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Factors Associated with Uremic Pruritus

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Abstract

Background: The etiopathogenesis of uremic pruritus (UP) is multifactorial aspect, and it is thus necessary to elucidate its associated factors to develop efficient therapeutics approaches. This study aimed to verify the prevalence of UP and its associated factors.

Methods and Findings: Prospective and cross-sectional study with patients undergoing hemodialysis at a university public hospital. The data were obtained between April 2014 and April 2015. The statistical analysis was carried out using multivariate regression models, and statistical significance was set at $p<0.05$. A total of 164 patients were included, and pruritus was reported in 64 (39%). In the multivariate analysis, a higher creatinine level was risk factor for pruritus (β=1.09, 95% CI 1.00-1.19; p=0.048), as was a lower level of hemoglobin (β=0.85, 95% CI 0.73-0.99; p=0.043). Dyslipidemia (β=1.52, 95% CI 0.12-2.91; p=0.03), obesity (β=2.40, 95% CI 1.03-3.78; p=0.001), higher levels of C-reactive protein (β=0.26, 95% CI 0.19-0.34; $p<0.001$) and black race (β=1.49, 95% CI -2.57 and 0.42; $p<0.006$) were associated with a greater intensity of pruritus. The use of a high-flux dialyzer was associated with a lower intensity of pruritus (β=-1.69, 95% CI -3.05-0.34; p=0.01).

Conclusion: Uremic pruritus has a high prevalence in hemodialysis patients, and the data suggest that the higher the creatinine and the lower the hemoglobin levels are, the greater the risk of developing pruritus is. Dyslipidemia, obesity, and higher levels of C-reactive protein were associated with a greater intensity of pruritus, whereas the use of a high-flux dialyzer was associated with lower pruritus intensity.

Keywords
Cutaneous Manifestations of Systemic Disease; General Dermatology; Internal Disease Associated with Dermatology.

Introduction

Uremic pruritus (UP) is one of the most common symptoms observed in patients with stage 5D chronic kidney disease (CKD). Its prevalence

is as high as 30 to 50% among patients in hemodialysis (HD) [1, 2], and it has an important impact on life quality (LQ) [3, 4].

The pathophysiology of UP is not completely clear, and it is believed to result from the integration of multiple factors, including central components, dermophatic, neuropathic, and psychogenic factors [5]. Previous studies have shown that in CKD, UP can be related to skin xerosis, secundary hyperparathyroidism, anemia, inadequate dialysis, mast cell proliferation and degranulation, pruritogenic cytokines (histamine, kallikrein, and interleukin-2), divalent iron metabolism, sudorese reduction, an abnormal pattern of cutaneous innervation and psychogenic elements secondary to chronic disease stress [6, 7]. Other studies have cited a possible relation between the accumulation of uremic toxins and inflammatory molecules of average and large molecular weight, such as β2-microglobulin, in the etiology of UP [8, 9].

The multifactorial aspect of its etiopathogenesis is reflected in the refractoriness of UP to general therapeutic approaches and highlights the need to elucidate its associated factors. This study aimed to verify the prevalence of UP at a dialysis facility of a public university hospital and identify the factors associated with UP.

Material and Methods

This was a cross-sectional and prospective study on patients in HD at a public university hospital. The data were obtained from the patients' electronic medical records and by the application of a structured questionnaire that was designed to acquire clinical, demographic, laboratory and dialysis information and was given to patients undergoing HD sessions between April 2014 and April 2015. The study was approved by the Ethics Committee of the institution (CAAE N° 24387713.1.0000.5411), and all participants signed the Informed Consent form.

In this study, we included patients of both sexes over 18 years of age who had previously been diagnosed with stage 5D CKD with chronic HD, in clinical and/or cognitive conditions. The presence of uremic pruritus was considered when the patient's report of the symptom. We excluded patients with other possible causes of pruritus not connected to CKD or to HD, such as allergic dermatosis, parasitic and infectious disease, liver disease and internal malignancy.

The dependent variables were defined as prevalence, intensity (Visual Analogic Scale of 10 levels) and clinical characteristics of pruritus (frequency, location and duration). The independents variables were grouped in clusters, demographics, laboratories, dialysis and clinical. Categorical variables were represented by absolute values and percentiles. Continuous variables were represented by the mean and standard deviations or by medians and quartiles (p25-p75), if indicated, and were analyzed by the Shapiro-Wilk test [10]. The number of affected body topographies was categorized by a score from 0 to 6, where each body region (face, back, trunk, lower limbs and others) received a score of 1, with a maximum total score of 6 in patients who reported pruritus in the whole body.

The association between UP and demographics, laboratories, dialysis and clinical factors was explored by multivariate regression models (linear log and generalized linear model) of hierarchical structure. The inclusion of covariables in the final models depended on the significance within each level of analysis ($p<0.2$ to linear log and $p<0.1$ to generalized linear model). The effect dimension was estimated by the prevalence ratio (PR) and beta (β) regression estimator, with confidence intervals set at 95%.

The data analysis was performed using the SPSS 22.0 software, and a p-value<0.05 was considered significant.

Results

Of the196 hemodialysis patients at the institution, 164 (83%) were included in the study. Pruritus was reported by 64 (39%) patients, and 11 patients noted having pruritus at other times. The main clinical, demographic, dialysis and laboratory information of the participants are shown in **Table 1**.

Table 1. Demographic, clinical, dialytic and laboratory characteristics of patients.

Variable	Population	With pruritus	Without pruritus	PR	95% CI	p-value
N	164	64 (39)[a]	100 (61)[a]			
Age (year)[b]	61.7±13.5	59±14	63±13	0.99	0.97 - 1.00	0.22
Gender[a]						
Male	94 (57)	40 (42.6)	54 (54)	-	-	-
Female	70 (43)	24 (37)	46 (46)	0.82	0.49 - 1.37	0.46
Race[a]						
White	76 (46)	26 (34.2)	50 (50)	-	-	-
Brown	59 (36)	24 (37)	35 (35)	1.11	0.63 - 1.95	0.72
Black	29 (18)	14 (22)	15 (15)	1.29	0.66 - 2.49	0.46
Comorbidities[a]						
Hypertension	131 (80)	44 (68.7)	87 (87)	0.67	0.37 - 1.22	0.19
Diabetes mellitus	77 (47)	29 (45.3)	48 (48)	0.86	0.36 - 2.05	0.73
Cardiovascular disease	35 (21)	12 (18.7)	23 (23)	0.92	0.47 - 1.80	0.80
Smoking/ Alcohol consumption	35 (21)	15 (23.4)	20 (20)	1.35	0.73 - 2.50	0.33
Dyslipidemia	24 (15)	7 (10.9)	17 (17)	0.82	0.35 - 1.91	0.65
Obesity	12 (7)	5 (7.8)	7 (7)	1.22	0.47 - 3.16	0.68
PAOD	8 (5)	2 (3.1)	6 (6)	0.71	0.17 - 2.99	0.64
Others	34 (21)	16 (25)	18 (18)	-	-	-
Etiology CKD[a]						
Diabetes mellitus	51 (31)	21 (32.8)	30 (30)	2.24	0.70 - 7.19	0.17
Hypertension	32 (19)	7 (10.9)	25 (25)	-	-	-
Glomerulonephritis	23 (14)	12 (18.7)	11 (11)	2.02	0.73 - 5.56	0.17
Cystic kidney disease	7 (4)	3 (4.6)	4 (4)	1.93	0.49 - 7.62	0.35
Others	51 (31)	21 (32.8)	30 (30)	-	-	-
URR[c]	0.69 (0.65-0.73)	0.69 (0.66-0.73)	0.68 (0.65-0.73)	-	-	-
Kt/v >1,2[a]	128 (78)	51 (79.6)	77 (77)	-	-	-
BUN (mg/dl)[b]	110 ±30.2	116 ±33	108±28	1.00	0.99 - 1.01	0.68
Creatinine (mg/dl)[c]	8.7 (6.9-10.9)	9.9 (7.4-11.6)	8.6 (6.6-10.6)	1.08	0.97 - 1.21	0.17
Calcium (mg/dl)[c]	9.2 (8.8-9.6)	9.1 (8.8-9.5)	9.3 (8.9-9.7)	1.01	0.98 - 1.03	0.38
PTH (pg/ml)[c]	286.6 (123.1-480.8)	289.5 (129-457.8)	277 (121.5-481.8)	1.00	0.99 - 1.00	0.64
Albumin (mg/dl)[c]	3.89 (3.69-4.09)	3.84 (3.58-4.04)	3.9 (3.7-4.1)	0.56	0.29 - 1.07	0.08
Hemoglobin (g/dl)[c]	12 (11-13)	11 (10-12.5)	12 (11-13)	0.82	0.70 - 0.96	0.01
Ferritin (mg/dl)[c]	767 (348.2-1266)	724 (309-1091)	831 (371-1335)	1.00	0.99 - 1.00	0.31
Transferrin Saturation (%)	37 (27-48)	36 (27-48)	37 (29-49)	1.00	0.98 - 1.03	0.87
Iron (mg/dl)[c]	84.5 (60-111)	83 (60-107)	85 (61-111)	0.99	0.99 - 1.01	0.84
Phosphorus (mg/dl)[c]	4.8 (4.1-6.2)	5.4 (4.3-6.6)	4.7 (4.0-5.6)	1.07	0.92 - 1.01	0.39
CRP (mg/dl)[c]	1.3 (0.7- 2.3)	1.5 (0.9-2.5)	1.2 (0.7-2.2)	1.04	0.95 - 1.13	0.41
Dialysis Vintage (months)[c]	30 (12-60)	36 (22-72)	24 (12-60)	1.00	0.99 - 1.00	0.78
Dialyzer: High-flux[a]	151 (92.1)	58 (90.6)	93 (93)	0.65	0.27 - 1.56	0.33
Time of HD (hours)[c]	4 (4-4)	4 (4-4)	4 (4-4)	1.72	0.71 - 4.16	0.23

Variable	Population	With pruritus	Without pruritus	PR	95% CI	p-value
N	164	64 (39)[a]	100 (61)[a]			
Period of HD[a]						
Morning	70 (42.7)	30 (46.8)	40 (40)	-	-	-
Afternoon	52 (31.7)	21 (33)	31 (31)	0.95	0.54 - 1.69	0.88
Night	42 (25.6)	13 (20.3)	29 (29)	0.64	0.33 - 1.25	0.19
Vascular access[a]:						
CVC	100 (61)	33 (51.5)	67 (67)	-	-	-
AVF	64 (39)	31 (48.4)	33 (33)	1.53	0.92 - 2.57	0.10
Erythropoietin (IV)[a]	143 (87)	55 (86)	88 (88)	0.79	0.38 - 1.64	0.53
Calcitriol-SC[a]	56 (34)	19 (30)	37 (37)	0.76	0.44 - 1.32	0.33
Iron supplements (IV)[a]	124 (76)	49 (77)	75 (75)	1.05	0.58 - 1.87	0.87
Vitamin C (IV)[a]	33 (20)	17 (27)	16 (16)	1.56	0.88 - 2.77	0.13
Heparin (IV)[a]	158 (96)	61 (95)	97 (97)	1.23	0.38 - 3.94	0.73

[a]: N (%); [b]: Mean ± s.d.; [c]: Median (p25-p75). PR: Prevalence Ratio; PAOD: peripheral arterial occlusive disease; CKD: Chronic Kidney Disease; URR: Urea Reduction Rate; Kt/V (amount of dialysis delivered: K=clearance of urea, t = time on dialysis, V= estimated total body water); BUN: blood urea nitrogen; PTH: parathyroid hormone; CRP: C-reactive protein; High-flux dialyzer: HF60S, HF80S and HdF100S; HD: Hemodialysis; CVC: central venous catheter; AVF: arteriovenous fistula; IV: intravenous; SC: subcutaneous.

Of the total number of patients in the sample, were mostly men (57%), had a mean age 61.7±13.5 years, and were generally Caucasian (46%). There was a high number of comorbidities, with systemic arterial hypertension (80%) and diabetes mellitus (47%) most frequently observed. With regards to the patients' dialysis data, the median time in HD was 30 (12-60) months, with a median therapy duration of 4 (4-4) hours. A central venous catheter (CVC) was the most frequent vascular access method (61%). Heparin was used as an anticoagulant in 96% of the patients, and 92.1% of the patients used high-flux polysulfone membranes dialyzers. When assessing the dialysis dose, the median URR (Urea Reduction Rate) was 0.69 (0.65-0.73), and 78% of the patients had Kt/V >1.2, which indicated that this dialysis dose was generally accurate. Of the medications prescribed during the dialysis, 76% of the patients used iron supplements, 34% received injected Calcitriol, 87% received Erythropoietin and 20% received Vitamin C. There was no statistically significant difference between the studied variables in patients presenting or not UP, except for hemoglobin (p=0.01), the lowest levels of which were found in the group with pruritus, with a median of 11 (10-12.5) g/dl.

The multivariate analysis of variables between the groups with and without UP are shown in **Table 2**. A higher creatinine level was a risk factor for pruritus (β=1.09 95% CI 1.00-1.19; p=0.048), as was a lower level of hemoglobin (β=0.85 95% CI 0.73-0.99; p=0.043).

Table 2. Multivariate final model (log-linear) of factors associated with pruritus (n=164)

Variables	PR	CI (95%)	p-value
Hypertension	0.63	0.37 - 1.07	0.86
Vascular access: AVF	1.45	0.88 - 2.39	0.15
Creatinine	1.09	1.00 - 1.19	0.048
Hemoglobin	0.85	0.73 - 0.99	0.043
Albumin	0.58	0.31 - 1.08	0.08
Period of dialysis: Night	0.75	0.40 - 1.40	0.37

Dependent variable: pruritus yes/no. p(model): 0,12. PR: prevalence ratio; AVF: arteriovenous fistula.

Table 3 describes the pruritus characteristics reported by the patients (n=64). The median pruritus time was 24 (8-51) months, with a frequency greater than thrice a week in 51% of patients. The median VAS was 7 (5-8), and the median number of affected topography was 2 (1-4), with the lower limbs being the most affected region. Regarding the pruritus period, 58% of the patients reported the episodic occurrence of some symptoms, and 69% used some relief measure, with oral antihistamine (10.4%) being the most frequent.

Table 3. Clinical characteristics of pruritus.

Variable	Values
N	64
Time of pruritus (months)[c]	24 (8-51)
Frequency of pruritus[a]	
< 3x a week	21 (33)
3x a week	10 (16)
> 3x a week	33 (51)
VAS[c]	7 (5-8)
Nº affected body topographies [c]	2 (1-4)
Affected body topographies [a]	
Lower limbs	19 (30)
Entire body	18 (28)
Back	15 (23)
Trunk	12 (19)
Face	8 (12)
Others	17 (26)
Period of pruritus[a]	
During HD	9 (14)
Nightly	8 (12)
Daytime	10 (16)
Episodic	37 (58)
Relief measure[a]	44 (68)
Oral antihistamine	17 (10.4)
Body cream	6 (3.7)
Body cream and bath	9 (5.5)
Others	12 (7.3)

[a]: N (%); [c]: Median (p25–p75). VAS: Visual Analogue Scale; HD: hemodialysis;

Table 4. Beta (β) regression estimador of the multivariate final model of pruritus intensity (n=64).

Variables	β	CI (95%)	p-value
Dyslipidemia	1.52	0.12 - 2.91	0.03
Obesity	2.40	1.03 - 3.78	0.001
Erythropoietin	-1.08	-2.56 - 0.41	0.15
Period of HD: Night	1.03	-0.19 - 2.25	0.10
High-flux dialyzer	-1.69	-3.05 - -0.34	0.014
CRP	0.26	0.19 - 0.34	<0.001
Albumin	0.95	-0.10 - 2.00	0.77
Race (black)	1.50	0.42 - 2.58	0.006
Vitamin C	0.32	-1.56 - 2.19	0.73
Gender (female)	0.36	-1.00 - 1.72	0.60
Dialysis vintage	-0.003	-0.13 - 0.00	0.60

Dependent variable: pruritus intensity. p(model): 0.17. HD: Hemodialysis; CRP: C-reactive protein.

The multivariate analysis of the pruritus characteristics **(Table 4)** showed that dyslipidemia (β=1.52, 95% CI 0.12-2.91; p=0.03), obesity (β=2.40, 95% CI 1.03-3.78; p=0.001), higher levels of C-reactive protein (RCP) (β=0.26 95% CI 0.19-0.34; p<0.001) and black race (β=1.50, 95% CI 0.42-2.58; p=0.006) were related to higher pruritus intensity. The use of high-flux dialyzers was related to lower pruritus intensity (β= -1.69 a 95% CI -3.05 and -0.34; p=0.014).

Discussion

Our results showed that UP is a frequent symptom in the studied population, with a similar prevalence to that reported in other studies [2, 11, 12], which reinforces the need to clarify the factors associated with this condition to design adequate therapies.

A low level of hemoglobin was found to be a risk factor for pruritus, in agreement with the results from the DOPPS study, which evaluated 18,801 patients and found that those with higher levels of hemoglobin or Kt/V>1.5 had a significantly lower probability of having moderate to severe pruritus [3]. However, Snit et al [12] reported that a higher level of hemoglobin was related to a higher risk of pruritus. These controversial results suggest the need for other studies using a specific methodology to clarify this discussion because although the hemoglobin median is lower in patients with UP, it is still within the recommended levels for patients with CKD [13]. Melo et al [14] found lower levels of transferrin in patients with pruritus (p=0.01) and associated this finding with a possible relation between pruritus and iron deficiency, which is a probable consequence of hepcidine elevation induced by inflammatory cytokines.

Higher levels of creatinine were also risk factors associated with UP, in agreement with Ko et al [15], who found that the higher the creatinine levels are, the greater the intensity of pruritus is. UP has been causally attributed to multiple factors, including possible uremic neuropathy [6]. Accordingly, higher

creatinine levels could be implicated in neuropathy and, consequently, indicate UP.

Although hemoglobin and creatinine values are considered risk factors for UP, they were not related to pruritus intensity. Our results showed a relation between a higher pruritus intensity and the presence of dyslipidemia, obesity, CRP higher levels and the black race. In contrast, a lower intensity of UP was associated with the use of high-flux dialyzers. Malekmakan et al [11] did not find any difference in the laboratory parameters of patients with or without pruritus, except for the CRP levels, which were significantly higher in patients with pruritus. Inflammation is associated with UP, and patients presenting severe pruritus could therefore have high CRP levels [16], which justify our findings. Narita et al noted that the development of severe pruritus (VAS>7) was related to multiple factors, such as higher levels of creatinine, urea, β2-microglobuline, PTH, calcium, phosphate and CRP, and they indicated that patients with higher levels of CRP had a lower survival rate [17].

Our findings of the relation between stronger pruritus and dyslipidemia and obesity are consistent with the findings by Wu et al [2], who found that higher levels of triglycerides were related to greater pruritus intensity. This association between hypertriglyceridemia and pruritus can be explained by the risk of developing neuropathy, which is a physiopathogenic path of UP. However, the relation between the higher intensity of pruritus and the black race is difficult to explain based on the described pathophysiology of UP. Because its etiology is multifactorial, including the possible influence of psychogenic elements secondary to the stress of a chronic disease, future studies are needed to address these findings.

In our patients, the use of high-flux dialyzers was related to lower pruritus intensity, as found by Ko et al [15], probably because theses dialyzers efficiently remove average-sized molecules and are associated with lipolytic plasmatic activities [18]. When comparing UP prevalence in patients undergoing HD or peritoneal dialysis, Min et al [9] found a greater prevalence among those who underwent peritoneal dialysis compared to HD and ascribed this finding to the fact that these patients did not use high-flux dialyzers; thus, average-sized inflammatory molecules were not removed. Dialysis adequacy has a fundamental role in metabolic control and the clearance of possible pruritogenic substances, which may result in the attenuation of UP-associated factors.

The classical risk factors associated with UP, as described in literature, including phosphorus, calcium and PTH, were not found in this population, probably because they presented adequate dialysis parameters and their dialysis dose was within the therapeutic target, as indicated by their Kt/V values. Similarly, Shirazian et al [19] did not find any relation in the serum levels of phosphorus, PTH and calcium in patients with or without pruritus.

With regards to UP characteristics, our results found that severe pruritus was observed in the studied population, as represented by a median VAS of 7 (5-8), according to the adopted classification in previous studies [9, 17, 20]. It is important to note that some studies have found an increased mortality risk in patients undergoing dialysis associated with severe pruritus, e.g., when the pruritus VAS score was greater than 7 [17, 21]. The DOPPS study found that patients presenting with UP had a 17% greater mortality risk [3].

The treatment of UP is a truly challenge because pruritus is frequently refractory to oral anti-histamines and central action drugs, such as gabapentin. For this reason, gaining a fundamental knowledge of the factors associated with pruritus and its intensity can aid in the implementation of measures, such as dialysis adequacy and metabolic stabilization, which could be adopted in addition to drug treatment, when possible.

Our study has some limitations. Because it was a transversal study, there were no patient follow-up

data that could be used to assess a possible relationship between pruritus improvement and the correction of some factors that were found to be associated with UP. Additionally, we did not evaluate other dermatological alterations that could be linked to UP, such as skin xerosis. Because our study was carried out at a single center, it is difficult to generalize our results. Finally, we did not evaluate uremic toxins, such as β-2 microglobulin, to verify whether the intensity of itching was associated with a higher level of these toxins because patients using high-flux dialyzers showed lower intensity UP.

UP occurs at a high prevalence in hemodialysis patients, and the data suggest that the higher the patient's creatinine value and the lower the patient's hemoglobin level are, the greater the risk of developing UP is. Dyslipidemia, obesity, and higher RCP levels were associated with greater pruritus intensity, whereas the use of high flow dialyzers was related to lower pruritus intensity. More studies are necessary to confirm these data.

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Conflicts of interest

None.

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