Relationship Between Serum Intact Parathyroid Hormone and Pruritus in Hemodialysis Patients

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Introduction. Pruritus is one of the most common cutaneous complications in hemodialysis patients. There is no consensus on etiologic and pathologic factors. This study is aimed to evaluate the correlation between serum intact parathyroid hormone (PTH) level and the severity of pruritus in hemodialysis patients.
Materials and Methods. In a cross-sectional study, all of the patients referred to hemodialysis center of two hospitals in Sari, Iran, were primarily examined by a dermatologist and those who had no pathologic findings were included in the study. Serum levels of calcium, phosphorus, albumin, creatinine, and intact PTH were measured and evaluated against the pruritus scores.
Results. A total of 153 patients were studied of whom 52.3% (n = 80) were men. The prevalence of pruritus and hyperparathyroidism were 61.4% and 60.7%, respectively, and these were not significantly different between men and women. There was a significant difference in the mean itching score between the patents with and without hyperparathyroidism (5.71 ± 5.39 and 4.93 ± 2.93, respectively; $P = .005$). Serum intact PTH level correlated with itching score in this population ($r = 0.294$, $P < .001$), while no correlations were found between itching score and other laboratory parameters.
Conclusions. Our study showed that intact PTH level is correlated to the severity of pruritus in hemodialysis patients. Therefore, control of hyperparathyroidism in hemodialysis patients is very important to overcome pruritus.

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INTRODUCTION

End-stage renal disease (ESRD) is one of the main health problems of the communities worldwide. After confirmation of ESRD, renal replacement therapy methods such as hemodialysis should be conducted.[1] According to the current data, over 500 000 patients live with ESRD in the United State, of whom 72% have undergone long-term dialysis and 28% have received kidney transplantation.[2] The incidence and prevalence of ESRD have been increasing in Iran in past ten years (63.8 pmp and 357 pmp, respectively, in 2006).[3]

Patients with ESRD who undergo hemodialysis usually suffer from coetaneous and mucosal lesions.[4] These lesions could be related to previous underlying disease, uremia, or medication, as well as hemodialysis therapy.[5] Common skin manifestations in hemodialysis patients consist of pruritus, hyperpigmentation, calcification, xerosis, impaired homeostasis (ecchymosis, and hematoma).[6] The main coetaneous symptom is pruritus. The incidence of pruritus has been estimated between 37% to 90% in ESRD patients and nearly 80% in hemodialysis patients.[4] Itching

is an unpleasant feeling of desire to scratch.[4] The etiology in ESRD patients is largely unknown yet. A few patients have severe itching, while 50% to 90% of hemodialysis patients complain of scratching that rarely responds to hemodialysis.[7]

The pathophysiology of pruritus is multifactorial. To date, while studies reported significant association between serum parathyroid hormone (PTH) and the itching, some other studies have found no specific relationship between pruritus and hyperparathyroidism, hypercalcemia, hyperphosphatemia, and level of PTH.[7,8] Kidney failure, hyperphosphatemia, hypocalcaemia, and decreased production of calcitriol all increase the production of PTH, which leads to secondary hyperparathyroidism.[9] According to the National Kidney Foundation Disease Outcomes Quality Initiative, serum intact PTH for patients with stage 5 kidney failure (ESRD) is defined as 150 pg/mL to 300 pg/mL.[10] Considering the high prevalence of pruritus in this population and lack of definite etiology and treatment, we aimed to design a study to evaluate the relationship between pruritus and serum level of intact PTH in hemodialysis patients.

MATERIALS AND METHODS

This cross-sectional study was conducted on all of the patients referred to the hemodialysis centers in Imam-Khomeini Hospital and Fatemeh-Zahra Hospital, in Sari, during autumn and winter 2010. The ethics committees working in both of these hospitals approved the study protocol. All patients were on hemodialysis 2 to 3 times per week for more than 3 months. We used polysulfone hemodialysis membranes with surface area of 1.3 m^2.

As the first step, the patients' skin were examined by a dermatologist and if the patients were found free of any pathological lesions such as allergies, scabies, and fungal lesions, they were included in the study. The participants were asked about demographic information, past medical history, and the presence and severity of pruritus. The severity of pruritus was scored as previously defined.[11] We assessed pruritus according to a modified detailed scoring system proposed by Duo,[12] considering the scoring of pruritus, distribution of pruritus and sleep disorder. Total scoring of pruritus was calculated as follows:

(severity of pruritus × distribution of pruritus) + sleep disorder scoring

The severity of pruritus was assessed as follows: slight itching, 1 point; itching with scratching, 2 points; itching with scratching and excoriation, 4 points; and pruritus causing total restlessness, 5 points. Distribution of pruritus was scored if pruritus was in maximum of 2 areas of the body (1 point), in more than 2 areas (2 points), and generalized (3 points). Sleep disorder was monitored as follows: every waking up due to itching received 2 points (maximum 10 points), and each one scratching received 1 point (maximum 5 points).[13] We assessed the quality of dialysis by KT/V, using an online measurement software (UpToDate version 19.2, Up To Date Inc, Wellesley, MA, USA) with normal a range above 1.2.

Before performing the dialysis, a 3-mL sample of blood was taken from every patient. The serum was immediately separated from the blood samples and the samples were transported to the laboratory. Serum calcium, phosphorus, albumin and creatinine levels were measured with Pars Azmoon Laboratory kits (Tehran, Iran), using the Auto-analyzer BT-3000 (Biotechnica, Rome, Italy). The results of the tests for measuring calcium, phosphorus, albumin, and creatinine were expressed as high, normal, and low. Serum intact PTH was measured using an electrochemiluminescence kit (Roche Diagnostics, Mannheim, Germany). A normal intact PTH was defined based on the National Kidney Foundation Disease Outcomes Quality Initiative criteria.

Statistical Analyses

Data was analyzed using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). Continuous variables were demonstrated as the mean ± standard deviation. In order to evaluate the quality and quantity parameters we used the chi-squared test and the *t* test, respectively. We used the Pearson correlation test for the evaluation of relationships of serum parameters. *P* values less than .05 were considered significant.

RESULTS

One hundred and sixty-four patients were entered in this study, of whom 11 were excluded (1 was diagnosed with basal cell carcinoma, 6 had used antihistamine medications, and 4 did not complete the follow-up routines). Overall, 153 hemodialysis patients were enrolled in the study, of whom 80

Table 1. Comparison of Clinical and Laboratory Parameters in Hemodialysis Patients*

Parameter	Pruritic Patients	Nonpruritic Patients	*P*
Age, y	59.61 ± 15.74	61.70 ± 13.07	.39
Dialysis session, /mo	38.83 ± 38.20	54.59 ± 50.86	.09
Serum PTH, ng/dL	369.65 ± 282.06	229.21 ± 239.44	.002
Serum calcium, mg/dL	8.63 ± 0.86	8.79 ± 0.07	.29
Serum potassium, mg/dL	5.77 ± 0.74	5.31 ± 0.68	.11
Serum albumin, mg/dL	4.19 ± 0.44	4.18 ± 0.39	.94
Serum creatinine, ng/dL	7.00 ± 2.57	7.71 ± 3.03	.13
Alkaline phosphatatse, U/L	361.72 ± 244.52	376.73 ± 268.78	.72
Serum calcium-phosphorus product	49.34 ± 14.25	46.18 ± 14.22	.18

*values are mean standard ± deviation. PTH indicates parathyroid hormone.

(52.3%) and 73 (47.7%) were men and women, respectively. Basic characteristics of the study population are shown in Table 1. No significant differences were found in age, sex, and serum levels of alkaline phosphatase, urea nitrogen, and creatinine between hemodialysis patients with pruritus and those without pruritus.

The prevalence of pruritus and hyperparathyroidism in the patients were 61.4% (n = 94) and 60.7% (n = 93), respectively. There was no significant differences was observed in the frequency of pruritus between men (51.1%) and women (48.9%; *P* = .35). The frequency of hyperparathyroidism in the men and the women were 54.8% and 45.1%, respectively (*P* = .21). The frequency distribution of itching in patient with hyperparathyroidism is shown in Table 2.

The mean itching score was 6.45 ± 5.60. The mean itching score in patients with and without hyperparathyroidism were 5.39 ± 5.71 and 2.93 ± 4.93, respectively (*P* = .005). In addition, there was a significant correlation between serum level of intact PTH and itching scores (r = 0.294, *P* < .001). There were no significant differences between other measured serum markers and itching scores in the patients. Overall, 25.5% of the patients (n = 39) had normal KT/V values (> 1.2), and the mean KT/V in all patients was 1.04 ± 0.24. There was no significant difference between itching score and KT/V between the two groups (*P* = .95)

Table 2. Distribution of Hyperparathyroidism in Men and Women With Pruritus

Subgroup	Hyperparathyroidism		*P*
	Yes	No	
Men			
Pruritic	37 (72.6)	11 (37.9)	
Nonpruritic	14 (27.4)	18 (62.1)	.001
Women			
Pruritic	27 (64.3)	19 (61.3)	
Nonpruritic	15 (35.7)	12 (38.7)	.18

DISCUSSION

In this study of 153 hemodialysis patients, pruritus was found in 62.1% of the patients. Pruritus is one of the most prevalent clinical presentations of uremia and occurs in 37% to 90% of hemodialysis patients.[4,6,7] Difficulty in clearly defining pruritus as a subjective symptom, limited number of patients in most series, and retrospective nature of some studies may have led to different reports. In our previous study performed in 2007, we found pruritus in 39% of our patients undergoing dialysis.[14]

In a study done by Stahle-Backdahl, the patients who had pruritus had been longer on dialysis as treatment in comparison with those without pruritus.[15] Szepietowski and associates showed a significant direct relationship between the total score of pruritus and duration of hemodialysis.[16] On the contrary, Altmeyer and coworkers[17] described a significant improvement of itching in patients who had been on hemodialysis for a long period of time; for instance, of 23 patients with short-term dialysis (2 to 3 years), 78% complained of pruritus, while pruritus was seen in only 43% of 28 patients with long-term dialysis (> 8 years). Murphy and colleagues,[19] however, could not confirm that pruritus decreased with increased duration of treatment with dialysis. In our study, we did not find any relationship between pruritus and duration of dialysis as seen in some previous studies.[7,19,20]

Increased serum levels of magnesium, phosphorus, and calcium have been proposed to be involved in uremic pruritus by some authors.[7,19] It

has been suggested that an increase in concentration of skin divalent ions may lead to microprecipitation of calcium or magnesium phosphate, which may be the cause of pruritus. On the other hand, the role of magnesium itself in the modulation of nerve conduction and release of histamine from mast cells has been mentioned.[7] While marked improvement of uremic pruritus with low dialysate calcium and magnesium has been reported,[22,23] only a few studies showed a significant correlation between serum or skin divalent ion content and the presence of pruritus.[7,24] Recently, Momose and colleagues found increased calcium ion concentration in the deepest layers of the epidermis, indicating a disrupted calcium ion gradient in the skin.[24] Like most of other studies,[25-27] we could not find any relationship between serum levels of calcium or phosphorus and pruritus in the patients.

Hyperparathyroidism has been proposed by some authors as a cause of uremic pruritus.[28] It has been reported that pruritus can completely disappear after parathyroidectomy.[29] Hyperparathyroidism can stimulate mast cells to release histamine and can promote microprecipitation of calcium and magnesium salts in the skin. On the other hand, all of the patients with severe hyperparathyroidism do not have pruritus. Moreover, there is no relationship between the plasma level of PTH and proliferation of dermal cell, and there is no difference in the number of mast cells and the levels of PTH between patients with or without pruritus.[30] On the other hand, a direct role for parathyroid hormone as a cause of uremic pruritus has been questioned because of the failure of intradermal injections of PTH analogs to produce pruritus, and because of negative immunohistochemical studies for PTH in the skin biopsy specimens.[20] Furthermore, no correlation between PTH levels and itching intensity was found in most studies.[7,18,27,31,32] Although pruritus in a patient improved after parathyroidectomy in a study done by Akhyani and coworkers, no relationship was found between serum PTH and pruritus.[8] However, in our study, we found a significant correlation between itching score and serum intact PTH level in hemodialysis patients.

Recently, Urbonas and colleagues[18] noticed a decreasing trend in the prevalence of pruritus in hemodialysis patients and attributed it to more precise calculation of hemodialysis doses based on KT/V or creatinine clearance measurements and introduction of new dialysis systems with larger surfaces.[16,18,21] In this study, no difference in itching prevalence and level of intact PTH between groups with normal and abnormal KT/V were seen.

CONCLUSIONS

This study demonstrates that the serum level of intact PTH is associated with the incidence and severity of pruritus in hemodialysis patients. Thus, therapeutic or preventive modalities for secondary hypoparathyroidism may be helpful to control and reduce itching in these patients. Further multicenter studies with more patients and investigation of other laboratory factors are suggested.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. [No author listed]. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266.
2. Rennke HG, Denker BM. Renal pathophysiology: the essentials. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 18.
3. Aghighi M, Mahdavi-Mazdeh M, Zamyadi M, Heidary Rouchi A, Rajolani H, Nourozi S. Changing epidemiology of end-stage renal disease in last 10 years in Iran. Iran J Kidney Dis. 2009;3:192-6.
4. Ghaderi R, Mohammadi FM. Comparison of emolinet and heliotherapy effect on palliation of pruritus in hemodialysis patients in Persian. Ofoghe Danesh. 2006;12:42-7.
5. Banerjee S. Cutaneous manifestations in renal failure patients: a case series. Indian J Dermatol Venereol Leprol. 2007;73:106-8.
6. Gupta AK, Gupta MA, Cardella CJ, Haberman HF. Cutaneous associations of chronic renal failure and dialysis. Int J Dermatol. 1986;25:498-504.
7. Narita I, Iguchi S, Omori K, Gejyo F. Uremic pruritus in chronic hemodialysis patients. J Nephrol. 2008;21:161-5.
8. Akhyani M, Ganji MR, Samadi N, Khamesan B, Daneshpazhooh M. Pruritus in hemodialysis patients. BMC Dermatol. 2005;5:7.
9. Bargman JM, Skorecki K. Chronic kidney Disease. In: Longo D, Fauci A, Kasper D, et al, editors. Harrison`s principles of internal medicine. 18th ed. New York: McGrow-Hill; 2011. p 2308-21.
10. [No author listed]. K/DOQI clinical practice guidelines for

bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42:S1-201.

11. Carmichael AJ. Renal itch. In: Bernhard JD, editor. Itch: mechanisms and management of pruritus. New York: McGrow-Hill;1992. p. 217-28.
12. Duo LJ. Electrical needle therapy of uremic pruritus. Nephron. 1987;47:179-83.
13. Makhlough A, Ala S, Haj-Heydari Z, Kashi Z, Bari A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. Iran J Kidney Dis. 2010;4:137-40.
14. Hajheydari Z, Makhlough A. Cutaneous and mucosal manifestations in patients on maintenance hemodialysis: a study of 101 patients in Sari, Iran. Iran J Kidney Dis. 2008;2:86-90.
15. Stahle-Backdahl M. Uremic pruritus. Clinical and experimental studies. Acta Derm Venereol Suppl (Stockh). 1989;145:1-38.
16. Szepietowski JC, Sikora M, Kusztal M, Salomon J, Magott M, Szepietowski T. Uremic pruritus: a clinical study of maintenance hemodialysis patients. J Dermatol. 2002;29:621-7.
17. Altmeyer P, Kachel HG, Junger M, Koch KM, Holzmann H. [Skin changes in long-term dialysis patients. clinical study]. Hautarzt. 1982;33:303-9.
18. Urbonas A, Schwartz RA, Szepietowski JC. Uremic pruritus--an update. Am J Nephrol. 2001;21:343-50.
19. Murphy M, Carmichael AJ. Renal itch. Clin Exp Dermatol. 2000;25:103-6.
20. Stahle-Backdahl M, Hagermark O, Lins LE. Pruritus in patients on maintenance hemodialysis. Acta Med Scand. 1988;224:55-60.
21. Mettang T, Pauli-Magnus C. The pathophysiological puzzle of uremic pruritus--insights and speculations from therapeutic and epidemiological studies. Perit Dial Int. 2000;20:493-4.
22. Price ME, Fisher-Hoch SP, Craven RB, McCormick JB. A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy. BMJ. 1988;297:584-7.
23. Kyriazis J, Glotsos J. Dialysate calcium concentration of</=1.25 mmol/l: is it effective in suppressing uremic pruritus? Nephron. 2000;84:85-6.
24. Momose A, Kudo S, Sato M, et al. Calcium ions are abnormally distributed in the skin of haemodialysis patients with uraemic pruritus. Nephrol Dial Transplant. 2004;19:2061-6.
25. Virga G, Visentin I, La Milia V, Bonadonna A. Inflammation and pruritus in haemodialysis patients. Nephrol Dial Transplant. 2002;17:2164-9.
26. Benchikhi H, Moussaid L, Doukaly O, Ramdani B, Zaid D, Lakhdar H. [Hemodialysis-related pruritus. A study of 134 Moroccans]. Nephrologie. 2003;24:127-31.
27. Ostlere LS, Taylor C, Baillod R, Wright S. Relationship between pruritus, transepidermal water loss, and biochemical markers of renal itch in haemodialysis patients. Nephrol Dial Transplant. 1994;9:1302-4.
28. Massry SG, Popovtzer MM, Coburn JW, Makoff DL, Maxwell MH, Kleeman CR. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. N Engl J Med. 1968;279:697-700.
29. Hampers CL, Katz AI, Wilson RE, Merrill JP. Disappearance of “uremic” itching after subtotal parathyroidectomy. N Engl J Med. 1968;279:695-7.
30. Cho YL, Liu HN, Huang TP, Tarng DC. Uremic pruritus: roles of parathyroid hormone and substance P. J Am Acad Dermatol. 1997;36:538-43.
31. Lugon JR. Uremic pruritus: a review. Hemodial Int. 2005;9:180-8.

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