Uremic Pruritus and Serum Phosphorus Level

Seyed Mansour Gatmiri[1], Mitra Mahdavi-Mazdeh[1,2], Mahboob Lessan-Pezeshki[1], and Mohammadreza Abbasi[1]

[1] *Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Iranian Tissue Bank & Research Center, Tehran University of Medical Sciences, Tehran, Iran*

Received: 30 Apr. 2012 ; Received in revised form: 20 Nov. 2012 ; Accepted: 5 Jan. 2013

Abstract- Pruritus is a common and bothersome problem among uremic patients which negatively affects life quality and prognosis of the patient. Various factors are known to be involved in the development of pruritus. The aim of this study was to assess the frequency and the factors which may have relationship with uremic pruritus, especially bone mineral metabolism indicators. Current cross-sectional study was done on 99 hemodialysis patients. Having pruritus, its duration, severity and correlation with patient's laboratory data was evaluated. For each patient a questionnaire was filled. The mean age of patients was 55.9±15.4 (23-87) years and 35.7% were female. They were on hemodialysis for 74.79±75.04 months. Frequency of pruritus was 58.6% (58 patients). Considering the severity, 16.2% suffered from severe pruritus, measured by visual analogue scale (VAS). Pruritus was more common in those on dialysis for more than 2 years (0.014). 82.8% of those with VAS of less than 3, in comparison with 37.5% of those with VAS of greater than 7, had no complaint of awakening due to pruritus. The frequency of pruritus and its severity was more in patients with higher serum phosphorus level (P=0.048). It seems that phosphate control which is not mainly attributed to dialysis adequacy and efficiency, needs more attention not only by medical team but also by patient. Decreasing the phosphate content of regimen may be cheap and helpful modality in pruritus management.

Acta Medica Iranica, 2013; 51(7): 477-481.

Keywords: Hemodialysis; Hyperphosphatemia; Kidney Failure; Phosphorous; Uremic Pruritus

Introduction

The prevalence of uremic pruritus, a considerable cause of morbidity in patients with end stage renal disease (ESRD) is still tremendously high. Approximately 50-90% of hemodialysis (HD) patients suffer from pruritus, which does not improve with dialysis and has no correlation with duration of dialysis or the cause of renal failure. The mechanism of uremic pruritus is not yet fully understood but it has prognostic value and is associated with poor survival (1-3). Pro-inflammatory state due to immune system derangement with high level of some cytokines, opioid-receptor system abnormalities, malnutrition, interface of dermal mast cells with distal ends of unmyelinated C fibers and possibly mineral bone metabolism and nutritional disturbances are among various mechanisms referred to as its cause or intensity (4-6). It usually starts half a year before dialysis and can be persistent or transient, localized or generalized. It may have great negative impact on the life quality of the patient. Moderate to severe pruritus increase mortality risk by 13% to 21% . Nevertheless, it is important to rule out other possible causes of pruritus due to gastrointestinal or hematologic diseases and allergic dermatitis (7).

Chronic kidney disease (CKD) is accompanied by profound disturbances in calcium, phosphate, vitamin D, and intact parathyroid hormone (PTH) homeostasis that may play a role in the pathophysiology of pruritus. Optimal serum levels of phosphorus (3.5-5.5 mg/dl) , serum calcium (8.4-9.5 mg/dl), calcium-phosphorus product, less than 55 mg^2/dl^2 and serum intact PTH (150-300 pg/ml) as bone mineral metabolism indicators, have been recommended by National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) guidelines (8). However, achieving such targets is a serious challenge in the management of patients. Mahdavi-Mazdeh *et al*. in a study in 2630 hemodialysis patients showed only 2% and 35% achieved all or 3 targets, respectively (9).

The main objective of this study was to estimate the frequency of pruritus in patients on chronic maintenance

Corresponding Author: Mitra Mahdavi-Mazdeh
Nephrology Research Center, Imam Khomeini Hospital, Keshavarz Boulevard, Tehran, Iran
Tel: +98 21 66581521, Fax: +98 21 66931818 E-mail: mmahdavi@tums.ac.ir

hemodialysis and evaluate its relation to some recognized factors in pathogenesis of uremic pruritus, especially bone mineral metabolism indicators.

Patients and Methods

99 patients on maintenance thrice weekly hemodialysis at our center (Imam Khomeini Hospital, Tehran, Iran) were included in a cross-sectional study in 2010. Duration of each session was 4 hours and dialyzer was polysulfone. A questionnaire was used to assess patient's pruritus. Those with history of dermatologic disease or chemical exposure were excluded. Patients were asked to report the severity of their pruritus on a visual analogue scale (VAS) graded from 0 to 10 with grade 0 representing no discomfort and grade 10 for unbearable severe pruritus. Duration and presence during dialysis session and/or the day after dialysis were questioned. The severity was evaluated by questions on the subject of awakening the patient from sleep, existence of excoriation due to scratching and/or scratches scars and administered drugs.

Blood samples were taken from all patients for assessment of serum levels of calcium, phosphate, PTH, KT/V (index of dialysis dose), lipid profile and other parameters on the first session of HD of the week. Then the findings were entered in software SPSS version 16 and the results were yielded after analyzing the data. The study was approved in research council, deputy of research of Tehran University of Medical Sciences.

Descriptive data are given as mean±standard deviation (range). Student's t-t test was used to compare means between patients with and without pruritus. Pearson correlation coefficient and Chi-square test were used for relationship of quantitative and comparison of qualitative variables respectively. The level of significance was $P<0.05$.

Results

The mean age of 99 studied patients was55.9±15.4 (23-87) years and 35.7% were female. Diabetes mellitus was the cause of ESRD in 28.4%. Patients were on HD for 74.79±75.04 (1-288) months. Frequency of pruritus was 58.6% (58 patients). Considering the severity of pruritus, measured by VAS, 16 patients (16.2%) suffered from severe pruritus. Duration of dialysis did not show correlation with perception or intensity of pruritus ($P=0.057$), but pruritus was more common in those on dialysis for more than 2 years (0.014). Demographic and laboratory data in two groups of those suffering from pruritus in comparison with those without pruritus are presented in table 1.

Mean of age, hemodialysis duration, albumin, calcium, PTH, uric acid, CRP, KT/V and lipid profile did not show any difference between those with versus without pruritus. However, the only variable which showed the significant difference was serum phosphate level ($P=0.048$). Regarding the severity of pruritus and its correlation with similar factors, it has been shown that none of the variables' means in table 1 was different in patients with different severity of pruritus.

Table 1. Patient Demographic data according to pruritus status.

	Patients without pruritus (41)	Patients with pruritus (58)	*P*-value
Age(year)	56.80±16.84	55.26±14.33	NS
Sex (male/female)	30/10	33/25	NS
HD duration (months)	59.25±68.30	86.09±78.25	NS
≤24	19 (47.5%)	13 (23.6%)	0.014*
>24	21 (52.5%)	42 (76.4%)	
KT/V	1.20±0.23	1.12±0.19	NS
Calcium	8.82±0.62	8.86±0.82	NS
PTH	337.28±396.06	423.09±637.82	NS
Phosphate	6.28±1.67	7.09±1.86	0.048*
Alk phoshatase	347.94±238.18	392.07±374.76	NS
Uric acid	9.92±15.60	7.41±1.35	NS
Cholesterol	146.88±38.42	150.08±38.09	NS
Triglyceride	142.53±72.69	161.55±93.11	NS
AST	15.29±5.89	16.90±13.06	NS
ALT	11.88±10.07	15.71±27.06	NS

Table 2. Univariate comparison and pruritus severity.

	1>VAS≤3	4≥VAS≤6	7≥VAS	*P*-value
Numbers of patients	29	13	16	
Age(year)	57.08±14.07	5.62±14.58	55.40±14.94	0.546
Sex (male/female)	15/14	7/6	11/5	0.527
Pruritus During HD (yes/no)	6/23 (20.7)	8/5 (61.5)	9/7 (56.2)	0.012
Having pruritus on the day after dialysis (yes/no)	27/2 (93.1)	13/0 (100)	16/0 (100)	0.36
Scar (yes/no)	3/26 (10.3)	3/10 (23.1)	8/8 (50)	0.012
Awakening no	24 (82.8)	7 (53.8)	6 (37.5)	<0.001
1dy/wk	3 (10.3)	1 (7.7)	1 (6.2)	
2dys/wk	1	3	0	
3dys/wk	1	1	1	
4dys/wk	0	1	8	
HD duration (month)	93.97±87.21	75.08±66.61	79.54±71.02	0.73
≤24	24.1%	23.1%	23.1%	0.99
>24	75.9%	76.9%	76.9%	
KT/V	1.12±0.18	1.15±0.21	1.09±0.20	0.74
Calcium (mg/dl)	8.97±0.82	8.59±0.93	8.85±0.73	0.41
<8.5	17.9%	33.3%	13.3%	0.40
8.5-10.2	82.1%	66.7%	86.7%	
PTH (pg/ml)	385.56±566.22	476.17±807.50	452.79±659.04	0.90
<150	50%	58.3%	35.7%	
150-300	17.9%	16.7%	21.4%	
>300	32.1%	25%	42.9%	
Phosphate (mg/dl)	7.07±1.91	7.29±1.93	6.98±1.82	0.91
3.5-5.5	21.4%	25%	26.7%	0.92
>5.5	78.6%	75%	73.3%	
Calcium-phosphorus product (mg^2/dl^2)	62.57±14.88	62.49±15.83	61.39±14.53	0.968
<55	52.9%	44.4%	50%	0.919
>72	47.1%	55.6%	50%	
Alk phoshatase	354.68±259.03	419.83±206.18	439.67±610.77	0.44
Uric acid (mg/dl)	7.49±1.50	7.33±1.48	7.35±0.97	0.92
Cholesterol (mg/dl)	155.08±39.05	152.25±45.35	139.67±29.76	0.46
Triglyceride (mg/dl)	175.21±105.82	168.75±90.80	130.27±62.45	0.31
AST	15.92±8.30	13.56±7.57	22.25±21.78	0.38
ALT	16.00±24.62	7.11±5.01	8.00±24.88	0.42
Albumin	4.09±0.57	3.79±0.52	3.99±0.45	0.30

However, more intense itching correlated with higher rate of pruritus during dialysis session (*P*=0.012) and interference with patient sleep (*P*<0.001). 82.8% of those with VAS of less than 3, in comparison with 37.5% of those with VAS of greater than 7, had no complaint of awakening due to pruritus. Regarding laboratory tests of bone metabolism (calcium, phosphorus, calcium-phosphorus product and PTH) it has been shown that only, phosphorus level correlated with pruritus duration (*P*=0.007), pruritus during hemodialysis session (*P*=0.010) and pruritus on the day after dialysis (0.016).

There was no significant finding with K/DOQI target ranges in three stages of pruritus intensity (Table 2). However, the patients with serum phosphorus level of <7 mg/dl experienced less frequent intradialysis pruritus than those with serum phosphorus level of >7 mg/dl (15.6% *versus* 34.1%) (*P*=0.039). The ratio of the patients suffering from pruritus for 6 months and more, in those with a serum phosphorus level of <7mg/dl was 21% in comparison with 48% in those with higher level (*P*=0.007). We also found that 54% of patients with serum phosphorus level of 7 mg/dl or less, suffered from pruritus the day after dialysis compared with 76% among patients with serum phosphorus level of more than 7 mg/dl (*P*=0.04).

Discussion

Our study as many others showed that pruritus is very common (58.6%) in HD patients. We also found that there is no correlation of its intensity with duration of

dialysis (10,11) but it was more common in those on dialysis for more than 2 years. In another study of this center 10 years ago the frequency of pruritus was 51% and similarly, it was more common in those who were on dialysis for more than 2 years (12).

Regarding mineral bone metabolism indices and pruritus the results are conflicting. We found phosphate level but not PTH correlated with the complaint of pruritus in hemodialysis patients. It is in sharp contrast with Stahle-Backdali *et al*. as well as Jamal and Subramanian studies who found higher PTH level in those with pruritus (11,13). However, they did not find correlation with calcium (11,13). Yazdanpanah *et al*. also found correlation of high PTH level with pruritus, but again they showed that there was no effect of calcium or phosphorus level on pruritus frequency (14). Welter *et al*. and Melo *et al*. did not find any impact from calcium, PTH and phosphate on this symptom (7,10). Afshar *et al.* found significant correlation of uremic pruritus with intact PTH and calcium phosphate product (15).

In DOPPS study with large sample size of 17,034 patients from seven countries, independent and strong relationships were seen between higher serum calcium (>10.2 mg/dl), higher serum phosphorus (>5.5 mg/dl), and higher serum calcium phosphorus product levels (>80 mg^2/dl^2) with uremic pruritus. It has also been emphasized that serum phosphorus less than 3.5 mg/dl and within 5.5-6.7 mg/dl range accompanied the occurrence of pruritus with odds ratio of 1 (P=0.97), and 1.2 (P<0.0001) respectively. The odds ratio increased to 1.37 in those with serum phosphorus level higher than 6.7 mg/dl (P<0.0001) (16).

In our study, the role of phosphorus was similar, but we could not find the effect of calcium and PTH. It may be due to the fact that we did not have any patient with calcium level higher than 10.2 mg/dl, which can also explain the lower mean of calcium phosphorus product and non-existence of statistically significant finding. The next limitation of current study was the method of PTH measurement which did not measure intact PTH. In conclusion, it seems that phosphate control which is not mainly attributed to dialysis adequacy and efficiency, needs more attention not only by medical team but also by patients. The nutritional guidelines to decrease phosphate content of regimen may be cheap and helpful. Further to other advantages of decreasing serum phosphorus level which is beyond the scope of this paper it may help uremic pruritus control.

Acknowledgment

The authors give thanks to Mrs. Jahanmardi, dialysis ward nurse for collaboration in filling the questionnaire and Dr. Abdollahi in laboratory department.

References

1. Murphy M, Carmichael AJ. Renal itch. Clin Exp Dermatol 2000;25(2):103-6.
2. Narita I, Iguchi S, Omori K, Gejyo F. Uremic pruritus in chronic hemodialysis patients. J Nephrol 2008;21(2):161-5.
3. Benchikhi H, Moussaid L, Doukaly O, Ramdani B, Zaid D, Lakhdar H. [Hemodialysis-related pruritus. A study of 134 Moroccans]. Nephrologie 2003;24(3):127-31.
4. Nordal EJ, Os I. [Uremic pruritus--pathogenesis and treatment]. Tidsskr Nor Laegeforen 2007;127(9):1201-3.
5. Mettang M, Weisshaar E. Pruritus: control of itch in patients undergoing dialysis. Skin Therapy Lett 2010;15(2):1-5.
6. Lugon JR. Uremic pruritus: a review. Hemodial Int 2005;9(2):180-8.
7. Welter Ede Q, Frainer RH, Maldotti A, Losekann A, Weber MB. Evaluating the association between alterations in mineral metabolism and pruritus in hemodialysis patients. An Bras Dermatol 2011;86(1):31-6.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(4 Suppl 3):S1-201.
9. Mahdavi-Mazdeh M, Zamyadi M, Norouzi S, Heidary Rouchi A. Management of Calcium and Phosphorus Metabolism in Hemodialysis Patients in Tehran Province, Iran. Iran J Kidney Dis 2007;1(1):25-8.
10. Melo NC, Elias RM, Castro MC, Romao JE, Jr., Abensur H. Pruritus in hemodialysis patients: the problem remains. Hemodial Int 2009;13(1):38-42.
11. Jamal A, Subramanian PT. Pruritus among End-Stage Renal Failure Patients on Hemodialysis. Saudi J Kidney Dis Transpl 2000;11(2):181-5.
12. Naderi N, Mahdavi Mazdeh M, Firooz A, Heydari Seraj M. Prevalence of cutaneous manifestations in end stage renal disease patients under hemodialysis in Imam Khomeini Hospital, Tehran in 2003. Iranian Journal of Dermatology 2006;8(34):495-89.
13. Stahle-Backdahl M, Hagermark O, Lins LE, Torring O, Hilliges M, Johansson O. Experimental and immunohistochemical studies on the possible role of parathyroid hormone in uraemic pruritus. J Intern Med 1989;225(6):411-5.

14. Yazdanpanah MJ, Mojahedi MJ, Ebrahimirad M, Bijandi M. Prevalence of skin manifestations in end stage renal disease patients under hemodialysis :Medical Journal of Mashad University of Medical Sciences 2006;49(92):167-72.
15. Afsar B, Elsurer Afsar R. HbA1c Is Related with Uremic Pruritus in Diabetic and Nondiabetic Hemodialysis Patients. Ren Fail 2012;34(10):1264-9.
16. Pisoni RL, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, Saran R, Mendelssohn DC, Young EW, Port FK. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2006;21(12):3495-505.