key words: substance P • uremic pruritus • end-stage renal disease • hemodialysis • peritoneal dialysis

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Background

Pruritus is a common skin problem in uremic patients. It remains one of the most frustrating and disabling symptoms in patients with end-stage renal disease and has a great impact on patient quality of life. Skin itching is not a direct cause of death but is associated with increased mortality in uremic patients [1]. It affects about 25–33% of predialyzed patients and 60–86% of patients undergoing dialysis [2]. Uremic pruritus does not depend on age or sex. A 10–14% reduction of itching is found in CAPD patients when compared to hemodialysed patients.

The mechanism underlaying uremic pruritus (UP) is poorly understood. The skin in most patients is atrophic and dry. A disturbed excretion of electrolytes, urea, lactates, and other substances potentially causing itching also affects uremic patients. An increase in blood level of calcium and phosphorus, due to hyperparathyroidism common in end-stage renal disease, leads to calcifications in soft tissues.

In the past 20 years, different hypotheses on the pathophysiology of UP have been generated. The most prominent concept focused on secondary hyperparathyroidism, precipitated calcium phosphate crystals, iron deficiency, neuropathy, and neurological disorders [2].

The receptors for itching are terminal branching of afferent non-myelinated C fibers localized in the lower epidermis. They respond to histamine, capsaicin, and some other substances generating pruritus and are called pruritus-specific. They are a subpopulation of non-mechanosensitive nociceptors, which produce erythema when stimulated by histamine, or without the stimulation. Many inflammatory substances take part in the pathogenesis of pruritus and are produced by mast cells during degranulation: histamine, tryptase, endothelin, acetylcholine, prostaglandins, and cytokines. Chronic infection and dysregulation of fetuin A might be the most harmful factors affecting itching and its intensity [3].

The neuropeptides and the other skin inflammation mediators are known to be of either systemic or local origin [4]. Some investigators hypothesize that UP is a generalized inflammatory status generated by T helper cell disequilibrium (TH1 predominance) [5,6]. Therapy with ultraviolet light (even administered on only half of the body) helps relieve skin itching in these patients [7]. One may conclude that UVB light has a systemic action. UVB can modulate leukocyte Th1 and Th2 differentiation, and also affect Th1 expression [5].

Histamine, which is released from mast cells in response to substance P, has been implicated in UP. According to some authors, UP depends on histamine release by dermal cells. The number of dermal mast cells is increased in uremic patients. Increased plasma level of protease leading to histamine secretion is also reported. Leukotrienes are pruritus mediators and the prostaglandins diminish histamine-dependent itching [8,9].

Pruritus may be generated by systemic or local (central or peripheral) impulses. Itching and transmission of impulses to the central nervous system are mediated by a complicated net of nerves in the skin, mainly nerve non-myelinated C fibers. Among the many mediating substances (e.g., histamine, acetylcholine, and IL-31 tryptase) responsible for producing itching in skin disorders such as atopic dermatitis, a neuropeptide called substance P is worth mentioning. Intradermal injection of substance P causes symptoms of neurogenic inflammation – erythema, edema, and intensive pruritus [10].

It seems that neuropeptides, including substance P (SP), calcitonin gene-related protein (CGRP), beta-nerve growth factor (β-NGF), vasoactive intestinal peptide (VIP), and bradykinin, play an important role in the pathogenesis of pruritus. They evoke enhanced mast cell degranulation and histamine release. Increased itching after administration of SP agonist was reported in an animal model of atopic dermatitis and the administration of SP antagonist resulted in relief of itching [11].

Very few studies have been published on the role of neuropeptides in chronic renal disease. Substance P, one of the neuropeptides, might be one of the main mediators of uremic pruritus. The aim of this study was to evaluate the correlation, if any, of substance P and uremic pruritus, and to compare the influence of hemodialysis or peritoneal dialysis on the development of itching and symptom intensity.

Material and Methods

Material

This study was conducted on all 197 patients (Caucasian) with chronic renal failure, dialyzed in the dialysis unit at the Medical University of Silesia, Zabrze, Poland. None of the patients presented with primary skin disease. The only exclusion criterion was lack of informed consent to participate in the study.

All patients expressed a clear consent. The Bioethics Committee of the Medical University of Silesia approved the experimental design.

We studied 197 patients with end-stage renal disease: 54 subjects on continuous ambulatory peritoneal dialysis (CAPD) and 143 subjects on hemodialysis.

The CAPD group consisted of 54 subjects; 30 men (55.56%) and 24 women (44.44%); age 19–86 years, mean age 56.39

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Table 1. Characteristics of patients.

	CAPD	HD	P
Number			
Total [n]	54	143	0.9688
Women [n] (%)	24 (44.44%)	64 (44.%)	
Men [n] (%)	30 (55.56%)	79 (55.24%)	
Age [yrs]	56.39±15.13	59.38±1.72	0.2086
Cause of chronic kidney disease			
Not known [n] (% total)	3 (5.56%)	1 (0.7%)	**<0.05**
Type 1 diabetic nephropathy	4 (7.41%)	10 (7.04%)	
Type 2 diabetic nephropathy	13 (24.07%)	33 (23.24%)	
Glomerulonephritis	7 (12.96%)	15 (10.56%)	
Hypertensive nephropathy	12 (22.22%)	40 (28.17%)	
Chronic intestitial nephritis	10 (18.52%)	11 (7.75%)	
Kidney stone	1 (1.85%)	1 (0.7%)	
Polycystic kidney disease	3 (5.56%)	20 (14.08%)	
Other	1 (1.85%)	11 (7.75%)	
Duration of chronic kidney disease [yrs]	7.89±6.06	9.72±8.26	0.1568
Duration of treatment CAPD/HD [yrs]	3.29±3.20	4.55±3.87	**<0.05**
Liver disorders [n,%]			
Type B hepatitis	1 (1.85%)	4 (2.8%)	–
Type C hepatitis	1 (1.85%)	10 (6.99%)	–
Cirrhosis	0	4 (2.8%)	–
Other	1 (1.85%)	4 (2.8%)	–
Concomitant disorders			
Hypothyreosis	3 (5.56%)	8 (5.59%)	0.7138
Hyperparathyroidismus	1 (1.85%)	8 (5.59%)	
Cancer	1 (1.85%)	1 (0.7%)	
Diabetes	18 (33.33%)	33 (23.08%)	
CAPD			
Baxter system	33 (61.11%)	–	–
Fresenius system	21 (38.89%)	–	–
Dialysate volume [l/24 hrs]	8.0/2.0	–	–
Number of dialysis/d >3	11 (18.52%)		
HD – access			
Arterio-venous fistula	–	128 (89.51%)	–
Venous catheter	–	15 (10.49%)	–
Dose of dialysis [h/week] >12	–	15 (12.82%)	–
Dializator polisulfonowy	–	143 (100%)	–
Dose of calcium carbonate [g/d]	5.85±3.35	5.03±3.50	0.1423
Use of alfacalcidiol [n, %]	10 (18.52%)	25 (17.48%)	0.5074
Dose of alfacalcidiol [µg/d]	0.25/0.18	0.25/0.87	0.7471

years (±15.13) with mean chronic kidney disease duration of 7.89 years (range, 2–34 years) and mean duration of CAPD treatment 3.29 years (range, 0.2–15 years). Characteristics of all included patients are shown in Table 1. Peritoneal dialysis was performed with use of Baxter (33 patients, 61.11%) or Fresenius system (21 patients, 38.89%); mean use of dialysate was 8.95 (4.5–13) liters per 24 hours.

The hemodialysed group consisted of 143 patients: 79 men (44.76%) and 64 women (55.24%): age range, 25–91 years; mean age, 59.38years (±14.72); chronic kidney disease duration, 9.7 years (1 to 52 years), and mean dialysis duration of 4.55 years (range, 0.5–23 years). Hemodialysis was given 4 hours 3 times per week using dialyzers with a high-flux polysulfone membrane. Approximately 90% of patients were

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Table 2. Self-reported pruritus, skin problems and sleep disturbances in studied groups.

Parameter	CAPD		HD		p
PVAS Intensity of itching	4.29±2.16		4.90±2.47		0.3084
Frequency					
Never [n; (%)]	28	(58.85%)	68	(58.62%)	0.8461
Sometimes	19	(36.54%)	38	(32.76%)	
Every day	5	(9.62%)	10	(8.62%)	
Time of itching					
Day	13	(59.09%)	12	(25.00%)	<0.01
Night	9	(40.91%)	20	(41.67%)	
Before HD session	0		1	(2.08%)	
After HD session	0		15	(31.25%)	
Skin problems	24	(46.15%)	39	(33.91%)	0.1307
Self-reported problems with sleep	15	(28.30%)	51	(44.35%)	<0.05

Table 3. Analysis of influence of sex, liver disorders or other concomitant disorders on skin problems and sleep problems.

Studied group	Skin problems	Problems with sleep
Women and men	38.9% *vs.* 36.8%; χ^2=0.07; p=0.7914	36.6% *vs.* 42.1%; χ^2=0.72; p=0.3933
Patients with and without liver disorders	43.5% *vs.* 36.9%; χ^2=0.14; p=0.7083	43.5% *vs.* 38.5%; χ^2=0.52; p=0.8201
Patients with and without other concomitant disorders	39.2% *vs.* 37.0%; χ^2=0.09; p=0.7643	44.0% *vs.* 35.5%; χ^2=1.26; p=0.2612

dialyzed with use of an arterio-venous fistula and 10.5% of patients by venous catheter.

The quality of dialysis was assessed during the study period by calculating Kt/V for all patients.

Pruritus assessment

A visual analog scale (VAS) measuring the general severity of pruritus was self-reported by patients. Patients were asked to evaluate itching over the previous 30 days.

Patients completed the questionnaires during their hemodialysis sessions or while they were physically in the dialysis unit (patients on CAPD) under staff supervision. The pruritus assessment took place on a randomly selected day.

Laboratory tests

The laboratory tests were performed according to a protocol of routine blood tests in dialyzed patients and were measured automatically in our clinical laboratory by routine methods. iPTH was measured by chemiluminescence method. Serum iron, albumin, and calcium levels were measured by direct colorimetry and transferrin level was measured by turbidimetric method. Phosphorus level was measured by photometry and ferritin by electrochemiluminescence method. Substance P was measured with ELISA (Cayman Chemical Company, Ann Arbor, Michigan, USA) (sensitivity =7.8 pg/ml); we used serum that remained after performing routine tests.

Statistical analysis

Results are expressed as means ±SD for normally distributed data and as medians (total range) for non-normally distributed data. Nominal and ordinal data are expressed as percentages. Statistical comparisons between the 2 groups were made by parametric unpaired t tests for normal distributions or Mann-Whitney U tests for skewed distributions. Distribution of variables was evaluated by the D'Agostino-Pearson test. Multivariate logistic regression adjusted to age was used to examine the relationship of studied parameters with pruritus. P values less than 0.05 were considered to be statistically significant. All tests were 2-tailed. Statistical analysis was performed using STATISTICA 10.0 PL.

Results

The sample size was representative and adequate. All calculations were done taking into account the power of statistical tests. Moreover, for all results of logistic regression, the 95% confidence intervals were added to ensure adequate inference.

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Table 4. Laboratory findings in studied groups.

Parameter	CAPD	HD	p
Haemoglobin [g/l]	11.59±1.45	10.96±1.28	<0.01
Iron [µg/dl]	166.34±93.16	46.65±31.25	<0.001
Ferritin [ng/ml]	273.40±225.12	564.93±482.13	<0.001
Transferin [mg/dl]	–	169.42±40.84	–
Albumin [g/l]	3.69±0.42	3.73±0.44	0.4307
CRP [mg/l]	5.00/12.25	5.70/17.30	0.5674
Calcium [mmol/l]	2.23±0.20	2.16±0.19	<0.01
Phosphorus [mg/dl]	4.98±1.66	5.06±1,67	0.7519
a × P product [mg²/dl²]	44.65±16.12	43.90±14.16	0.7504
PTH [pg/ml]	62.40/62.95	170.50/346.30	<0.001
Kt/V [1/1]	2.62±0.95	1.43±0.29	–
Substance P [pg/ml]	55.58±8.24	58.59±8.51	0.1617

Two (3.7%) patients on CAPD and 26 (18%) HD patients did not complete the questionnaire (VAS).

Skin problems (eg, xerosis, erythema, and crusting) were found in 46% of patients on CAPD and in 34% of patients on HD (Table 2), but this difference was not significant. No significant differences in skin problems between women and men (3.9% *vs.* 36.8%; χ^2=0.07; p=0.7914), patients with and without liver disorders (43.5% *vs.* 36.9%; χ^2=0.14; p=0.7083), patients with and without diabetes, cancer, hypothyreosis, or hyperparathyroidism (39.2% *vs.* 37.0%; χ^2=0.09; p=0.7643) were found.

Itching was reported by 46.16% of peritoneal dialysis patients and 41.38% of hemodialysis patients. Pruritus was reported as being present every day by 9.62% of CAPD and 8.62% of HD patients (Table 2). Among pruritic patients, 25% of patients on HD reported itching during day and a 41.7% at night compared with 59.1% and 40.9%, respectively, in CAPD patients (p<0.01). Several patients had itching shortly after hemodialysis (31%) (Table 2). The severity of itching was less in CAPD (mean 4.29±2.16, VAS) compared to HD patients (mean 4.9±2.47, VAS), but the results were not statistically significant.

Problems with sleep were reported by 28% of CAPD and 44% of HD patients (p<0.05) (Table 2). No differences were found in the incidence of sleep problems between women and men (36.6% *vs.* 42.1%; χ^2=0.72; p=0.3933), patients with and without liver disorders (43.5% *vs.* 38.5%; χ^2=0.52; p=0.8201), or patients with and without hypothyreosis, hyperparathyroidism, diabetes, and cancer (44.0% *vs.* 35.5%; χ^2=1.26; p=0.2612) (Table3).

Mean Kt/V was 2.62 in the CAPD group and 1.43 in the HD group (Table 4).

Mean hemoglobin level was significantly higher in the CAPD group (11.59 g/l) than in the HD group (10.96 g/l) (p<0.01) (Table 4).

A higher level of iron was found in CAPD patients when compared to HD patients (166.34 ug/dl *vs.* 46.65 ug/dl, p<0.001). A higher concentration of ferritin (273.4 ng/ml *vs.* 564.93 ng/ml, p < 0.001) was also found in peritoneal dialysis patients. There were no differences in CRP and albumin level between the 2 groups (Table 4).

A significantly higher calcium level was found in the HD group (2.23 mmol/l *vs.* 2.16 mmol/l, p<0.01). Phosphorus level and Ca x P product were not significantly different between groups. PTH level was significantly lower in CAPD than in HD patients (62.4 pg/ml *vs.* 170.5 pg/ml, p<0.001) (Table 4).

There were no significant differences in substance P concentration between the studied groups (Table 4) and no correlation between this parameter and pruritus was found (Table 5).

The following parameters increased the risk of itching: female sex (OR 1.077; p<0.001), chronic kidney disease duration (OR 1.039; p<0.05), liver disease (OR 2.776; p<0.001), other concomitant disorders (OR 2.125; p<0.001), higher dialysate volume in CAPD patients (OR 1.057; p<0.001), alfacalcidol therapy (OR 1.382; p<0.001), higher dose of alfacalcidol (OR 1.076; p<0.05), increased calcium concentration (OR 1.782; p<0.001),

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Table 5. Logistic regression analysis adjusted to type of dialysis.

Parameter	OR	± 95% CI	z	p
Age [yrs]	0.989	0.979–0.998	–2.35	<0.05
Female	1.077	1.050–1.105	5.71	<0.001
Duration of chronic kidney disease [yrs]	1.039	1.005–1.074	2.26	<0.05
Duration of dialysis treatment [yrs]	1.040	0.990–1.093	1.56	0.119
Liver disorders	2.776	1.782–4.324	4.51	<0.001
Concomitant disorders	2.125	1.682–2.685	6.32	<0.001
Dose of dialysis (HD)	1.035	0.908–1.179	0.51	0.607
Dialysate volume [l/24 hrs]	1.057	1.052–1.061	27.10	<0.001
Kt/V [1/1]	0.913	0.490–1.702	–0.29	0.774
Calcium carbonate dose [g/d]	0.968	0.877–1.067	–0.66	0.511
Alfacalcidiol treatment	1.382	1.318–1.447	13.58	<0.001
Dose of alfacalcidiol [µg/d]	1.076	1.003–1.153	2.05	<0.05
Calcium [mmol/l]	1.782	1.408–2.255	4.81	<0.001
Phosphorus [mg/dl]	1.163	1.023–1.323	2.31	<0.05
Ca × P [mg^2/dl^2]	1.022	1.013–1.030	5.22	<0.001
log10(PTH) [pg/ml]	1.526	1.277–1.824	4.65	<0.001
Albumin [g/l]	1.011	1.007–1.015	5.17	<0.001
Haemoglobin [g/l]	1.096	1.010–1.190	2.19	<0.05
Iron [µg/dl]	1.004	1.003–1.005	11.17	<0.001
Ferritin [pg/ml]	1.106	0.807–1.518	0.63	0.530
Transferin [mg/dl]	0.998	0.996–0.999	–2.79	<0.01
log_{10} (CRP) [mg/l]	0.961	0.905–1.022	–1.26	0.206
Substance P [pg/ml]	1.004	0.995–1.012	0.80	0.421

increased phosphorus concentration (OR 1.163; p<0.05), higher Ca × P product (OR 1.022; p<0.001), higher serum PTH level (OR 1.526; p<0.001), albumin concentration (OR 1.011; p<0.001), hemoglobin level (OR 1.096; p<0.05), and iron level (OR 1.004; p<0.001) (Table 5).

We also found that age (OR 0.989; p<0.05) and serum transferrin concentration (OR 0.998; p<0.01) significantly decreased the risk of pruritus (Table 5).

Discussion

This study provides description of uremic pruritus in patients on dialysis. We assessed the frequency and intensity of self-reported itching in 197 patients with end-stage renal disease; 143 hemodialysed patients *versus* 54 patients on peritoneal dialysis.

The prevalence of UP in our patients was 46.16% in CAPD and 41.38% in HD patients. The percentage of hemodialysed subjects reported by other authors varies from 41.9% to 84% [12–20].

According to some authors, the method of renal replacement therapy in end-stage renal disease does not play a role in the intensity of itching [21]. Other authors [7] have reported more severe UP in HD when compared to CAPD patients. We found that patients receiving peritoneal dialysis had a higher rate but lower intensity of itching (10-degree scale VAS) in comparison

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Table 6. Factors which influence pruritus. Multivariate logistic regression analysis adjusted to type of dialysis.

Parameter	OR	±95% CI	z	p
Duration of chronic kidney disease [yrs]	1.0253	1.0080–1.0428	2.88	<0.01
$\log_{10}$ (PTH) [pg/ml]	1.7600	1.1590–2.6723	2.65	<0.01
Iron [µg/dl]	1.0063	1.0030–1.0096	3.77	<0.001
Alfacalcidiol use	1.0845	1.0733–1.0959	15.27	<0.001
Liver disorders	2.7822	0.8431–9.1813	1.68	0.093
Concomitant disorders	2.2468	1.0879–4.6403	2.19	<0.05

to hemodialysed patients (4.29 in CAPD *vs.* 4.9 in HD patients) (Table 2). The result was not statistically significant and was in the range of 10–14% itching reduction previously reported in peritoneal dialyzed patients [7,22].

No influence of age or sex on itching was found in many studies [17,19,22–24]. Men in the DOPPS I and I Studies had UP more often than women [20]. In contrast, we report that UP occurred statistically significantly more often in women, independent of method of renal replacement therapy (Table 5). HD and CAPD treatments are usually associated with problems with motor functioning, sleep, and lack of energy. According to Laudański et al, these complaints were more frequent in younger patients [25]. In our study, the younger patients suffered had more pruritus than older patients (Table 5).

The influence of duration of renal replacement therapy on itching intensity is reported to be positively correlated [18,22], negatively correlated [26], or not correlated at all [23,24,27,28]. We did not find any correlation between duration of dialysis treatment, but the duration of renal chronic disease correlated positively with occurrence of pruritus in both studied groups (Tables 5 and 6).

Intensive itching in patients with advance kidney failure or on dialysis may lower quality of life, reduce physical and intellectual ability, and affect sleep [19,20,29]. In 2 multicenter studies, severe sleep disturbances were found in 70% of hemodialysed patients with pruritus (VAS >7), but no problems with sleep have been reported in subjects without itching or with mild itching [18,30]. Our study showed significantly more problems with sleep in patients on HD than in patients on CAPD (44.35% *vs.* 28.3%). Hemodialysed patients reported higher rates of itching and they had from itching more frequently at night (Table 2). Neither sex nor concomitant disorders influenced sleep (Table 3).

We showed that liver disease significantly increased the risk of itching (Tables 5 and 6). Liver diseases such as cirrhosis or cholestasis are often associated with pruritus [31]. Type B or C chronic hepatitis can increase itching in hemodialysed patients, and type C hepatitis is a strong independent predictor of pruritus [14]. Likewise type C hepatitis was more frequent in hemodialysed patients with pruritus (10.0%) than in patients without itching (8.6%). Until now, no influence of hepatic disorders on UP in patients on CAPD has been reported.

We were not surprised that pruritus was more frequent in patients who also had diabetes, cancer, hypothyreosis, or hyperparotidism (Table 6), and with higher intensity. The results of the DOPPS I and II Studies revealed that hemodialysed patients with pruritus significantly more often were diabetic (33%) when compared to patients without itching (30.4%) [20]. Cancer is a chronic inflammatory status and may cause itching. Only 1 subject in our study had cancer, so we did not exclude him.

Patients on CAPD had itching more often during the day and patients on HD had more itching during the night (Table 2). The increase in skin temperature during sleep may stimulate vanilloid receptors in sensory fibers, and various methods of skin cooling can relieve pruritus [31]. Our patients reported itching more often after HD session than before sessions. Pruritus occurred in 31.4% of patients during and after hemodialysis. Itching during HD might be explained by low biocompatibility of dialyzers [5,27,32], but we used only biocompatible polysulfone membranes.

Some studies have shown that increasing the dose of dialysis leads to an improvement in UP [33–35]. Nevertheless, several studies have not shown such an association [3,9,17,19,23,24]. Likewise, we did not find an association between KT/V and the incidence of itching, regardless of method of dialysis used (Table 5). A fairly low response rate in hemodialysed patients in our study might have also influenced the results.

According to some investigators, UP is a symptom of systemic inflammatory disorder [10]. Inflammation is principally associated with uremic pruritus in hemodialysis patients, and the patients with severe skin itching have higher CRP levels [14]. Inflammatory infiltration has been found in the skin of

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patients with severe UP [36]. According to Chen, elevated CRP predicts a worse outcome in the population of hemodialysed patients and in moderate/severe pruritic patients, those with higher CRP had worse overall mortality [37]. Nevertheless, other authors have not confirmed the association between CRP concentration and itching [3,6,9,23,24]. We found that our patients on hemodialysis had slightly higher CRP levels (Table 4) and that there was no correlation between concentration of CRP and itching in patients on hemodialysis and peritoneal dialysis both (Table 5). Ferritin concentration, which is also an indicator of inflammation, was significantly higher in hemodialysed patients when compared to CAPD patients (Table 4). Higher concentration of CRP and ferritin in hemodialysed patients may reflect increased inflammatory status (eg due to vascular access), method *per se*, and more advanced age of patients, which result in more concomitant inflammatory disorders and more advanced age of patients, which result in more concomitant inflammatory disorders. Lack of correlation between ferritin concentration and itching (Table 5) found in our study confirms the observations of other investigators [6,9,23,38]. It appears that clinicians need to resolve the underlying inflammatory status to improve patient survival on dialysis.

Anaemia was proven by Virga to have no direct link with UP [24]. In our study, higher hemoglobin was related to higher risk of itching (Table 5); higher iron level also significantly increased the risk of itching and its intensity (Tables 5 and 6). It seems that higher transferrin level significantly lowers the risk of itching in hemodialysis (Tables 4 and 5.). We did not measure level of transferrin in our patients on CAPD; this is a limitation of our study.

In contrast to some authors reporting lower albumin level in pruritic patients on HD [20,24,38], we did not find differences in albumin level between patients on HD when compared to patients on CAPD (Table 4). We showed that higher albuminemia significantly increased the risk of itching in patients receiving HD and patients receiving CAPD (Table 5) and some authors did not find an association between these 2 parameters [3,6,23,28].

Numerous studies have shown that disturbances in mineral metabolism such as calcium, phosphorus, and intact parathyroid hormone (iPTH) level are not related to itching in patients on hemodialysis [3,6,19,23,24,28,38,39]. According to the other reports, pruritus may be independently associated with higher calcium [18,20,35], phosphorus, and iPTH concentrations [40]. We showed that higher Ca × P product significantly increased the risk of itching on dialysis (Table 5). The influence of augmented Ca × P product on the incidence of itching in peritoneal dialysis has been reported by only 1 author so far [41]. Ca × P product above 70 mg^2/dl^2 was related to itching in a large group of hemodialysed patients [1]. Similar results (when Ca × P product > than 50–60 mg^2/dl^2) have been found in the DOPPS I and II studies [20]. In contrast, numerous studies have not found any correlation between itching and Ca × P product [6,19,23,38].

This study, according to our knowledge, is the first to evaluate the concentration of substance P in serum of patients on hemodialysis and CAPD.

Neurophysiological factors are postulated to take part in uremic pruritus. Recently published studies report an important role of expression of neuropeptides and their receptors in development of pruritus in several chronic skin disorders. The disturbance in number and structure of nerve fibers and of neuropeptide expression may affect the pathogenesis of pruritus. Substance P might affect itching via mast cells and keratinocytes [11,36,42]. Mast cells release several substances such as histamine, proteases, interleukin-2, and tumor necrosis factor. Substance P has strong abilities to stimulate mast cell degranulation. Nakamura found increased number of fibers with substance P surrounding blood vessels, diminished activity of SP degrading enzymes, and increased NGF expression in keratinocytes in skin of patients who have psoriasis with itching when compared to patients without itching [11,43]. A relation between brain-derived neurotropic factor (BDNF) level and intensity of pruritus has been studied in children with atopic dermatitis [44]. Hon reported a positive correlation between serum SP, as well as BDNF level and nocturnal motor activity, in children with atopic dermatitis [44]. According to Jiang, patients with psoriasis have nearly twice the number of SP-reactive fibers in skin compared to healthy people [45]. Reich reported no significant differences in plasma neuropeptides levels in patients with psoriasis with and without itching [46] and also found a negative correlation between the studied neuropeptide levels and intensity of itching [46]. The increased expression of neuropeptides in inflammatory infiltration related with itching might produce an increase in the activity of enzymes responsible for degradation of neuropeptides. This could in turn result in decrease in plasma SP concentration. Heppt reported increased level of substance P in nerve fibers in patients with atopic asthma or seasonal intermittent allergic rhinitis during over-exposure to allergens [47].

It has been found that substance P stimulates u-opioid receptors in peripheral nerves and the brain, and that altered balance between μ-opioid and κ-opioid stimulation leads to itching. The effects of μ-opioid stimulation and substance P are countered by the stimulation of μ-opioid receptors by the κ-opioid agonist, nalfurafine [1].The study of Wikstrom seems to confirm the role of μ-opioid receptors in uremic pruritus [1].

Żołądź assessed BDNF level in dialyzed patients and reported a significantly lower basic BDNF level in chronic kidney disease when compared to an age-matched control group. No changes in this neuropeptide level have been observed after a single

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hemodialysis session [48]. We have not found any studies that assessed substance P level in patients on dialysis.

We hypothesized that the level of substance P in patients with end-stage renal disease with itching would be related to itching and its intensity. However, the results of our study do not confirm the influence of substance P on uremic pruritus in patients on hemodialysis or peritoneal dialysis (Table 5). Our sample size was adequate, but the limitation of our study is the low response rate in HD patients, which might have influenced the results.

Conclusions

Uremic pruritus is common in patients on dialysis. The pathophysiological mechanisms of UP remain largely unknown. Although neuropeptides are postulated to play an important role in uremic pruritus, this study demonstrates that substance P is not related to incidence or intensity of itching in patients on hemodialysis or peritoneal dialysis. However, further extensive studies in larger patient cohorts will be necessary to assess the exact role of neuropeptides in uremic pruritus.

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