

## Itchy skin—a clinical problem for haemodialysis patients

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### Abstract

**Background.** Uraemic pruritus affects many patients receiving chronic dialysis therapy for end-stage renal disease. It is a distressing symptom which has a negative impact on quality of life (QoL) of the patients. The condition is also very frustrating for both patients and physicians since no effective treatment for relief of the itch has been demonstrated. The pathophysiological mechanisms of pruritus are mainly unknown despite several hypotheses presented. Recent concepts refer to changes in the opioidergic system and derangements of the immune system.

**Methods.** In the Dialysis Outcomes and Practice Pattern Study (DOPPS I, 1996–2001) pruritus was assessed by a self-reported questionnaire. The relationship of pruritus to morbidity, mortality, QoL, sleep quality and patient biochemical laboratory data was studied in >200 randomly selected haemodialysis (HD) facilities in seven countries. Pruritus data were collected from >6000 HD patients. Analyses were adjusted for age, gender, race, Kt/V, haemoglobin, serum albumin, serum calcium, serum phosphorus, 13 comorbidities, depression, years on dialysis, country and facility clustering effects.

**Results.** Moderate-to-extreme itch was observed in 46% of prevalent HD patients. Differences in pruritus prevalence were found between countries (ranging from 38% in France to 55% in Italy) and facilities (5–75%). Pruritus was more common in patients on HD >3 months than in patients starting HD. A number of patients' serum characteristics, including high calcium, phosphorous and calcium  $\times$  phosphorous product levels, were significantly associated with pruritus.

Patients with moderate-to-severe pruritus were more likely to feel washed out and to have poor sleep quality, physician-diagnosed depression and a reduced QoL than patients with no or mild pruritus. A significant 15% higher mortality risk was observed in pruritic HD patients but this significance was

not seen after adjusting the data for sleep quality measures.

**Conclusions.** The self-reported prevalence of pruritus in HD patients is relatively high, 40–50%. Pruritus is associated with poor outcomes and a higher mortality risk, probably attributed to poor sleep quality. Better therapeutic treatments are needed for relief of distressing uraemic itching in HD patients.

**Keywords:** DOPPS; haemodialysis; mortality; pruritus; quality of life; sleep quality

### Introduction

Pruritus is a relatively common complaint in patients receiving chronic dialysis therapy for end-stage renal disease (ESRD) [1–3]. Although pruritus is, in itself, not life threatening, its symptoms negatively affect the quality of life (QoL) of uraemic patients [4,5]. Several hypotheses have been proposed to explain the pathophysiology of pruritus including derangements of the immune system and/or changes in the opioidergic system [1,5]. Other disease processes have been reported to be associated with pruritus. Some of these are iron deficiency anaemia, inflammation, metabolic disturbances such as hypercalcaemia, hyperphosphataemia and secondary hyperparathyroidism [6–11]. Many treatments have been tried with limited success [12–19].

There are large variations reported in the prevalence of uraemic pruritus [1–3]. But, most studies have used small sample sizes of patients (<300). An observational study, The Dialysis Outcomes and Practice Patterns Study (DOPPS), evaluated the relationships between HD practices and patient outcomes with detailed data being collected.

### Methods

#### *Patient population*

In this trial (DOPPS I), there were 6137 ESRD patients on regular haemodialysis who were selected to provide information regarding their uraemic pruritus. The data were collected from 1996–2001 in over 200 randomly selected centres in

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Question 1: To what extent were you bothered by itchy skin the past 4 weeks?

- ☐ Not at all
- ☐ Somewhat
- ☐ Moderately
- ☐ Very much
- ☐ Extremely bothered

Question 2: How often during the past 4 weeks did you wake up at night and having problems falling asleep again?

- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

Question 3: How often during the past 4 weeks had you problems getting the amount of sleep you needed?

- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

Question 4: How often during the past 4 weeks had you trouble staying awake during the day?

- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

**Fig. 1.** Survey on uraemic pruritus (itchy skin) within dialysis department.

seven countries (France, Germany, Italy, Japan, Spain, UK and the US).

A questionnaire was used (Figure 1) and the patients were asked to indicate the extent to which they were bothered by itchy skin during a 4-week period using the categories: not at all bothered, somewhat bothered, moderately bothered, very much bothered or extremely bothered [20]. Since somewhat bothered was intermediate between not at all bothered and moderately bothered, somewhat bothered was defined as mild itchiness for some analyses. Sleep quality was assessed using three different self-reported indications of sleep quality: problems getting the amount of sleep needed, trouble staying awake during the day and problems with being awake at night and falling asleep again. Whether a patient was diagnosed with depression by his/her physician was also collected.

### Statistical methods

Logistic regression was used to examine the relationship of the degree of pruritus (primary variable) with the likelihood of a patient having poor sleep quality, feeling washed out or drained or having physician-diagnosed depression. These logistic models were adjusted for age, gender, race, years on dialysis, single-pool Kt/V, haemoglobin, serum albumin, country, depression (except it was not used when depression was the outcome) and 13 summary comorbid conditions [coronary artery disease (CAD), congestive heart failure (CHF), cardiac disease other than CAD or CHF, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease (PVD), cancer, HIV/AIDS, lung disease, neurological disorders, gastrointestinal bleed and recurrent cellulitis/gangrene].

Logistic regression also was employed to examine patient characteristics associated with the odds of a patient reporting moderate-to-extreme itchiness vs not being bothered or being somewhat bothered by itchiness. In these models, predictors included age, gender, race, country of residence, smoking status, white blood cell (WBC) count, hepatitis B or C infection, presence of ascites, years on dialysis, whether new to ESRD in the prior 3 months, single-pool Kt/V, haemoglobin concentration, serum albumin and ferritin level, serum calcium corrected for albumin levels, serum phosphorus levels and the 13 summary comorbid conditions listed earlier. All logistical regression models used generalized

estimating equations (GEE) to account for clustering at the facility level, assuming a compound symmetry covariance structure [21].

At the time patients reported the extent to which they were bothered by itchy skin, they also completed a standardized health-related SF-36 or SF-12 QoL questionnaire from which mental and physical composite summary scores were calculated based on eight subscales of function: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Mixed linear regression was used to examine the associations between a patient's mental component summary (MCS) score or physical component summary (PCS) score and degree of itchiness. These models were adjusted for age, gender, race, years on dialysis, single-pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, physician-diagnosed depression and country.

Cox proportional hazards regression models were used to examine the relationship between mortality and degree of itchiness, with adjustments for age, gender, race, years on dialysis, single-pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, physician-diagnosed depression and country. These models used a robust estimator [22] to account for facility clustering. Time at risk was defined as the time period from when a patient completed the pruritus-related question until death, departure from the study or end of study follow-up.

All analyses were performed using the SAS statistical package, version 9.1 (SAS Institute, Cary, NC, USA) [21].

### Results

The degree of pruritus reported by cross sections of prevalent HD patients in DOPPS I was 26.4, 27.7, 18.6, 15.7 and 11.7% for no itching, mild itching, moderate itching, very itching and extremely itching, respectively with the total percentage of patients having moderate to severe pruritus being 46%. The percentage of dialysis unit patients reporting moderate-to-extreme pruritus varied from 75% of patients in some dialysis units to only 5% of patients in other dialysis units. Similarly, the percentage of HD patients having moderate-to-extreme pruritus substantially differed across the seven countries: France (38%), Japan and US (45%), Spain (46%), UK (48%), Germany (49%) and Italy (55%).

The significant predictors of itchiness are summarized in Table 1. Patients had a significantly higher odds of having moderate-to-extreme pruritus if they were male (AOR = 1.10,  $P < 0.05$ ). In contrast, patients were less likely to have moderate-to-extreme pruritus if they relatively new to ESRD ( $\leq 3$  months) (AOR = 0.80,  $P = 0.0003$ ). Patients in the UK and Japan were significantly more likely to have moderate-to-extreme symptoms of itchiness. Patients in Italy were more likely (AOR = 1.86,  $P < 0.0001$ ) to have moderate-to-extreme symptoms of itchiness compared with patients in the US.

Patients had a significantly higher odds of having moderate-to-extreme pruritus if they had higher serum calcium (albumin-corrected,  $> 10.2$  mg/dl), serum

phosphorous levels ( $> 5.5\text{mg/dl}$ ) or calcium phosphorous product concentrations  $> 70\text{ mg}^2/\text{dl}^2$ .

Several patient outcomes, including mortality and different aspects of QoL, were examined to determine their relationship to the degree of itchiness in HD patients. As the extent of being bothered by pruritus increased, HD patients displayed increasingly lower mental and physical composite summary scores (MCS and PCS). In fact, patients extremely bothered by itchiness had MCS and PCS scores that were 4.3 and 3.3 points, respectively, lower than scores among patients not bothered by itchiness ( $P < 0.0001$ ). Furthermore, patients with moderate-to-extreme pruritus had a 2.3–5.2-fold higher odds of feeling drained ( $P < 0.0001$ ) and a 1.3–1.7 times higher odds of physician-diagnosed depression ( $P = 0.01$ ,  $P < 0.0001$ , respectively) compared with patients not bothered by pruritus.

The degree of being bothered by pruritus also was strongly related to patient sleep quality. HD patients who were, very moderately to extremely bothered by itchy skin had 1.5–4.1 higher odds ( $P < 0.002$ ) of being awake at night, feeling sleepy during the day, or not having enough sleep than did patients not bothered by itchy skin (Table 2). Seventy-two percent of prevalent HD patients with pruritus reported being moderately to extremely bothered by at least one of these sleep-related conditions (data not shown).

An investigation of the relationship between pruritus and mortality demonstrated that patients with moderate-to-extreme pruritus had a 15% higher mortality risk ( $P = 0.008$ ) compared with patients not bothered by pruritus (Table 3). Adjustment for sleep

quality displayed specificity in the mortality model in affecting the relationship of pruritus with mortality, but not affecting the relationship of mortality with other model covariates such as serum haemoglobin, phosphorus, calcium and albumin.

## Discussion

Uraemic pruritus was found to be strongly associated with multiple outcomes examined in this investigation. The severity of patient-reported pruritus displayed a strong, inverse relationship with patient PCS and MCS QoL scores. This finding is similar to that recently reported by Curtin *et al.* [4] who described a significant inverse relationship between pruritus and PCS scores.

Since episodes of uraemic pruritus have been reported to occur more often at night [23], it is expected that pruritus could have a negative impact upon sleep quality and ultimately affect physical and mental functioning. In a study of 145 haemodialysis patients with uraemic pruritus, Yosipovitch *et al.* [23] found that pruritus was a frequent cause of, difficulties in falling asleep in 33% of pruritic patients and an occasional cause in 28% and that pruritus was aggravated during the night in 60% of pruritus patients. This investigation found that patients with moderate-to-extreme pruritus were bothered by being kept awake at night and patients with extreme pruritus had a 2.3–4.1 times greater adjusted odds ratio of not having enough sleep, being sleepy during the day or

**Table 1.** Significant predictors of itchiness: Demographic & comorbid factors and relative country differences

Characteristic	AOR Itchy vs non-itchy	P-value
Male (vs female)	1.10	0.05
Time with ESRD <3 months	0.80	0.0003
Italy (vs US)	1.86	<0.0001
Japan	1.21	0.02
UK	1.35	0.001

Includes moderately, very and extremely itchy;  $n = 9,836$ ; adjusted for albumin-corrected calcium, albumin, phosphorus, time with ESRD, country and nine other comorbid conditions; accounted for facility-clustering effects.

**Table 2.** Degree of itchiness as a predictor of patient's sleep quality

Sleep measure	AOR of indicated sleep measure				
	No itch	Mild itch	Moderate itch	Very itchy	Extremely itchy
Wake at night ( $n = 9920$ )	1.0	1.3*	1.7*	2.5*	4.1*
Sleepy during day ( $n = 9820$ )	1.0	1.2	1.5*	2.0*	2.9*
Not enough sleep ( $n = 9789$ )	1.0	1.3*	1.5*	1.8*	2.3*

Results are from a logistic regression model that simultaneously adjusts for age, race, sex, Kt/V, haemoglobin, serum albumin, albumin-corrected calcium, serum phosphorus, 13 comorbidities, depression, years on dialysis and country. Accounted for facility-clustering effects.

\* $P \leq 0.002$ .

**Table 3.** Itchiness and risk of overall mortality

Characteristic	Without sleep variables in the model		With sleep variables in the model	
	RR of death	P-value	RR of death	P-value
Itchiness	1.15	0.008	1.06	0.217
Albumin	0.77	<0.0001	0.77	<0.0001
Calcium	1.08	0.005	1.08	0.040
Haemoglobin	0.95	0.004	0.96	0.005
Kt/V	0.9	0.297	0.89	0.259
Phosphorus	1.05	0.002	1.05	0.002
Depression	1.21	0.002	1.16	0.017

Moderately-extremely itchy vs not-mildly itchy; also adjusted for age, race, sex, 13 comorbidities, years on dialysis and stratified by country;  $n = 9836$ .

being awake at night. The importance of the relationship between pruritus and sleep quality is further highlighted in the mortality risk analysis which revealed that most of the 15% higher mortality risk ( $P=0.008$ ) seen in patients with moderate-to-extreme pruritus is explained by poor sleep quality and once sleep quality of the patients is accounted for, the relationship between pruritus and mortality was greatly diminished and no longer significant (data not shown). It is especially important to emphasize that this finding concerning the sleep quality adjustment displayed specificity in attenuating the risk relationship between pruritus and death but not the risk relationship between serum albumin, serum calcium, serum phosphorus or haemoglobin with death. Since the mortality analyses were adjusted for these laboratory measures, the relationship of pruritus with mortality indicates an added risk beyond that explained by the individual laboratory measures, with poor sleep quality appearing as a pre-dominating characteristic of the pathway lying between uraemic pruritus and mortality risk.

There have been several studies reported in haemodialysis patients indicating a significant relationship of uraemic pruritus with higher serum calcium and phosphorus levels [7,24]. Applying the large sample size in the present study, independent, strong relationships are seen between higher serum calcium ( $>10.2$  mg/dl), higher serum phosphorus ( $>5.5$  mg/dl) and higher serum calcium phosphorus product levels ( $>70$  mg<sup>2</sup>/dl<sup>2</sup>) with uraemic pruritus. The mechanism of this relationship between serum calcium and serum phosphorus with uraemic pruritus is not understood at the present time.

Although the present study has shown many factors to be significantly related to uraemic pruritus in haemodialysis patients, one of the key observations is that large unexplained differences still remained between some countries in the likelihood of patients having uraemic pruritus, even after extensive adjustment for patient demographics, numerous comorbidities and laboratory measures. Large differences in the likelihood of patients having uraemic pruritus also remained between dialysis facilities within a country, even after extensive covariate adjustment in the uraemic pruritus predictor models. What is particularly intriguing is that the higher prevalence of self-reported uraemic pruritus in the UK and Japan is also seen when the analyses are restricted to haemodialysis patients at the time of ESRD onset. In these patients, one would expect that there would be insufficient exposure to haemodialysis practice for the haemodialysis treatments *per se* to be causally linked to pruritus. This suggests that the higher uraemic pruritus seen is due to conditions, which patients carry with them from the pre-ESRD period into ESRD. Further understanding of the pathogenesis of uraemic pruritus may benefit substantially from additional studies examining the prevalence and onset of pruritus and associated factors during chronic kidney disease prior to stage 5.

Observational studies such as DOPPS I serve an important role in describing relationships between treatments and outcomes after extensive adjustments for case-mix and facility characteristics. These results provide valuable information for developing additional hypotheses and designing future clinical trials. A limitation of observational studies is the determination of causality. The issue of causality must be kept in mind when interpreting the results from patient-based observational studies.

## Limitations of the study

The patients for whom pruritus data were unavailable display higher mortality rates and thus one limitation of the current study is that there may be some under-representation of higher risk patients in the analyses.

The questionnaire used to assess the relationship of itching with sleep irregularities (Figure 1) was designed to obtain the patients' perceptions of their degree of itching and the quality of their sleeping. Although the instrument was not fully validated prior to its use, it was a reasonable tool to obtain observational data based on subjective findings. An issue with such a tool is how accurately the patients could recall for 4 weeks their degree of itching and sleep disturbances, during each of the weeks. Even if all patients could not specifically recall all 4 weeks of the findings, it is probable the patients could remember this information for at least the 1 to 2 weeks prior to marking the questionnaire, therefore not invalidating the results. Furthermore the questionnaire used in this study was developed originally for the DOPPS and the subsequent study [20] shows a similar trend in separate data collection and across the countries participated, suggesting that consistency of the results was obtained by the questionnaire.

## Conclusions

In summary, this large international investigation provides further evidence of the common occurrence of uraemic pruritus in haemodialysis patients. The self-reported prevalence of pruritus in the patients is high and pruritus is associated with a 15% higher mortality risk, which appears to be mediated in large part through disturbances in sleep quality. These outcomes were obtained by using the self-reported questionnaire, which is an important tool to identify the patients with uraemic pruritus.

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