

Uremic Pruritus in Haemodialysis Patients; Prevalence, Severity and Possible Associations

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ABSTRACT:

BACKGROUND:

Uremic pruritus is a common distressing complication of end stage renal disease and it is a common problem in dialysis patients. It causes serious discomfort and skin damage, negatively affects the quality of life.

OBJECTIVE:

To determine the prevalence, severity of pruritus and possible association with the laboratory parameters in patients with chronic renal disease on haemodialysis.

METHODS:

One hundred and three patients on chronic haemodialysis were included in this study. Fasting blood sugar, urea, creatinine, albumin, alkaline phosphatase, parathyroid hormone, sodium, potassium, chloride, calcium, phosphorus, calcium × phosphorus product, were determined.

RESULTS:

Of the 103 patients included in the study the, 79 patients (76.7%) had pruritus of whom, 27 (34.1%) had mild pruritus, 30 (37.9%) had moderate and 22 (27.8%) had severe pruritus. No significant association ($p > 0.05$) was found between pruritus and each of sex, age, frequency and duration of haemodialysis. There was a significant association ($p < 0.05$) between duration of haemodialysis and pruritus onset. No significant difference ($p > 0.05$) in the FBS, urea, creatinine, albumin, parathyroid hormone, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorus, calcium phosphorus product, average among patients who had no pruritus, mild, moderate and severe pruritus. A significant positive correlation ($p < 0.05$) was found between severity of pruritus in pruritic patients and age.

CONCLUSION:

WE CONCLUDED THAT there was a significant association between duration of haemodialysis and pruritus onset more over the age had a significant positive correlation with the severity of pruritus in pruritic patients.

KEYWORDS: uremic pruritus, haemodialysis.

INTRODUCTION:

Uremic pruritus (UP) is a common and distressing complication of end-stage renal disease (ESRD).⁽¹⁾ It causes serious discomfort and skin damage, negatively affects the quality of life, and may be associated with sleep disturbance, inflammation, and higher mortality.⁽²⁾ The quality of UP varies between patients. It is persistent extensive and intractable in some but it may be transitory and localized in others.⁽³⁾ It may involve the entire skin (generalized pruritus) or only particular areas, such as the scalp, upper back, arms, or groin (localized pruritus). The incidence of chronic

pruritus increases with age.⁽⁴⁻⁵⁻⁶⁾ The mechanism underlying pruritus is poorly understood; current theories include secondary hyperparathyroidism (SHPT), divalent-ion abnormalities, histamine, allergic sensitization, proliferation of skin mast cells, iron deficiency anemia, hypervitaminosis A, xerosis, neuropathy and neurologic changes, opioid system involvement, cytokines, serum bile acids, nitric oxide, or some combination of these.⁽³⁾

AIM OF THE STUDY:

The objective of this study is to determine the prevalence, severity of pruritus and possible association with the laboratory parameters in patients with chronic renal disease on haemodialysis (HD).

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MATERIAL AND METHODS:

One hundred and three patients, on maintenance HD were included in the present study. The study was carried out from February 2014 to May 2014 at Alkindy teaching hospital in Baghdad. All patients were treated by conventional HD 4-5 hours, one- three times a week. Polysulphone membranes were used as dialyser, a dialysate was produced from 140 mmol /L sodium, 2 mmol/L potassium, 1.5 mmol/L calcium, 0.5 mmol/L magnesium, 111 mmol/L chloride, 3 mmol/L acetate and 32 mmol/L bicarbonate. Information related to the patients, including age, gender, duration on dialysis, pruritus period, pruritus severity, pruritus distribution, pruritus frequency, effect of pruritus on sleeping and waking up were extracted from questionnaires and medical reports.

Pruritus Measurement:

To study pruritus that might occur in chronic HD patients, the patients were questioned, if they had pruritus. Severity of pruritus was assessed by a method based on the one proposed by Layegh et al.⁽⁷⁾

The questionnaire included the items below:

1- Pruritus period: one point for each time of the day (morning, afternoon, and night). If the patient suffers from the pruritus all day, give 3 points.

2- Pruritus severity: The severity of pruritus was assessed subjectively and scored as follows: pruritus without the need to scrape (1), limited need to scrape (2), consistent need to scrape (3), scrape without improving (4), and irritant pruritus (5).

3- Pruritus distribution: limited to one or two regions for example arm, leg, or trunk (1), generalized pruritus (5).

4- Pruritus frequency and duration: every two short episodes (<10 min) or one long episode (≥10 min) received 1 point, with a maximum of 5 points for ten or more short episodes or for five or more long episodes.

5- Sleeping: the sleeping effect of pruritus was measured by asking individuals whether their pruritus interfered partially, completely, or not at all with certain sleep hours: no night sleep because of pruritus (10) sleep less than 7 hours.

6- Waking up: each wake up (1) and wake up more than 5 times (5).

For severity, distribution and frequency, separate scores were recorded for the morning and afternoon. Thus, as table 1 shows, the highest possible score for a 24-hour period was 48 points.

Based on the patients sign and symptoms, points allocate to the patients then categorized as mild: 1 to 16; moderate: 17 to 32; severe: 33 to 48.

Table 1: Pruritus-pointing system.

Item	Morning	Afternoon	Night	Total
Period	1	1	1	3
Severity	5	5	—	10
Distribution	5	5	—	10
Frequency	5	5	—	10
Sleeping	—	—	10	10
Waking up	—	—	5	5
Total	16	16	16	48

Biochemistry and heamatology:

Venous blood sampling was collected in the morning immediately before dialysis sessions. The serum was obtained after centrifugation and serum intact parathyroid hormone (iPTH) was measured by using PTH intact ELISA kit. Fasting blood sugar (FBS), urea, creatinine, albumin, serum calcium, serum phosphorus, serum sodium, serum potassium, serum chloride, total alkaline phosphatase (ALP) were measured by standard laboratory techniques using diagnostic kits.

Statistical Analysis:

Statistical package for social sciences version 20 (SPSS 20) was used for data analysis. Chi-square test (χ^2) of independence used to test the significance of association between discrete variables. ANOVA and t tests used to test the significance of variation of means of biochemical variables between study groups. Spearman's non-parametric correlation coefficient (r) used to test the degree and significance of correlation between continuous variables. Findings with P value less than 0.05 were considered significant.

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RESULTS:

Of the 103 patients included in the study, 79 patients (76.6%) had pruritus of whom, 27 (34.1%) had mild pruritus, 30 (37.9%) had moderate and 22 (27.8%) had severe pruritus. The remaining 24 (23.3%) cases had never suffered from pruritus.

There was no significant association ($p > 0.05$) between pruritus ($\chi^2 = 3.178$, $p=0.075$) and HD duration (table 2).

The results indicated that there was a significant association ($p < 0.05$) between duration of HD and pruritus onset ($\chi^2 = 10.722$, $p=0.001$).

It was found that those with HD duration < 1 year are significantly more to have a pruritus onset prior to HD while those with HD duration ≥ 1 year are significantly more to have a pruritus onset after the initiation of HD treatment.

It was noticed that 13 (39.4%) of pruritic subjects in patients less than 1 year on HD, itching appeared before the initiation of HD treatment and the remaining 20(60.6%) itching appeared after the initiation of HD treatment but in pruritic patients with HD duration ≥ 1 year itching appeared before the initiation of HD in 4 (8.7%) of subjects while it appeared after the initiation of HD treatment in 42 (91.3%) of them.

Table 2: Distribution of study sample according to finding related to pruritus.

Variables	Classification	Duration of HD		χ^2	P value
		< 1 year	≥ 1 year		
		N (%)	N (%)		
Pruritus	Present	33 (68.8%)	46 (83.6%)	3.178	0.075
	Not	15 (31.2%)	9 (16.4%)		
Pruritus onset	Before HD	13 (39.4%)	4 (8.7%)	10.722	0.001*
	After HD	20 (60.6%)	42 (91.3%)		

* P value < 0.05 , significant association

No significant association ($p > 0.05$) was found between pruritus and each of sex ($\chi^2 = 4.844$, $p=0.184$), age ($\chi^2 = 11.265$, $p=0.081$), duration of HD ($\chi^2 = 6.660$, $p=0.084$) as well as frequency of HD ($\chi^2 = 3.418$, $p=0.332$) (Table 3).

Table 3: Distribution of study sample according to different degrees of pruritus and to personal and HD factors.

Variables	Pruritus				χ^2	P value
	No pruritus	Mild	Moderate	Severe		
	N=24 (100%)	N=27 (100%)	N=30 (100%)	N=22 (100%)		
Sex					4.844	0.184
Male	16(66.7%)	12 (44.4%)	12 (40.0%)	13 (59.1%)		
Female	8 (33.3%)	15 (55.6%)	18 (60.0%)	9 (40.9%)		
Age group					11.265	0.081
Up to 45	8 (33.3%)	15 (55.6%)	11 (36.7%)	6 (27.3%)		
46-65	10 (41.7%)	11 (40.7%)	16 (53.3%)	9 (40.9%)		
> 65	6 (25.0%)	1(3.7%)	3 (10.0%)	7 (31.8%)		
Duration of HD					6.660	0.084
< 1 year	15 (62.5%)	11 (40.7%)	16 (53.3%)	6 (27.3%)		
≥ 1 year	9 (37.5%)	16 (59.3%)	14 (46.7%)	16 (72.7%)		
Frequency of HD					3.418	0.332
3time/week	13 (54.2%)	19 (70.4%)	15 (50.0%)	15 (68.2%)		
1-2 time/week	11 (45.8%)	8 (29.6%)	15 (50.0%)	7 (31.8%)		

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The results of biochemical tests showed no significant difference ($p > 0.05$) in the FBS ($p=0.531$), urea ($p=0.177$), creatinine ($p=0.337$), albumin ($p=0.337$), PTH ($p=0.224$), and total ALP levels ($p=0.500$) among patients who had no pruritus, mild, moderate and severe pruritus

(table 4). No significant difference ($p > 0.05$) was found in the levels of serum sodium ($p=0.623$), potassium ($p=0.399$), chloride ($p=0.759$), calcium ($p=0.390$), phosphorus ($p=0.873$) and $Ca \times p$ product ($p=0.865$) among patients who had no pruritus, mild, moderate and severe pruritus.

Table 4: descriptive statistics for biochemical variables and serum electrolytes in patients with different degrees of pruritus.

Variables	Pruritus				P value
	No pruritus N=24	Mild N=27	Moderate N=30	Severe N=22	
	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	
FBS (mg/dl)	99.0 \pm 27.2	105.5 \pm 48.0	118.5 \pm 61.5	109.7 \pm 51.9	0.531
urea (mg/dl)	157.6 \pm 56.2	160.4 \pm 49.7	150.1 \pm 42.9	183.2 \pm 68.2	0.177
creatinine (mg/dl)	5.1 \pm 1.5	4.7 \pm 1.3	4.4 \pm 1.9	5.1 \pm 1.9	0.337
Albumin (g/l)	34.8 \pm 9.3	35.7 \pm 6.8	36.3 \pm 8.9	33.3 \pm 8.3	0.627
PTH (pg/ml)	403.6 \pm 383.9	386.6 \pm 424.0	268.3 \pm 249.8	238.5 \pm 329.8	0.224
ALP (U/L)	161.7 \pm 114.0	167.0 \pm 133.2	181.1 \pm 224.3	183.0 \pm 176.7	0.500
sodium (mmol/l)	142.4 \pm 4.3	144.3 \pm 4.1	144.3 \pm 8.4	143.7 \pm 5.1	0.623
potassium (mmol/l)	5.0 \pm 1.3	5.1 \pm 1.0	4.9 \pm 1.3	5.4 \pm 1.3	0.399
chloride (mmol/l)	103.1 \pm 4.7	103.6 \pm 4.5	104.0 \pm 5.9	102.6 \pm 4.4	0.759
calcium (mg/dl)	8.3 \pm 1.4	9.0 \pm 1.8	9.0 \pm 1.8	8.8 \pm 1.3	0.390
phosphorus (mg/dl)	7.0 \pm 2.3	6.7 \pm 1.8	6.7 \pm 2.4	6.5 \pm 2.0	0.873
Ca \times P (mg ² /dl ²)	57.7 \pm 17.9	59.3 \pm 16.9	61.5 \pm 28.1	56.8 \pm 18.6	0.865

Correlation of severity of pruritus with study variable in pruritic patients:

The results showed a significant positive correlation ($p < 0.05$) between severity of pruritus in pruritic patients and age ($r = 0.288$, $p = 0.010$). There was no significant correlation ($p > 0.05$) between severity of pruritus in pruritic patients and each of HD duration ($r = 0.181$, $p = 0.111$), frequency of HD ($r = -0.035$, $p = 0.758$), FBS ($r = 0.037$, $p = 0.748$), blood urea ($r = 0.114$, $p = 0.317$), creatinine ($r = 0.062$, $p = 0.587$), albumin ($r = -0.158$, $p = 0.164$), PTH ($r = -0.160$, $p = 0.159$), ALP ($r = 0.068$, $p = 0.549$), serum sodium ($r = -0.009$, $p = 0.938$), potassium ($r = 0.062$, $p = 0.588$), chloride ($r = -0.071$, $p = 0.535$), calcium ($r = -0.035$, $p = 0.757$), phosphorus ($r = -0.087$, $p = 0.447$) and $Ca \times p$ product ($r = -0.100$, $p = 0.383$) (table 5).

DISCUSSION:

The incidence of uremic itch varies between studies and depends on patients included for evaluation.⁽⁸⁾ In this study, pruritus was found in 76% of the patients of whom, (34.1%) had mild pruritus, (37.9%) had moderate and (27.8%) had severe pruritus. The study of Resic et al.⁹ showed that pruritus was found in 45 patients (58.44%), severe in 17.78%, moderate in 40.0% and mild in 42.2% of the patients. These differences may be due to the prevailing climatic conditions,⁽¹⁰⁾ moreover, it is worth mentioning that a major drawback for studying and comparing results from different studies is the lack of a uniform way for assessment of this very subjective symptom.⁽³⁾ In present study no significant association was found between pruritus and HD duration consistent with the study of Akhyani et al.⁽³⁾

Table 5: Correlation of severity of pruritus with different study variables in pruritic patients.

Variables	Spearman's rho	
	Correlation coefficient	P value
Age	0.288	0.010*
Duration of HD	0.181	0.111
Frequency of HD/week	-0.035	0.758
FBS (mg/dl)	0.037	0.748
urea (mg/dl)	0.114	0.317
creatinine (mg/dl)	0.062	0.587
Albumin (g/l)	-0.158	0.164
PTH (pg/ml)	-0.160	0.159
ALP (U/L)	0.068	0.549
sodium (mmol/l)	-0.009	0.938
potassium (mmol/l)	0.062	0.588
chloride (mmol/l)	-0.071	0.535
calcium (mg/dl)	-0.035	0.757
phosphorus (mg/dl)	-0.087	0.447
Ca×P product (mg ² /dl ²)	-0.100	0.383
* P value < 0.05, significant correlation		

In our study a significant association was found between duration of HD and pruritus onset. Previous study reported itch in up to 85% of patients receiving dialysis and pruritus occurred before dialysis in about one third of patients, and after dialysis in most.⁽¹¹⁾ The prevalence of dermatological disorders is associated with severity and duration of CKD and may precede or follow the onset of dialysis.⁽¹²⁾ Snit et al.⁽¹³⁾ found that the duration of renal chronic disease correlated positively with occurrence of pruritus. Xerosis could be another factor in the pathogenesis of itching in uremic patients before and after the initiation of HD treatment. However, Mistik et al.⁽¹⁴⁾ in their studies, showed that UP was observed more in men than women, in our study, there was no statistically significant association between pruritus and sex similar to the results of Tajbakhsh et al.⁽¹⁰⁾ The possible reason is no possible role of male and female sex hormones on pruritus. No significant association was found between age and pruritus in our study consistent with Tajbakhsh et al.⁽¹⁰⁾ study. The results of previous study found that patients undergoing HD twice or less per week were more involved with pruritus compared to patients with twice or more HD per week.⁽¹⁵⁾ In our study no significant association was found between pruritus and frequency of HD. In the current study, both urea and creatinine had no significant difference among the patients who had no pruritus, mild, moderate and severe pruritus similar to the studies of Virga et al.⁽¹⁶⁾, Chiu et

al.⁽¹⁷⁾ and Chen et al.⁽¹⁸⁾ In the current study, there were statistically insignificant differences in the levels of both albumin and PTH among patients of four groups similar to the studies of Chiu et al.⁽¹⁷⁾ and Razeghi et al.⁽¹⁹⁾ Regarding to association of uremic pruritus with sodium, potassium and chloride ions levels, no previous research was recorded in the literature. In this study no significant differences were observed in the level of serum sodium, potassium and chloride among patients of four groups. Moreover, no significant correlation was also found between severity of pruritus in pruritic patients and each of serum sodium, potassium and chloride. In present study the levels of these three ions were within the normal range in most patients and this may explain this result. However, further studies are required to confirm this observation.

The results of current study showed no significant difference in the levels of both serum calcium and phosphorus among patients of four groups similar to the studies of Chiu et al.⁽¹⁷⁾, Chen et al.⁽¹⁸⁾ and Razeghi et al.⁽¹⁹⁾ In Dialysis Outcomes and Practice Patterns Study (DOPPS) independent and strong relationships were seen between higher serum Ca × P product levels (>80 mg²/dl²) with uremic pruritus.⁽²⁰⁾ Similar results when Ca × P product above 70 mg²/dl².⁽¹³⁾ In this study, Ca × P product was not significantly different among patients of four groups which consistent with the study of Razeghi et al.⁽¹⁹⁾ and less than the levels of two previous studies.

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Regarding to the correlation of pruritus severity with study variable in pruritic patients:

Present study found a significant positive correlation between severity of pruritus in pruritic patients and age. This result disagrees with result of Narita et al.⁽²¹⁾ It may be explained to more skin xerosis in older patients in this study. Additionally, the aging skin is susceptible to pruritic disorders because of the cumulative effects that the environment has on the skin and because of changes to the skin structure that occur as individual gets older.⁽²²⁾

No significant correlation was also found between severity of pruritus in pruritic patients and HD duration. In contrast, the result of Narita et al.⁽²¹⁾ revealed that the group with severe pruritus had a significantly longer duration of dialysis.

In the detailed analysis of Ramakrishnan et al.⁽²³⁾, concluded that missed HD sessions was observed with increasing itchiness severity. In our study no significant correlation was found between severity of pruritus in pruritic patients and frequency of HD.

The result of Narita et al.⁽²¹⁾ revealed that the group with severe pruritus had a significantly higher levels of serum creatinine and blood urea. Conversely, no significant correlation was found in this study between severity of pruritus in pruritic patients and both of blood urea and creatinine. Other factors may have attributable role such as pruritogenic middle-molecular weight molecules⁽²¹⁾ that accumulate in the dialysis patient because they are poorly dialyzable as a result of their molecular size.⁽²⁴⁾ Similar to the study of Narita et al.⁽²¹⁾ our result indicated that no significant correlation was observed between severity of pruritus in pruritic patients and albumin.

In a study by Narita et al.⁽²¹⁾ the group with severe pruritus had a significantly higher level of intact PTH. In present study, no significant correlation was observed between severity of pruritus in pruritic patients and PTH. In this study the level of PTH in sever pruritic patients was lower than those with moderate and mild pruritus and this may explain our result.

Narita et al.⁽²¹⁾ in their study, showed that The group with severe pruritus had a significantly higher levels of serum calcium and phosphorus. In this study no correlation was found between each of calcium and phosphorus levels and severity of pruritus in pruritic patients. Our result may because we have few patients with calcium level higher than normal and it seem that the

average level of phosphate in patients with severe pruritus is not differ from those with mild and moderate pruritus. These data suggest that raised phosphorus level is not the cause of severity of itching.

In this study no significant correlation was found between Ca × P product and severity of pruritus in pruritic patients. In contrast, in a study by Pisoni et al.⁽²⁵⁾ higher Ca × P product concentrations >80 mg²/dl² were found to be associated with patients having moderate to extreme symptoms of itchiness. Our result may be attributed to the lower mean of Ca × P product than previous study.

CONCLUSION:

Our study indicates that there was a significant association between duration of HD and pruritus onset moreover the severity of pruritus in pruritic patients was significantly correlated with age.

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