Prevalence and determinants of severity of uremic pruritus in hemodialysis patients: a multicentric study

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ABSTRACT

Uremic pruritus (UP) is a common and distressing symptom in patients with advanced or end-stage renal disease under hemodialysis (HD). The present multicentric study aimed to identify prevalence and determinants of severity of UP among Egyptian patients. Performed investigations included serum urea, creatinine, calcium, phosphorus, parathormone, ferritin and liver enzymes. Pruritus was evaluated using the visual analog scale. The study included 295 patients on maintenance HD. They comprised 151 patients (51.2%) with UP. Independent predictors of UP included associated hypertension (OR: 0.48, 95% CI 0.28 to 0.83, p=0.008), higher calcium levels (OR: 1.29, 95% CI 1.02 to 1.62, p=0.032), higher phosphorus levels (OR: 1.18, 95% CI 1.02 to 1.37, p=0.03) and higher high-sensitivity C-reactive protein (hsCRP) levels (OR: 1.0, 95% CI 1.0 to 1.01, p=0.049). Independent predictors of significant UP included longer HD duration (OR: 1.23, 95% CI 1.1 to 1.38, p<0.001), lack of vitamin D supplementation (OR: 3.71, 95% CI 1.03 to 13.4, p=0.045), lower albumin levels (OR: 0.32, 95% CI 0.14 to 0.74, p=0.008) and higher hsCRP levels (OR (CRP): 1.02 (1.0–1.03), p=0.011). In conclusion, UP is fairly common among Egyptian HD patients. Independent predictors of UP severity include longer HD duration, lack of vitamin D supplementation, lower albumin levels and higher hsCRP levels.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Uremic pruritus (UP) remains a frequent and distressing symptom in patients with advanced or end-stage renal disease.

WHAT THIS STUDY ADDS

⇒ UP is fairly common among Egyptian patients with chronic kidney disease. Independent predictors of UP severity include longer hemodialysis duration, lack of vitamin D supplementation, lower albumin levels and higher high-sensitivity C-reactive protein levels.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identification of factors related to UP and its severity is essential for proper management of the problem.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. The major outcomes of CKD, regardless of cause, include progression to kidney failure, complications of decreased kidney function, and cardiovascular disease. Fortunately, some of these adverse outcomes can be prevented or delayed by early detection and treatment.[1]

Uremic pruritus (UP), now better named 'chronic kidney disease-associated pruritus', remains a frequent and distressing symptom in patients with advanced or end-stage renal disease under hemodialysis (HD).[2] Many treatment options were suggested. However, most therapeutic trials have shown only limited success.[3]

The main obstacle in the effort to create effective treatment modalities for UP is the incomplete knowledge of the underlying pathophysiological mechanisms and associated risk factors. Furthermore, given the great clinical heterogeneity of patients with kidney failure, systematically performed studies are hard to undertake and results are therefore inconsistent.[4] The present multicentric study aimed to identify prevalence and determinants of severity of UP among Egyptian HD patients.

MATERIALS AND METHODS

The present cross-sectional study was conducted at 5 HD units. The study included 295 adult patients on maintenance HD. Patients were excluded if they had associated dermatological or allergic disease or if they received a medication for UP in the previous 3 months.

All patients were submitted to careful history taking and through clinical examination. Performed investigations included serum urea, creatinine, calcium, phosphorus, ferritin, uric acid, parathormone, high-sensitivity C-reactive protein (hsCRP) and liver enzymes. Hepatitis C virus (HCV) antibodies, hepatitis B surface antigen and HIV antibodies were also assessed.

Pruritus was evaluated using the visual analog scale (VAS). The VAS is 10 cm long line (oriented horizontally or vertically) on which patients indicated the intensity of pruritus by

Table 1 Clinical and laboratory findings in the studied patients

	All patients n=295	Uremic pruritus n=151	No uremic pruritus n=144	P value
Age (y), mean±SD	51.8±14.5	52.5±14.2	51.1±14.7	0.4
Male/female, n	156/139	91/60	65/79	0.009
HD duration (y), median (IQR)	4.0 (1.5–7.0)	3.9 (1.5–6.0)	4.0 (1.1–8.0)	0.35
History/comorbidities, n (%)				
History of allergy	27 (9.2)	17 (11.3)	10 (6.9)	0.2
Hypertension	207 (70.2)	116 (76.8)	91 (63.2)	0.01
Diabetes mellitus	61 (20.7)	32 (21.2)	29 (20.1)	0.82
HCV	98 (33.2)	59 (39.1)	39 (27.1)	0.03
Used medications, n (%)				
Calcimate	258 (87.5)	128 (84.8)	130 (90.3)	0.15
Cinacalcet	22 (7.5)	11 (7.3)	11 (7.6)	0.91
Vitamin D	47 (15.9)	19 (12.6)	28 (19.4)	0.11
Analgesics	28 (9.5)	17 (11.3)	11 (7.6)	0.29
Antihypertensives				
Beta blockers	173 (58.6)	88 (58.3)	85 (59.0)	0.44
Calcium channel blockers	138 (46.8)	76 (50.3)	62 (43.1)	0.21
ACE inhibitors	121 (41.0)	65 (43.1)	56 (38.9)	0.47
Vasodilators	110 (37.3)	52 (34.4)	58 (40.3)	0.3
Clonidine	19 (6.4)	8 (5.3)	11 (7.6)	0.41
Hemodialysis parameters, mean±SD				
Frequency (session/wk)	2.9±0.4	2.9±0.4	2.9±0.4	0.56
Duration of session (h)	3.9±0.4	3.9±0.3	3.9±0.5	0.85
Ultrafiltration volume (L)	2.3±0.9	2.3±0.9	2.3±0.8	0.83
Pump flow rate (mL/min)	263.8±34.6	265.0±37.3	262.5±31.7	0.54
Kt/V	1.32±0.14	1.31±0.15	1.33±0.13	0.15
Dry weight (kg)	66.1±6.5	66.7±5.8	65.5±7.2	0.13
Intradialytic weight gain (kg)	2.6±0.5	2.6±0.6	2.7±0.4	0.09
Laboratory findings, mean±SD/median (IQR)				
Hb (g/L)	10.2±0.2	10.4±0.3	9.9±0.2	0.86
Creatinine (mg/dL)	9.0±3.0	8.6±3.1	9.3±2.9	0.06
Urea (mg/dL)	115.3±45.2	112.5±47.6	118.3±42.5	0.27
Albumin (g/dL)	3.8±0.6	3.8±0.6	3.7±0.6	0.09
Calcium (mg/dL)	8.9±1.1	9.1±1.2	8.7±1.1	0.004
Phosphorus (mg/dL)	5.3±1.7	5.6±1.9	5.0±1.5	0.001
PTH (pg/mL)	660.0 (389.9–1109.0)	669.9 (427.8–1216.3)	648.7 (335.6–977.3)	0.26
AST (U/L)	4.4±1.9	4.4±1.7	4.3±2.3	0.7
ALT (U/L)	20.6±13.9	20.4±15.4	20.9±12.1	0.74
Uric acid (mg/dL)	4.4±2.1	4.4±2.2	4.3±2.0	0.84
Ferritin (ng/mL)	492.0 (348.0–964.0)	503.0 (365.0–1034.0)	485.0 (343.8–874.3)	0.29
hsCRP (mg/L)	109.6±36.5	115.7±33.7	103.2±38.2	0.003

ALT, alanine transferase; AST, aspartate transferase; Hb, hemoglobin; HCV, hepatitis C virus; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.

crossing the line at the point that corresponded to their pruritus severity. Patients were instructed that the beginning of the scale refers to no pruritus (0 point) and the end to the most severe pruritus they can imagine (10 points). The following VAS categories were proposed: 0=no pruritus, >0 to <4 points=mild pruritus, ≥4 to <7 points=moderate pruritus, ≥7 to <9 points=severe pruritus, and ≤9 points=very severe pruritus.[5]

Data obtained from the present study were presented as number and per cent, mean and SD or median and IQR. Comparison between variables was achieved using Fisher's exact test, χ^2 test, Mann-Whitney U test, or t-test as appropriate. Binary logistic regression was used to identify predictors of certain outcome. All statistical operations were computed using SPSS V.25 with p value less than 0.05 considered statistically significant.

RESULTS

The present multicentric study included 295 patients on maintenance HD. They comprised 151 patients (51.2%) with UP. Comparison between patients with pruritus and patients without pruritus revealed a significant association between pruritus and male sex, hypertension, HCV infection, higher calcium and phosphorus levels and higher hsCRP levels (table 1). In logistic regression analysis, independent predictors of UP included associated hypertension (OR: 0.48, 95% CI 0.28 to 0.83, p=0.008), higher

Table 2 Relation between uremic pruritus severity and the clinical and laboratory data

	Mild n=75	Moderate/severe n=76	P value
Age (y), mean±SD	51.9±15.6	53.0±12.7	0.54
Male/female, n	42/33	49/27	0.29
HD duration (y), median (IQR)	3.0 (1.0–5.0)	4.0 (2.0–10.0)	0.002
History/comorbidities, n (%)			
History of allergy	5 (6.7)	12 (15.8)	0.08
Hypertension	61 (81.3)	55 (72.4)	0.19
Diabetes mellitus	14 (18.7)	18 (23.7)	0.45
HCV	28 (37.3)	31 (40.8)	0.66
Used medications, n (%)			
Calcimate	65 (86.7)	63 (82.9)	0.52
Cinacalcet	5 (6.7)	6 (7.9)	0.77
Vitamin D	14 (18.7)	5 (6.6)	0.03
Analgesics	12 (16.0)	5 (6.6)	0.07
Antihypertensives			
Beta blockers	42 (56.0)	46 (60.5)	0.57
Calcium channel blockers	41 (54.7)	35 (46.1)	0.25
ACE inhibitors	33 (44.0)	32 (42.1)	0.81
Vasodilators	30 (40.0)	22 (29.0)	0.15
Clonidine	5 (6.7)	3 (4.0)	0.46
Hemodialysis parameters, mean±SD			
Frequency (session/wk)	2.9±0.5	2.9±0.3	0.95
Duration of session (h)	3.9±0.5	3.9±0.4	0.46
Ultrafiltration volume (L)	2.1±0.8	2.4±1.0	0.06
Pump flow rate (mL/min)	267.9±38.1	262.1±36.5	0.33
Kt/V	1.3±0.14	1.31±0.15	0.88
Dry weight (kg)	66.5±5.5	66.9±6.2	0.7
Intradialytic weight gain (kg)	2.4±0.6	2.7±0.5	0.68
Laboratory findings, mean±SD/median (IQR)			
Hb (g/L)	10.1±1.9	10.1±2.1	0.88
Creatinine (mg/dL)	8.7±3.4	8.6±2.8	0.87
Urea (mg/dL)	121.7±43.9	103.4±49.6	0.17
Albumin (g/dL)	4.0±0.6	3.7±0.5	0.01
Calcium (mg/dL)	9.1±1.2	9.0±1.2	0.38
Phosphorus (mg/dL)	5.5±1.9	5.8±1.9	0.28
PTH (pg/mL)	645.9 (423.7–962.9)	683.5 (446.0–1287.6)	0.72
AST (U/L)	4.5±2.3	4.4±2.2	0.87
ALT (U/L)	20.7±17.9	20.1±12.6	0.83
Uric acid (mg/dL)	4.6±2.0	4.4±2.4	0.93
Ferritin (ng/mL)	455.0 (325.5–1109.3)	526.0 (372.0–965.0)	0.48
hsCRP (mg/L)	108.0±38.2	121.6±29.5	0.02

ALT, alanine transferase; AST, aspartate transferase; HCV, hepatitis C virus; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.

calcium levels (OR: 1.29, 95% CI 1.02 to 1.62, p=0.032), higher phosphorus levels (OR: 1.18, 95% CI 1.02 to 1.37, p=0.03) and higher hsCRP levels (OR: 1.0, 95% CI 1.0 to 1.01, p=0.049) (table 2).

In patients with pruritus, there were 75 with mild pruritus and 76 with significant (moderate/severe) pruritus. Comparison between these subgroups identified an association between significant pruritus and longer HD duration,

Table 3 Predictors of uremic pruritus in the studied patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Sex	1.84	1.16 to 2.93	0.01	1.62	0.99 to 2.65	0.05
Hypertension	0.52	0.31 to 0.96	0.01	0.48	0.28 to 0.83	0.008
HCV	0.58	0.35 to 0.95	0.03	0.66	0.39 to 1.12	0.12
Calcium	1.36	1.1 to 1.68	0.005	1.29	1.02 to 1.62	0.03
Phosphorus	1.26	1.1 to 1.45	0.001	1.18	1.02 to 1.37	0.03
hsCRP	1.0	1.0 to 1.02	0.007	1.0	1.0 to 1.01	0.05

HCV, hepatitis C virus; hs-CRP, high-sensitivity C-reactive protein.

Table 4 Predictors of significant (moderate/severe) uremic pruritus in the studied patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
HD duration	1.17	1.07 to 1.29	0.001	1.23	1.1 to 1.38	<0.001
Vitamin D supplementation	3.3	1.11 to 9.57	0.03	3.71	1.03 to 13.4	0.05
Albumin	0.42	0.21 to 0.84	0.01	0.32	0.14 to 0.74	0.01
hsCRP	1.01	1.0 to 1.02	0.02	1.02	1.0 to 1.03	0.01

HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein.

lower frequency of vitamin D supplementation, lower albumin levels, and higher hsCRP levels (table 3). On logistic regression analysis, independent predictors for significant pruritus included longer HD duration (OR: 1.23, 95% CI 1.1 to 1.38, p<0.001), lack of vitamin D supplementation (OR: 3.71, 95% CI 1.03 to 13.4, p=0.045), lower albumin levels (OR: 0.32, 95% CI 0.14 to 0.74, p=0.008) and higher hsCRP levels (OR (CRP): 1.02 (1.0–1.03), p=0.011) (table 4).

DISCUSSION

In the present study, 51.2% of HD patients experienced UP. In comparison, the prevalence of UP in HD patients reported in the literature shows wide variation ranging from 35% to 84%.[6–12] This variation is mainly attributed to the different definitions of pruritus and the different scales used to assess its levels in different studies.

In our study, we identified hypertension, higher calcium levels, higher phosphorus levels and higher hsCRP levels as independent predictors of UP. In accordance with our conclusions, Mistik *et al*[9] reported a significant association between UP and higher calcium levels. The same study suggested an association between UP intensity and HD duration, Kt/V and dry skin. In addition, the study showed that patients receiving statins were less likely to report pruritus. On the other hand, Shirazian *et al*[13] failed to document a relation between calcium or phosphorus levels and UP in their longitudinal study on HD patients.

In our work, augmented inflammatory status as shown by elevated CRP levels was found to be a significant predictor of UP and its severity. Likewise, Malekmakan *et al*[14] noted a link between development of UP and elevated CRP levels. Moreover, other studies reported an association between UP and other proinflammatory markers including interleukin-33[10] and interleukin-2[15] which suggests a strong inflammatory basis of UP. In contrast, the study of Azim *et al*[16] found no significant relation between interleukin-2 levels and UP in HD patients.

Independent predictors of significant (moderate/severe) UP in our study included longer HD duration, lack of vitamin D supplementation, lower albumin levels and higher hsCRP levels. In line with our findings, Szepietowski *et al*[11] recognized an inverse correlation between serum albumin levels and pruritus intensity score in HD patients. The association between lack of vitamin D administration and severe UP in the present study is a novel finding which is probably related to the amplified proinflammatory status in HD patients in the presence of low vitamin D levels.[17 18]

In other studies, reported predictors of significant pruritus included higher calcium and phosphorus levels, high levels of blood urea nitrogen, male gender, beta-2 microglobulin,[19] associated liver disease, history of pruritus[8] and associated diabetes.[20]

Conclusively, the present study found that UP is highly prevalent in HD patients. The intensity of the condition is related to longer HD duration, lack of vitamin D supplementation, lower albumin levels and higher hsCRP levels.

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