Evaluating the association between alterations in mineral metabolism and pruritus in hemodialysis patients *

Avaliação da associação entre as alterações no metabolismo mineral e o prurido nos paciente em hemodiálise

Elisângela de Quevedo Welter [1]
Adriana Maldotti [2]
Magda Blessmann Weber [4]
Renata Hubner Frainer [2]
Alexandre Losekann [3]

Abstract: BACKGROUND: Uremic pruritus is the most frequent symptom in long-term hemodialysis patients. Abnormal laboratory parameters have been found with conflicting data.
OBJECTIVE: To correlate the prevalence of pruritus with alterations in mineral metabolism in hemodialysis patients.
METHODS: This was a case-control study. A hundred and five patients on maintenance hemodialysis were evaluated: a group of patients with pruritus and a control group. They answered a research protocol questionnaire; laboratory data were collected from medical records and the patients with pruritus filled out a visual analogue scale (VAS) to measure pruritus level.
RESULTS: The mean age was 51.9 years; 59% of the patients were men and 43% of the patients had pruritus. Xeroderma occurred in 45% of the patients. High levels of calcium were demonstrated in 55% of the patients and 47% had pruritus. 60% of the patients had high phosphorus levels and 43% had pruritus. The Ca/P ratio was normal for all the patients. Parathyroid hormone was high in 95% of the patients, all of them referring pruritus.
CONCLUSION: There was a statistically significant association between the group of patients with pruritus and xeroderma. Serum calcium and phosphorus levels, Ca/P ratio, PTHi and size of the dialyzer did not show a statistically significant association with pruritus. Therefore, we found an important relationship between xeroderma and pruritus, with no relation with the assessed laboratory parameters.
Keywords: Kidney failure, chronic; Pruritus; Renal dialysis; Renal insufficiency, Chronic

Resumo: FUNDAMENTOS: prurido é o sintoma mais freqüente nos pacientes nefropatas em hemodiálise. Parâmetros laboratoriais anormais têm sido encontrados, com dados conflitantes.
OBJETIVO: relacionar a prevalência de prurido com alterações no metabolismo mineral de pacientes em hemodiálise.
MÉTODOS: estudo caso-controle. Avaliados 105 pacientes, sendo os pacientes com prurido os casos, preencheram o questionário do protocolo de pesquisa e a escala análoga visual, os dados laboratoriais foram coletados dos prontuários eletrônicos.
RESULTADOS: a média de idade foi de 51,9 anos, 59% dos pacientes eram homens e 43% dos pacientes tinham prurido. Xerodermia ocorreu em 45% dos pacientes. Níveis elevados de Ca foram demonstrados em 55% dos pacientes e 47% tinham prurido. Quanto ao fósforo 60% tinham valores elevados e 43% tinham prurido. A relação Ca/P foi normal em todos. O paratormônio mostrou-se elevado em 95% dos pacientes, todos referindo prurido.
CONCLUSÃO: houve associação estatisticamente significativa entre o grupo de pacientes com prurido e xerodermia. Os níveis séricos de Cálcio, Fósforo, relação Ca/P, PTHi e o tamanho do dialisador não apresentaram associação estatisticamente significativa com o prurido. Logo, encontramos relação importante entre xerodermia e prurido, sem relação com os parâmetros laboratoriais avaliados.
Palavras-chave: Diálise renal; Falência renal crônica; Insuficiência renal crônica; Prurido

Received on 23.10.2009.
Approved by the Advisory Board and accepted for publication on 13.12.10.
* Work conducted at the Health Sciences Federal University of Porto Alegre (UFCSPA) - Santa Casa de Porto Alegre Hospital Complex - Porto Alegre (RS), Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

[1] Dermatologist, Health Sciences Federal University of Porto Alegre (UFCSPA) - Porto Alegre (RS), Brazil.
[2] MD – Intern, Dermatology Service, Health Sciences Federal University of Porto Alegre (UFCSPA) - Porto Alegre (RS), Brazil.
[3] Nephrologist, Santa Casa de Porto Alegre Hospital Complex (HSCPA); Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Pontifical Catholic University of Rio Grande do Sul (FAMED - PUCRS) - Porto Alegre (RS), Brazil.
[4] Professor (PhD) of Dermatology, Health Sciences Federal University of Porto Alegre (UFCSPA) - Porto Alegre (RS), Brazil.

INTRODUCTION

The prevalence and incidence of chronic kidney disease increased in the last decade, so the disease has become a public health issue. The symptom that most frequently affects these patients is pruritus, [2-12] ranging between 22% and 90% in prevalence.[1-4,6-9,13-15] It often begins six months before the start of dialysis and manifests itself in markedly different ways; it may be persistent, intense and widespread or just localized and transient.[4,14] Pruritus causes changes in quality of life and [11] has a physical and mental impact, which contribute to depression, agitation, sleep disturbances and fatigue.[1,12,15] It is also associated with increased risk of mortality in 17% of the patients, [16] being considered an important prognostic marker and an independent predicting factor of mortality in patients with this disease in its severest form.[12] Patients with moderate to severe pruritus have a 13% to 21% higher risk of death than those with mild pruritus [17] showing that there is a relationship between the degree of pruritus and mortality, probably related to sleep disorders induced by this symptom.[16]

It is important to perform differential diagnosis with other causes of pruritus: biliary tract obstruction, endocrinological diseases, myeloproliferative disorders, cancer, neurological and psychiatric disorders, scabies, atopic dermatitis, contact dermatitis, drug and allergic reactions in general. [1,18]

Xerosis is the most common dermatologic manifestation in patients with chronic renal failure; reduction of [12,19] the hydration of the stratum corneum has been reported, suggesting that this may be a cause of pruritus.[12,19] Morto et al. assessed the prevalence and severity of pruritus in patients with xerosis who underwent hemodialysis and demonstrated that they show a significant reduction in skin hydration, as compared with those who had no pruritus.[12] However, these data were not confirmed in other studies.

The pathophysiology of pruritus related to chronic renal failure patients remains unknown, but is believed to be multifactorial. [2 to 5,7] Several mechanisms are cited in attempting to explain this event, such as hyperparathyroidism, [14,16,20] allergic reactions, proliferation of mast cells in the skin, iron deficiency anemia, hypervitaminosis A, xerosis, neuropathy , cytokines, bile acids, nitric oxide, electrolyte [2-4, 21], creatinine, total protein [5,8], urea, ferritin, and transferrin disorders and [8] alterations of the immune system.[22] Many authors believe that altered levels of magnesium, parathyroid hormone, phosphorus, calcium and calcium/phosphorus ratio are involved in renal pruritus.[17, 21,23 to 28]

With regard to dialyzers, there are studies showing that patients dialyzed with a less permeable biocompatible membrane have more pruritus than patients dialyzed with a more permeable polysulfone membrane. [28] Others have reported that patients dialyzed with polysulfone membrane have more pruritus than those who undergo hemodialysis with hemofane and cuprofane membranes.[1]

Although some studies show a relationship between these factors and pruritus, the data remain conflicting, demonstrating the need for further research on the subject.

OBJECTIVES

To assess the prevalence and degree of pruritus and correlate them with changes in mineral metabolism, urea levels, xeroderma, dialysis time and the size of the dialyzer in chronic renal patients on hemodialysis.

METHODOLOGY

The project was approved by the Research Ethics Committee of the hospital. This was an unpaired case-control study that evaluated 105 patients in the hemodialysis service from July to September 2008. Patients with pruritus were defined as cases and those without pruritus, as controls. The study included all the patients who underwent hemodialysis, who were over 18 years old and who agreed to participate in the research by signing an informed consent. Case group patients were examined to rule out other causes of pruritus; they answered the research protocol questionnaire and had the degree of pruritus assessed through visual analogue scale. Laboratory data were collected by review of electronic medical records of the patients. For the presentation of the results and descriptive measures, the t-Student or Mann Whitney tests were used to compare quantitative variables, and the chi-square test was used to evaluate associations between qualitative variables. Fisher's exact test was used in situations in which the chi-square test had limitations. The Spearman's correlation coefficient was used to correlate ordinal qualitative and quantitative variables. The level of significance adopted was 0.05. The data were stored in an anonymous database and evaluated using the SPSS 13.0 software.

RESULTS

Of the 117 patients initially selected for the research, 10 refused to participate, one had a mental disability and one was in unfavorable clinical conditions. These factors prevented them from answering the questionnaire, totaling a sample of 105 patients. Of the total sample, 46 patients (43.8%)

belonged to the group with pruritus (Table 1).

In the evaluation of gender, 56.2% (n = 59) were male and 43.8% (n = 46), female, showing no statistically significant difference, both for the total sample (p = 0.097) , and for the distribution between the groups (p = 0.148). The mean age was 51.9 years (SD = 15.7), and there was no statistically significant difference between the groups (p = 0.698).

In assessing the comparison of the duration of dialysis with xeroderma, independently related to pruritus, the results showed no difference in the duration of hemodialysis between the two groups (p = 0.94). In relation to xeroderma, 57 patients (54.3%) did not have this characteristic and, when comparing the groups, those who had xeroderma showed more pruritus (p = 0.03) (Table 2).

Concerning the comparison between serum levels of minerals, urea and pruritus, there were no statistically significant differences between the two groups (Table 3). However, it is noteworthy that, in the comparison between the values of parathyroid hormone (iPTH), a borderline significance (0.05 <P) was detected.

Comparing the serum levels of minerals, measured in categories (below normal, normal or above normal), urea levels and the size of the dialyzer in relation to the presence or absence of pruritus, none of the comparisons showed a statistically significant association (Table 4).

Table 1: Descriptive measures regarding the presence and degree of pruritus

Pruritus	Total
Presence*	
No	59 (56,2)
Yes	46 (43,8)
Degree (n=46)*	
Mild (0 – 3,9)	9 (19,6)
Moderate (4 – 8,9)	28 (60,9)
Severe (9 – 10)	9 (19,6)

* Values presented as n (%), where the percentage was obtained based on the total of each group

DISCUSSION

The prevalence of pruritus observed in our study was 43.8%, which is consistent with data from the literature, which reports frequencies around 22% to 90%. [1, 2,3,4,6,7,8,15,16,18,26] We also found no correlation between pruritus and age, sex and duration of dialysis. These data are consistent with the studies reviewed.[1, 2,3,28, 29,30]

The authors of this paper, in an earlier study in the same hemodialysis unit, found similarities between the mean age of patients. Pruritus had a prevalence of 34.5% and most patients also had a moderate degree of pruritus (56.5%).[31] This difference between the prevalence of pruritus in different works is in line with the great variability in the prevalence of pruritus found in the literature.

In relation to xeroderma, of the total sample, 45.7% had this characteristic and, when comparing the groups, a statistically significant association between patients with xeroderma and pruritus (p = 0.031) was found, a fact confirmed in previous studies. [27] The time that the patient is on dialysis did not correlate with the presence of pruritus, which is also in agreement with the literature.

Comparisons of serum levels of minerals analyzed in the study (calcium, phosphorus, calcium/phosphorus ratio, parathyroid hormone) in relation to case and control groups did not show statistically significant differences, a result also found in previous studies. [4, 7, 10, 11] However, Pisoni *et al.*, in a

Table 2: Descriptive measures for the variables of time of hemodialysis and xeroderma, for the total sample and by group

Variables	Total (n = 105)	Pruritus		S
		Yes (n=46)	No (n=59)	
TIME ON DIALYSIS (years)				0,947
Mean ± SD	3,9 ± 3,0	4,1 ± 3,3	3,7 ± 2,8	
Minimum - Maximum	0,01 – 14,0	0,01 – 14,0	0,08 – 11,0	
XERODERMA				0,031
Yes	48 (45,7)	27 (58,7)	21 (35,6)	
No	57 (54,3)	19 (41,3)	38 (64,4)	

* Values presented as n (%), where the percentage was obtained based on the total of each group

Table 3: Descriptive measures for the variables related to serum levels for the total sample and by group

Serum levels	Total	Pruritus		S
		Yes	No	
CALCIUM (Ca)	(n=103)	(n=45)	(n=58)	0.522
Mean/Standard deviation	5.2 ± 1.2	5.0 ± 1.0	5.3 ± 1.4	
Minimum/Maximum	3.4 – 9.6	3.8 – 9.3	3.4 – 9.6	
PHOSPHORUS (P)	(n=103)	(n=44)	(n=59)	0.257
Mean/Standard deviation	5.5 ± 1.8	5.8 ± 2.1	5.4 ± 1.6	
Minimum/Maximum	1.4 – 10.7	1.4 – 10.7	2.8 – 8.5	
Ca/P	(n=102)	(n=44)	(n=58)	0.344
Mean/Standard deviation	1.0 ± 0.5	1.0 ± 0.6	1.1 ± 0.5	
Minimum/Maximum	0.11 – 3.14	0.40 – 3.14	0.11 – 2.46	
PARATHYROID HORMONE (PTHi)	(n=95)	(n=38)	(n=57)	0.069
Mean/Standard deviation	698.1 ± 597.9	833.2 ± 635.3	607.9 ± 559.4	
Minimum/Maximum	2.5 – 1900.0	96.4 – 1900	2.5 – 1900	
UREA	(n=104)	(n=45)	(n=59)	0.479
Mean/Standard deviation	163.2 ± 40.3	164.7 ± 38.2	162.0 ± 42.2	
Minimum/Maximum	38 – 279	38 – 223	81 – 279	

* Values presented as n (%), where the percentage was obtained based on the total of each group

Table 4: Descriptive measures for the variables related to the normal parameters of serum levels, measured in categories, for the total sample and by group

Serum levels	Total	Pruritus		S
		Yes (n=45)	No (n=58)	
CALCIUM (Ca) *	(N = 103)	(N = 45)	(N = 58)	0.589
Below 4.0	4 (3.9)	1 (2.2)	3 (5.2)	
Normal (4.0 - 4.8)	42 (40.8)	17 (37.8)	25 (43.1)	
Above 4.9	57 (55.3)	27 (60.0)	30 (51.7)	
PHOSPHORUS (P) *				0.101
Below 2.5	3 (2.9)	3 (6.8)	0 (0,0)	
Normal (2.5 - 5.0)	38 (36.9)	14 (31.8)	24 (40.7)	
Above 5.0	62 (60.2)	27 (61.4)	35 (59.3)	
Ca / P				- - -
Normal (<4.4)	102 (100.0)	44 (100.0)	58 (100.0)	
Above (≥ 4.4)	0 (0.0)	0 (0.0)	0 (0.0)	
PARATHYROID HORMONE (PTHi) *				0.249
Below 14.0	1 (1.1)	0 (0.0)	1 (1.8)	
Normal (14-72)	3 (3.2)	0 (0.0)	3 (5.3)	
Above 72	91 (95.8)	38 (100.0)	53 (93.0)	
UREA *				0.433
Normal (15-45)	1 (1.0)	1 (2.2)	0 (0.0)	
Above 45	103 (99.0)	44 (97.8)	59 (100.0)	
CAPILLARY				0.150
Mean ± SD	1.85 ± 0.18	1.88 ± 0.19	1.82 ± 0.16	
Minimum - Maximum	1.50 to 2.20	1.60 to 2.20	1.50 to 2.20	

* Values presented as n (%), where the percentage was obtained based on the total of each group

major multicenter study involving 12 countries, noted the important association between an increase in calcium, phosphorus and C/P ratio with pruritus, which was also found in other studies .[12.16, 22, 23]

CONCLUSION

There was a similar distribution between the groups regarding gender and age. In relation to xerosis, 54.3% of the patients did not have it. In comparing the two groups, patients with pruritus were associated with the presence of xerosis. This was not observed in the group without pruritus ($p < 0.05$). Serum levels of calcium, phosphorus, Ca/P ratio and PTHi were not statistically significant in their association with pruritus. We found a significant relationship between the presence of pruritus and xerosis, a fact not observed in relation to laboratory parameters.

Pruritus is a symptom frequently observed in CRF patients on dialysis, and little is known about its pathophysiology. It is important to understand this mechanism mainly because this symptom significantly alters the patients' quality of life and increases the risk of mortality.

Several studies have been conducted in an attempt to elucidate this issue; however, we found discrepancies between their results, which leads us to continue research into the matter and examine the presence of a possible variable related to the pathophysiology that has not yet been investigated. ❑

REFERENCES

1. Patel TS, Freedmann BI, Yosipovitch G. An update on pruritus associated with CKD. Am J Kidney Dis. 2007;5:11-20.
2. Robinson-Bostom L, Digiovanna JJ. Cutaneous Manifestations of end-stage renal disease. J Am Acad Dermatol. 2000; 43: 975-986.
3. Lugon JR. Uremic Pruritus: A Review. Hemodial Int. 2005;9:180-8.
4. Akhyani M, Ganji MR, Sadami N, Khamesan B, Daneshpazhooh M. Pruritus in hemodialysis patients. BMC Dermatology. 2005;5:7.
5. Mistik S, Utas S, Ferahbas A, Tokgoz B, Unsal G, Sahan H, et al. An epidemiology study of patients with uremic pruritus. J Eur Acad Dermatol Venereol. 2006;20:672-8.
6. Mettang T, Pauli-Magnus C, Alscher DM. Uremic pruritus - new perspectives and insights from recent trials. Nephrol Dial Transplant. 2002;17:1558-63.
7. Virga G, Visntin I, Milia VL, Bonadonna A. Inflammation and pruritus in haemodialysis patients. Nephrol Dial Transplant. 2002;17:2164-9.
8 Kimmel M, Alscher DM, Dunst R, Braun N, machleidt C, Kiefer T, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. Nephrol Dial Transplant. 2006;21:749-55.
9. Zucker I, Yosipovitch G, David M, Gafter U, Boner G. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: Uremic pruritus is still a major problem for patients with end-stage renal disease. J Am Acad Dermatol. 2003;49:5.
10. Dyachenko P, Shustak A, Rozenman D. Hemodialysis-related pruritus and associated cutaneous manifestations. Int J Dermatol. 2006;45:664-7.
11. Lin HH, Liu YL, Liu JH, Chou CY, Yang YF, Kuo HL, et al. Uremic, cytokines and polymethylmethacrylate artificial kidney. Artif Organs. 2008;32:468-72.
12. Narita I, Iguchi S, Omori K, Gejvo F. Uremic pruritus in chronic hemodialysis patients. J Nephrol. 2008;21:161-5.
13. Manenti L, Vaglio A, Costantino E, Danisi D, Oliva B, Pini S, et al. Gabapentin in the treatment of uremic itch: an index case and a pilot evaluation. J Nephrol. 2005;18: 86-91.
14. Razeghi E, Tavakolizadeh S, Ahmadi F. Inflammation and pruritus in hemodialysis patients. Saudi J Kidney Dis Transpl. 2008;19:62-6.
15. Melo NCV, Elias RM, Castro MCM. Pruritus in hemodialysis patients: the problem remains. Hemodial Int. 2009;13:38-42.
16. Pisoni RL, Wikstrom B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in hemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOOPPS). Nephrol Dial Transplant. 2006;21:349 -505.
17. Aucella F, Vigilant M, Gesuete A, Maruccio G, Specchio A, Gesualdo L. Uraemic itching: do polymethylmethacrylate dialysis membranes play a role. Nephrol Dial Tranplant. 2007;22:8-12.
18. Seckin D, Demircay Z, Akin O. Generalized pruritus treated with narrowband UVB. Int J Dermatol. 2007;46:367-70.
19. Yosipovitch G, Duque MI, Patel TS, Ishiuji Y, Guzman-Sanchez DA, Dawn AG, et al. Skin barrier structure and function and their relationship to pruritus in end-stage renal disease. Nephrol Dial Transplant. 2007;22:3268-72.
20. Hampers CL, Katz AI, Wilson RE, Merril JP. Disappearance of "uremic" itching after subtotal parathyroidectomy. N Engl J Med. 1968;279: 695.
21. Ashmore SD, Jones CH, Newstead CG, Daly MJ, Chystyn H. Ondansetron Therapy for Uremic Pruritus in hemodialysis patients. Am J Kidney Dis.2000;35:827-31.
22. Wikström B. Itchy skin - a clinical problem for haemodialysis patients. Nephrol Dial transplant. 2007;22:3-7.
23. Noordzij M, Boeschoten EW, Boss WJ, Dekker FW, Bossuyt PM, Krediet RT, et al. Disturbed mineral metabolism is associated with muscle and skin complains in a prospective cohort of dialysis patients. Nephrol Dial Transplant. 2007;22:2944-9.
24. Massry SG, Popovtzer MM, Coburn JW. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. N Engl J Med.1968;279:697-700.
25. Parfitt AM, Massry SG, Winfield AC. Disordered calcium and phosphorus metabolism during maintenance hemodialysis. Correlation of clinical, roentgenographic and biochemical changes. Am J Med. 1971;51:319-30.
26. Blachley JD, Blankenship DM, Menter A, Parker TF 3rd, Knochel JP. Uremic pruritus: Skin divalent ion content and response to ultraviolet phototherapy. Am J Kidney Dis. 1985;5:237-41.
27. Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int. 2006;69:1626-32.
28. Duque MI, Thevarajah S, Chan YH, Tuttle AB, Freedman BI, Yosipovitch G. Uremic pruritus is associated with higher kt/V and serum calcium concentration. Clin Nephrol. 2006;66:184-91.
29. Costa MG, Karnopp T, Weber MB, Campos BM, Burmaeister JB. Prurido e achados dermatológicos em pacientes em hemodiálise. Rev HCPA. 2006;26:5-11.
30. Welter EQ, Bonfá R, Petry V, Moreira LL, Weber MB. Relação entre grau de prurido e qualidade de vida de pacientes em hemodiálise. An Bras Dermatol. 2008;83:137-40.

MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Elisângela de Quevedo Welter
Rua Florêncio de Abreu, 1660/504, centro
98804-560, Santo ângelo - RS
E-mail: eliswelter@yahoo.com.br

How to cite this article/*Como citar este artigo*: Welter EQ, 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.