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Assessment of the psychological burden associated with pruritus in hemodialysis patients using the kidney disease quality of life short form

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Abstract
Purpose To assess whether depression symptoms, poor sleep and dry skin bother explain association between pruritus and the burden of kidney disease in maintenance hemodialysis (MHD) patients.
Methods Cross-sectional study of 980 *patients from* a prospective study in dialysis units of Salvador, Brazil (*PROHEMO*). The Kidney Disease Quality of Life Short Form was used to determine scores of kidney disease burden (*KDB*) and sleep with *higher scores indicating lower perceived burden and better sleep quality, respectively*. The Center for Epidemiological Studies Depression Scale was used for depression symptoms.
Results Prevalence of severe pruritus (very much or extreme) was 19.4%. Significantly ($P < 0.001$) lower mean *KDB* score by 11.44 points was observed for patients with severe pruritus (34.18 ± 27.51) than for those with no pruritus (45.62 ± 30.73). Severe pruritus was associated with poorer sleep quality, higher odds of dry skin bother and higher depression symptoms score. Association of pruritus with *KDB score* was virtually eliminated after adjustment for sleep, dry skin bother and depression symptoms.
Conclusions This study shows strong associations of severe pruritus with higher depression symptoms, poorer sleep and dry skin bother among MHD patients. The results support special attention to MHD patients with pruritus who often face high psychological burden.

Keywords Hemodialysis · Quality of life · Depression · Sleep · Dry skin · Xerosis · Pruritus · Itch

Abbreviation

BMI	Body Mass Index
Ca_{Alb}	Albumin-corrected serum calcium
$CaxPO_4$	Calcium-phosphate product
CES-D	Center for Epidemiological Studies Depression Scale
CKD	Chronic kidney disease
DOPPS	Dialysis Outcome and Practice Patterns Study
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
KDB	Kidney Disease Burden
KDQOL-SF	Kidney Disease Quality of Life Short Form
Kt/V	Dialysis dose
MHD	Maintenance hemodialysis patients

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PO_4	Phosphate
PROHEMO	Prospective Study of the Prognosis of Chronic Hemodialysis Patients
PTH	Parathyroid hormone
RLS	Restless legs syndrome

Introduction

Pruritus is a frequent unpleasant symptom among maintenance hemodialysis (MHD) patients [1–3]. In the Dialysis Outcome and Practice Patterns Study (DOPPS), the frequency of patients bothered by pruritus in the previous 4 weeks was very high, above 70% [3]. In a study developed in the United States, daily or nearly daily pruritus was reported by 84% of the patients [4]. Variations in the frequency of pruritus across regions and studies, however, have been observed [3, 5]. It is interesting to verify if this variation could be explained by the season of data collection, considering the evidence that the prevalence of pruritus is higher during the winter in regions of the Northern hemisphere, perhaps because of associations with dry skin (xerosis) during the coldest months of the year [6]. Similar to pruritus, the prevalence of dry skin in maintenance dialysis patients is very high, ranging from 50% to approximately 80% [6]. There are data to indicate that dry skin is positively correlated with pruritus severity and inversely correlated with health-related quality of life (HRQOL) in maintenance dialysis patients [6, 7].

The lack of treatments to effectively control pruritus associated with chronic kidney disease (CKD) may contribute to the poor HRQOL in MHD patients. As observed in DOPPS, patients who reported higher degree of pruritus were more likely to report poorer mental and physical HRQOL as well as poorer sleep quality [3]. Pruritus severity has also been associated with higher degree of depression symptoms and higher odds of restless legs syndrome (RLS) [3, 8, 9]. Despite the data showing that pruritus is very distressing for dialysis patients, this health problem is often largely overlooked by nephrologists and health care professionals [2]. Moreover, there is a lack of studies to assess the prevalence and psychological consequences of pruritus, particularly in less developed regions of the Southern hemisphere.

One of the few Brazilian studies on pruritus among hemodialysis patients was developed in the city of São Paulo in Southeastern Brazil [5]. The prevalence of pruritus in a sample of 101 patients was 30.7%. This prevalence was much lower than the one reported in DOPPS, but as pruritus is associated with season, it would also be interesting to evaluate when the data were collected.

The present study is likely the largest on pruritus in a MHD population from an equatorial region. It expands previous works by providing a detailed assessment of associations between pruritus severity and a HRQOL component from the Kidney Disease Quality of Life Short Form (KDQOL-SF) that addresses the feelings of MHD patients about how the kidney disease affects their lives in several aspects, such as time spent with the disease, frustrations in dealing with disease and the perceived burden on family. We hypothesized that the burden of kidney disease reported by these patients would be higher for those more severely bothered by pruritus. Using data of MHD patients treated in renal units of a large city from Northeast Brazil, the present study determined the frequency of patients bothered by pruritus according to season of data collection and assessed whether the severity of pruritus was associated with the degree of psychological burden reported by the patients. We also explored associations of pruritus with dry skin, depression symptoms and sleep quality and assessed whether these factors influence an association between pruritus severity and the kidney disease burden reported by MHD patients.

Methods

Cross-sectional study of MHD patients enrolled in the Prospective Study of the Prognosis of Chronic Hemodialysis Patients (PROHEMO) [10] developed since 2005 at four dialysis units in Salvador, a coastal city located in Northeast Brazil, between the Tropic of Capricorn and the Equator Line. The temperature of Salvador is very stable and mild during most of the year; however, high temperatures around 86°F (30°C) are observed during the summer period, January to March. Cold weather is not common in Salvador even during the winter period (June to August) when the average of lower temperatures varies from 71 to 72°F (22°C). The study was conducted from May 2005 to December 2009. From an original sample of 1,152 patients, 980 had information for pruritus severity, disease burden, sleep quality and dry skin. The data of these 980 patients were used for the present analysis.

Measures

Using the version of the Kidney Disease Quality of Life Short Form (KDQOL-SF) validated for the Brazilian population [6, 7], the patients were asked about the extent to which they were bothered by itchy skin (pruritus) and dry skin for the last 4 weeks. Possible responses to these questions were not at all, somewhat, moderately, very much and extremely bothered. For the current analysis, these options of responses were collapsed into three categories: no, mild (somewhat or moderately) and severe (very much or extremely).

Perceived disease burden was assessed by asking the patients how true or false was each of the following items of the kidney disease burden scale of the KDQOL-SF: (1) my kidney disease interferes too much with my life, (2) too much of my time is spent dealing with my kidney disease, (3) I feel frustrated dealing with my kidney disease, (4) I feel like a burden on my family. These questions have five options of response, ranging from definitely true to definitely false. To assess sleep quality, the patients were asked to rate their sleep on a scale ranging from 0 (zero) representing very bad to 10 representing very good. Additionally, the patients were asked how often during the past 4 weeks they have (1) awakened during the night and had trouble falling asleep again, (2) gotten the amount of sleep needed and (3) had trouble staying awake during the day. The responses for these sleep questions could also vary from none of the time to all of the time. Based on the patient responses, the scores (range from 0 to 100) of the disease burden and the sleep quality were determined. Higher score in the kidney disease burden scale indicates lower perceived burden, and higher score in the sleep scale of the KDQOL indicates better sleep quality [11]. The 20-item Portuguese version of the Center for Epidemiological Studies Depression (CES-D) scale was used to assess depression symptoms [12]. The scores of the 20-item version of the CES-D may vary from 0 to 60, with higher scores indicating greater depressive symptoms. CES-D scores $\geq$18 points were used to identify patients with higher probability of depression [13].

The diagnoses of comorbidities were based on information provided by the attending nephrologists. Dialysis dose was assessed by the average of three consecutive measures of single pool Kt/V, where K = clearance of urea by the dialyzer, t = the length of the dialysis section and V = urea distribution volume [14]. Data on laboratory variables were based on pre-dialysis measurements.

Statistical analysis

The chi-square test was used for associations between categorical variables and for trends in proportions. One-way analysis of variance (ANOVA) and linear regression were used for comparing means and assessing trends in continuous variables. To evaluate whether the data of continuous variables were consistent with the normal distribution assumption for comparisons using parametric tests, it was taken into consideration the size of the comparison groups and the shape of the distribution according to histogram plots and measures of kurtosis and skewness. For PTH, a logarithmic transformation was used to correct for a large deviation from the normal distribution.

Multivariable logistic regression was used to assess association of mild and severe pruritus (no pruritus as referent) with dry skin adjusted for sociodemographic variables (age, gender, race, education and living status); vintage (years after diagnosis of end-stage renal disease); single pool Kt/V; serum hemoglobin; serum albumin and serum creatinine as indicators of nutritional status or inflammation [15–17]; serum PTH, albumin-corrected serum calcium; serum phosphorus as indicators of disturbances of mineral metabolism; and comorbidities (heart failure, peripheral vascular disease, cerebrovascular disease and diabetes mellitus). Logistic regression was also used to assess associations between pruritus and the period of data collection, with and without adjustment for dry skin bother. The Hosmer and Lemeshow goodness-of-fit test was used to assess whether the predicted values were consistent with the observed values. No evidence of lack of fit was observed.

Multivariable linear regression was used to assess associations of mild and severe pruritus (no pruritus as referent) with sleep and depression scores adjusted for the same covariates used for the logistic regression analysis. Linear regression models, without adjustments (model 1), and with seven different levels of adjustments were used to assess associations of mild and severe pruritus (no pruritus as referent) with the kidney disease burden score. For the adjusted analyses, the following groups of covariates were sequentially included in the multivariable linear regression models: model 2—sociodemographic variables and vintage; model 3—dialysis dose by single pool Kt/V, laboratory variables plus covariates in model 2; model 4—comorbidities plus covariates in model 3; model 5: dry skin plus covariates in model 4; model 6—depressive symptoms score plus covariates in model 4; model 7—sleep plus covariates in model 4; model 8—dry skin bother, depressive symptoms and sleep plus group 4 covariates.

Normal probability plots of the residuals (Normal P–P Plot of Regression Standardized Residual) were used to assess whether the patterns were linear, consistent with a normal distribution of error terms. The patterns were reasonably linear supporting the use of regression models.

The data of the 980 participants were complete (no missing data) for age, gender, time on dialysis, race, education, living status, kidney disease burden, sleep, dry skin, serum creatinine, serum phosphorus and depression symptoms. For the other variables, missing data were observed for less than 3%, except for PTH (5.2%) and heart failure (3.3%). Covariates were included in the multivariable models independent of statistical significance. For categorical variable, missing data were handled through the use of indicator variables that were coded as 1 or 0 to indicate the presence or absence of information. Mean values specific for pruritus severity categories were used to replace missing information for quantitative variables.

Two-tailed P value < 0.05 was considered statistically significant. The statistical analyses were performed using the SPSS version 16.0 for Windows (SPSS Inc, Chicago, IL).

Results

Table 1 shows patient characteristics by degree of pruritus. Patients with severe pruritus (19.4%; 190/980), as compared with those with mild (24.4%; 239/980) or no pruritus (56.2%, 551/980), were older and had lower serum albumin and higher prevalence of heart failure. Mean albumin-corrected serum calcium, phosphorus, PTH and calcium-phosphate product ($CaxPO_4$) varied minimally by degree of pruritus.

The percentage of patients who referred being bothered by pruritus was lower ($P = 0.001$) among those interviewed from January to March than among those interviewed during the rest of the year (31.2% vs. 46.1%). The unadjusted odds of pruritus were 47% lower for patients interviewed from January to March as compared with other months (odds ratio (OR) = 0.53, $P = 0.001$). This association was unchanged after adjustments for dry skin by logistic regression (OR = 0.54, $P = 0.002$). These data are not shown in the table.

Table 1 Characteristics by degree of pruritus

	No $N = 551$	Mild $N = 239$	Severe $N = 190$	P value*
Age (mean ± SD)	47.60 ± 14.3	49.59 ± 14.14	51.21 ± 13.52	<0.01
% Male	58.6	62.8	58.9	0.77
%<High school	59.5	66.4	37.4	0.03
% Non-white	89.7	87.9	87.4	0.33
% Living with family/friends	89.8	91.2	88.4	0.74
Vintage				
%<3 months	20.4	19.7	18.9	
%3 months to <1 year	22.4	25.1	18.9	0.44
%≥ 1 year	57.3	55.2	62.1	
% Vascular access by catheter	27.6	25.9	22.1	0.147
Albumin, g/dL (mean ± SD)	3.9 ± 0.6	3.9 ± 0.6	3.8 ± 0.6	0.04
Hemoglobin, g/dL (mean ± SD)	9.8 ± 1.8	9.7 ± 1.9	9.9 ± 1.9	0.88
% Saturation of transferrin < 20%	37.0	43.0	33.8	0.82
Kt/V (mean ± SD)	1.45 ± 0.26	1.45 ± 0.23	1.50 ± 0.31	0.10
Urea (mean ± SD)	136.5 ± 40.8	142.9 ± 58.3	138.6 ± 42.5	0.25
Creatinine, mg/dL (mean ± SD)	10.3 ± 3.6	10.5 ± 3.6	10.3 ± 3.6	0.99
% Diabetics	26.1	22.6	24.7	0.33
% Heart failure	10.3	15.5	17.5	<0.01
% Cerebrovascular disease	4.5	4.3	5.9	0.51
% Peripheral vascular disease	4.1	3.9	7.0	0.17
% Ca-based phosphate binders	40.3	41.4	38.5	0.75
% Sevelamer alone	34.0	35.0	35.3	0.72
% Vitamin D/analogs	27.4	23.2	31.0	0.61
PTH (mean ± SD)	414.7 ± 558.4	368.8 ± 500.6	360.9 ± 518.1	0.49
Ca_{Alb} (mean ± SD)	9.3 ± 0.9	9.4 ± 0.9	9.4 ± 1.0	0.13
PO_4 (mean ± SD)	5.1 ± 1.7	5.1 ± 1.6	5.2 ± 1.6	0.37
$CaxPO_4$ (mean ± SD)	46.7 ± 16.0	47.2 ± 16.2	48.1 ± 16.2	0.30
% Hepatitis C vírus (HCV)	4.7	4.2	5.8	0.68
% HIV	0.0	0.4	0.0	–

SD standard deviation, Ca_{Alb} albumin-corrected serum calcium, PO_4 phosphate, *HIV* human immunodeficiency virus, $CaxPO_4$ calcium-phosphate product

* To assess for trend, continuous variables were regressed on pruritus categories. For PTH, the analysis was performed using the natural logarithm of PTH. The log-transformed values of PTH were 5.35 ± 1.24 for "no pruritus", 5.33 ± 1.14 for "mild pruritus" and 5.27 ± 1.13 for "severe pruritus". The P values for the categorical variables were determined by using chi-square for trend

Table 2 shows that the percentage of patients severely bothered by dry skin increased monotonically by degree of being bothered by pruritus (P for trend < 0.001). The adjusted odds of being severely bothered by dry skin were more than nine times higher among patients who were severely bothered by pruritus than among those not bothered by pruritus (OR $= 9.15$, $P < 0.001$).

Figure 1 shows dose–response associations of pruritus with items of the sleep scale. Patients with worse pruritus were progressively more likely to awake during the night and have trouble falling asleep again, not get the amount of sleep that they need or have trouble staying awake during the day. The average sleep rate was 7.37 ± 2.68 for patients with no pruritus, 7.11 ± 2.75 with mild pruritus and 6.67 ± 2.97 with severe pruritus, $P = 0.01$. (data are not shown) As shown in Table 3, the mean score of the quality of sleep scale decreased as the degree of pruritus increased. A difference of approximately eight points ($P < 0.001$) was observed in the mean sleep score between patients severely bothered (65.4) and not bothered by pruritus (73.5). The magnitude of this difference was not reduced substantially after adjusting for covariates.

As shown in Table 4, the scores of depression symptoms increased steadily with the degree of being bothered by pruritus. Compared with patients not bothered by pruritus, the mean score of depression symptoms was more than 6 points higher for patients severely bothered by pruritus, even after adjusting for sociodemographic factors and comorbidities ($P < 0.001$). The frequency of patients with scores of depression symptoms (CES-D) $\geq$18 points was 36.8% (203/551) for patients with no pruritus, 42.3% (101/239) for those with mild pruritus and 58.4% for patients with severe pruritus; P for trend < 0.001 (data are not shown in the table).

Positive associations between degree of pruritus and disease burden were observed for each of the four items of the kidney disease burden scale, in a dose–response fashion

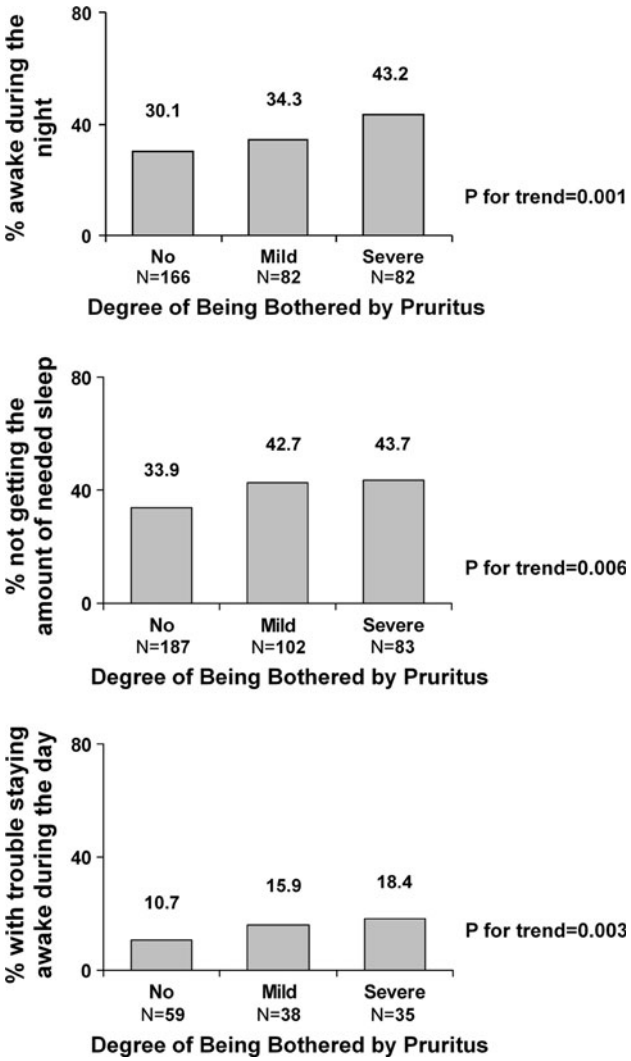

Fig. 1 Percentage of patients who reported problems with sleep at least a good bit of the time during the past 4 weeks, by degree of being bothered by pruritus. The denominators used to calculate the percentages by degree of being bothered by pruritus were 551 for No, 239 for mild and 190 for severe

Table 2 Associations between being bothered by pruritus and severely bothered by dry skin

Bothered by pruritus	% Bothered severely by dry skin*	Odds ratio (95% confidence interval)†	
		Unadjusted	Adjusted‡
No	8.7% (48/551)	Reference = 1	Reference = 1
Mildly	14.6% (35/239)	1.79 (1.13–2.85)	1.92 (1.19–3.10)
		$P = 0.01$	$P < 0.01$
Severely	45.3% (86/190)	8.63 (5.72–13.02)	9.13 (5.89–14.13)
		$P < 0.01$	$P < 0.01$

* P value for trend < 0.001

† Severely bothered by dry skin was used as dependent variable in the logistic regression model

‡ Odds ratios were adjusted for sex, age, education, living status, race, months on dialysis, Kt/V, serum hemoglobin, serum creatinine, serum calcium corrected to albumin, PTH, heart failure, peripheral vascular disease, cerebrovascular disease and diabetes mellitus; the P value for the Hosmer and Lemeshow goodness-of-fit test was 0.69 for the unadjusted model and 1.0 for the adjusted model

Table 3 Linear regression differences in sleep scores by degree of being bothered by pruritus

Degree of being bothered by pruritus	*N*	Sleep scores* (mean ± SD)†	Linear regression difference (95% confidence interval) in the sleep scores by degree of pruritus	
			Unadjusted	Adjusted‡
No	551	73.5 ± 23.0	Reference = 0	Reference = 0
Mildly	239	67.4 ± 20.1	−6.03 (−2.50, −9.55)	−5.77 (−2.25, −9.28)
			$P = 0.01$	$P = 0.01$
Severely	190	65.4 ± 24.0	−8.08 (−4.25, −11.91)	−7.18 (−3.35, −11.01)
			$P < 0.01$	$P < 0.01$

* Sleep scores may vary from 0 to 100, and a higher score means better sleep quality

† One-way ANOVA *P* value was lower than 0.001 for differences in sleep scores by degree of being bothered by pruritus

‡ Adjusted for sex, age, education, living status, race, months on dialysis, *Kt/V*, serum hemoglobin, serum creatinine, serum calcium corrected to albumin, PTH, heart failure, peripheral vascular disease, cerebrovascular disease and diabetes mellitus

Table 4 Means and differences in depression scores by degree of being bothered by pruritus

Degree of being bothered by pruritus	*N*	CES-D scores* (mean ± SD)†	Linear regression difference (95% confidence interval) in the CES-D scores by degree of pruritus	
			Unadjusted	Adjusted‡
No	551	15.0 ± 10.7	Reference = 0	Reference = 0
Mildly	239	16.9 ± 10.0	+1.91 (+0.25, +3.57)	+2.19 (+0.57, +3.81)
			$P = 0.03$	$P < 0.01$
Severely	190	21.7 ± 12.7	+6.68 (+4.88, +8.49)	+6.51 (+4.74, +8.27)
			$P < 0.01$	$P < 0.01$

* CES-D score may vary from 0 to 100, and higher score means higher probability of depression

† One-way *P* value was lower than 0.001 for differences in CES-D scores by degree of being bothered by pruritus

‡ Adjusted for sex, age, education, living status, race, months on dialysis, *Kt/V*, serum hemoglobin, serum creatinine, serum calcium corrected to albumin, PTH, heart failure, peripheral vascular disease, cerebrovascular disease and diabetes mellitus

(Fig. 2). Compared with patients not bothered by pruritus, those severely bothered by pruritus indicated more often that the kidney disease interfered too much with their life, that too much of their time was spent dealing with the disease, that they felt frustrated dealing with the disease and that they considered themselves a burden on their family.

Table 5 shows that the unadjusted scores of the burden of kidney disease decreased steadily as the degree of pruritus increased. The mean score of the kidney disease burden was approximately six points lower (indicating higher psychological burden) for patients mildly bothered (mean score = 39.59 ± 28.07) as compared with patients not bothered by pruritus (mean score = 45.62 ± 30.73), $P = 0.008$. A statistically significant ($P < 0.001$) and even larger difference (11.44 points) in the disease burden score was observed by comparing severe pruritus (mean score = 34.18 ± 27.51) with no pruritus. After adjustments for demographics, vintage, *Kt/V*, laboratory variables and comorbidities, the differences in scores remained virtually unchanged. By contrast, the differences in the scores of the burden of kidney disease scale by degree of pruritus were reduced and nearly eliminated after adding dry skin, sleep score and depression symptoms score in the model.

Discussion

The present study developed in an equatorial region shows strong dose–response associations of pruritus with higher depression symptoms, poorer sleep and dry skin bother among MHD patients. The frequency of patients with high probability of depression, as defined by CES-D scores ≥18, was almost sixty percent higher in patients severely bothered by pruritus than in those not bothered by pruritus. Greater severity of pruritus was also associated with lower quality of sleep score and higher percentage of patients who referred problems related to each question of the sleep scale, i.e., get the amount of needed sleep, sleep again after awakening in the night and remain awake during the day. The associations of higher degree of pruritus with higher scores of depression symptoms and lower scores of sleep could not be explained by differences in demographic variables, dialysis dose and comorbidities.

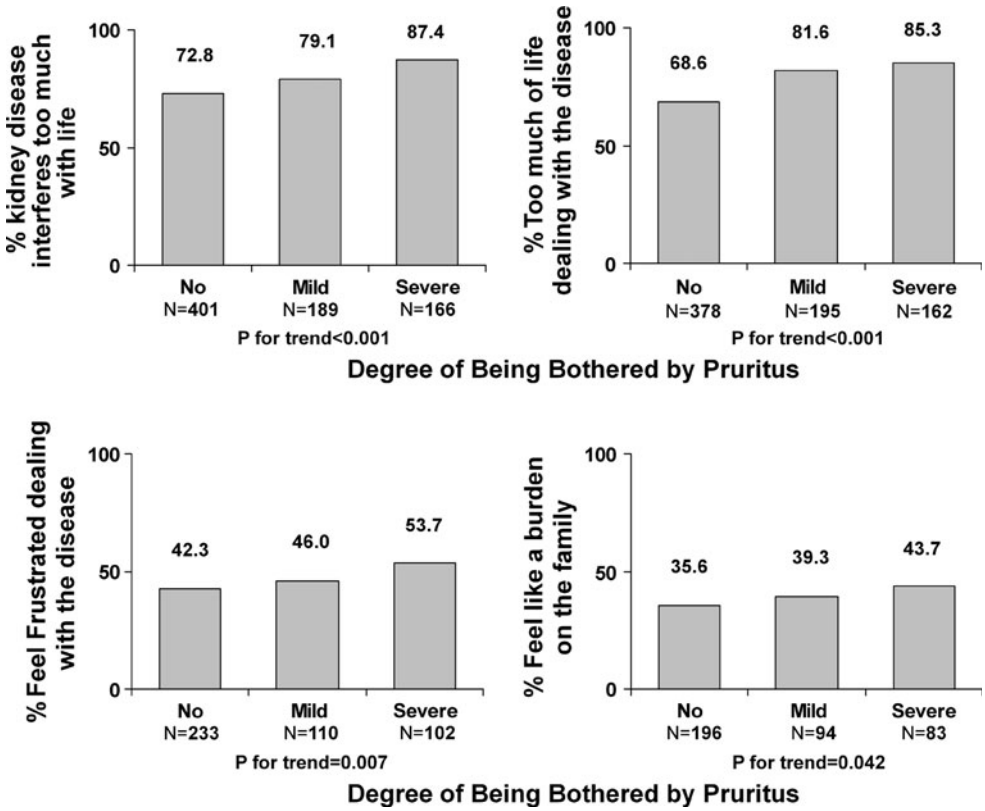

Fig. 2 Percentages of patients who responded definitively true or mostly true to each item of the burden scale, by degree of being bothered by pruritus. The denominators used to calculate the percentages by degree of being bothered by pruritus were 551 for No, 239 for mild and 190 for severe

Greater severity of pruritus was strongly associated with lower kidney disease burden score, which suggests that MHD patients with more severe pruritus face a higher psychological burden than patients without pruritus. The results indicate that the percentage of patients expressing concerns about the burden of the disease to their family, frustrations with the disease, interference of the disease with their life and time spent dealing with the kidney disease was much higher among patients with severe pruritus than among those with mild or no pruritus. Differences in comorbidities, socioeconomic covariates, dialysis dose and hemodialysis by catheter could not explain the higher perceived burden in patients with severe pruritus. By contrast, the results suggest that the higher kidney disease burden reported by patients with pruritus is largely explained by poorer sleep quality, higher degree of depression symptoms and the bother caused by dry skin. The weakening of the association between pruritus severity and kidney disease burden after the inclusion of depression symptoms and sleep on the multivariable model is consistent with strong associations of poor sleep and depression with both pruritus and the HRQOL of MHD patients [3, 8]. The reduction in the strength of the association between pruritus and kidney disease burden after the inclusion of dry skin in the multivariable model is consistent with data showing more severe pruritus and poorer HRQOL among maintenance dialysis patients with xerosis [6, 7, 18, 19]. Dry skin among maintenance dialysis patients tends to affect the entire surface of the body and is often associated with scaling, roughness and reduction in the turgor [6, 18]. The higher psychological burden reported by MHD patients with dry skin could be perhaps due to the negative effects of xerosis on the personal appearance and self-esteem.

The mechanisms of pruritus among CKD patients are not clear. Secondary hyperparathyroidism, iron deficiency anemia, hepatitis C virus (HCV) infection, inflammation and alterations of mineral metabolism are some of the suggested causal mechanisms [20–23]. The results of the present study do not support strong associations of pruritus with serum calcium, PTH and phosphorus levels. However, this study cannot rule out the role of disturbances of mineral metabolism in the pathogenesis of pruritus among MHD patients. It is important to observe that a previous study has shown a greater deposition of calcium in the deepest layer of the dermis of chronic hemodialysis patients with more severe pruritus as compared with patients without pruritus, despite similar serum concentrations of calcium, PTH and calcium-phosphate product between patients without pruritus and those with more severe pruritus [20]. This finding is consistent with the possibility of an alteration in the mechanism that controls the calcium ion gradient between extracellular and intracellular fluids in hemodialysis patients with pruritus [20].

Table 5 Unadjusted and adjusted differences in the burden of kidney disease by pruritus severity

Degree of pruritus	Burden score (mean ± SD)	Linear regression difference (95% confidence interval) in score by level of adjustments							
		Model 1 Unadjusted	Model 2 Adding demographics* and vintage	Model 3 Adding *Kt/V* and laboratory variables†	Model 4 Adding comorbidities‡	Model 5 Adding dry skin	Model 6 Adding sleep without dry skin	Model 7 Adding depressive symptoms without dry skin and sleep	Model 8 Adding dry skin, sleep and depression symptoms
No $N = 551$	45.62 ± 30.73	Reference = 0	Reference = 0	Reference = 0	Reference = 0	Reference = 0	Reference = 0	Reference = 0	Reference = 0
Mild $N = 239$	39.59 ± 28.07	−6.03 (−1.55, −10.51) ($P = 0.008$)	−5.50 (−1.03, −9.97) ($P = 0.02$)	−5.37 (−0.88, −9.86) ($P = 0.02$)	−5.11 (−0.59, −9.64) ($P = 0.03$)	−2.51 (+2.03, −7.05) ($P = 0.279$)	−3.38 (+1.04, −7.79) ($P = 0.13$)	−2.67 (+1.48, −6.82) ($P = 0.21$)	−0.87 (+3.31, −5.01) ($P = 0.68$)
Severe $N = 190$	34.18 ± 27.51	−11.44 (−6.57, −16.31) ($P < 0.001$)	−11.31 (−6.45, −16.16) ($P < 0.01$)	−11.36 (−6.47, −16.25) ($P < 0.01$)	−11.16 (−6.24, −16.64) ($P < 0.01$)	−5.33 (+0.10, −10.57) ($P = 0.279$)	−8.96 (−4.41, −13.77) ($P < 0.01$)	−3.81 (+0.81, −8.44) ($P = 0.11$)	−0.87 (+3.98, −5.72) ($P = 0.73$)

Differences in burden of kidney disease scores were determined by linear regression analyses adjusted for the indicated covariates

* Demographic variables are age, sex, race, education and living status

† Laboratory variables are serum hemoglobin, albumin, creatinine, PTH, calcium correct to albumin and phosphorus

‡ Comorbidities are heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, HIV and infection by virus C

A lower serum albumin observed for patients with severe pruritus in the present study is consistent with the possibility that inflammation plays a role in the development of pruritus among MHD patients [24].

The present study is one of the few investigations on pruritus in MHD patients developed in an equatorial region of the Southern Hemisphere. It is interesting to note that even though a large fraction (43.8%) of the patients in the studied sample indicated being bothered by pruritus, the frequency was much lower than the frequency above 70% observed in the international DOPPS and in a more recent US study [3, 4]. The lower prevalence of pruritus in MHD patients in the present study, as compared with studies developed in other regions, could be due to differences in climate conditions. It is important to note that despite the smaller seasonal variation in environmental temperature in Salvador, a lower frequency of pruritus was observed among patients interviewed during the summer months. Consistent with previous observations, the odds of severe pruritus were higher among MHD patients who reported being bothered by dry skin [6]. The odds of dry skin were also lower during the summer; however, dry skin could not explain the lower prevalence of severe pruritus in patients interviewed during the hottest month of the year.

While the present study offers some additional insights into the associations between pruritus and the psychological burden faced by MHD patients, methodological limitations cannot be ignored. Because the study is cross-sectional, it is not possible to determine whether pruritus anteceded the appearance of depression symptoms and sleep problems among MHD patients. As severe uremic pruritus is a very distressing symptom, it is plausible to assume that its presence favors the development of depression in MHD patients. There are data to suggest, however, that MHD patients with higher degree of depressive symptoms have higher risk of severe pruritus and that the presence of depression modulates pruritus perception [8, 25]. Bidirectional associations are also possible between pruritus and sleep. Whereas severe uremic pruritus may contribute to poorer sleep quality in hemodialysis patients, those who stay awake for longer hours are more likely to be bothered by pruritus, particularly at night [26]. Unfortunately, we could not assess restless legs syndrome (RLS) in the present study, but there are data to support its role as another potential mediator of the observed associations. RLS is a highly prevalent bothersome disorder for hemodialysis patients, particularly during the evening or night [9, 27]. Moreover, RLS has been associated with severe pruritus, lower scores in the kidney disease burden scale of the KDOQOL-SF, higher depression symptoms scores and poorer sleep quality among hemodialysis patients [9, 27, 28].

If pruritus contributes to depression symptoms and sleep problems, then effective interventions to control pruritus should reduce the psychological burden faced by MHD patients. Encouraging evidence that treatment interventions can control or reduce pruritus among hemodialysis patients has been provided by clinical trials [18, 29, 30]. One of these trials in patients with dry skin showed evidence that an emollient and skin protective product combining glycerol and paraffin is efficacious in improving skin appearance, alleviate pruritus and improving quality of life [18]. Research is still needed to assess the efficacy of sleep and depression medications in reducing the psychological burden in MHD patients with pruritus.

Conclusions

Our study shows strong associations of severe pruritus with greater disease burden, poorer sleep quality and depression symptoms in MHD patients. According to the results, the large differences in perceived disease burden by degree of pruritus are almost entirely explained by differences in sleep quality, depression symptoms and the bother of dry skin. Our results support greater attention to identify MHD patients bothered by pruritus, as these patients often face a high psychological burden.

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