

Original Article

Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Abstract

Background. Pruritus affects many haemodialysis (HD) patients. In this study, pruritus and its relationship to morbidity, mortality, quality of life (QoL), sleep quality and patient laboratory measures were analysed in >300 dialysis units in 12 countries.

Methods. Pruritus data were collected from 18 801 HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) (1996–2004). Analyses were adjusted for age, gender, black race, Kt/V, haemoglobin, serum albumin, albumin-corrected serum calcium, serum phosphorus, 13 comorbidities, depression, years on dialysis, country and facility clustering effects.

Results. Moderate to extreme pruritus was experienced by 42% of prevalent HD patients in DOPPS during 2002/2003. Many patient characteristics were significantly associated with pruritus, but this did not explain the large differences in pruritus between countries (ranging from 36% in France to 50% in the UK) and between facilities (5–75%). Pruritus was slightly less common in patients starting HD than in patients on dialysis >3 months. Pruritus in new end-stage renal disease (ESRD) patients likely results from pre-existing conditions and not haemodialysis *per se*, indicating the need to understand development of pruritus before ESRD. Patients with moderate to extreme pruritus were more likely to feel drained [adjusted odds ratio (AOR) = 2.3–5.2, $P < 0.0001$] and to have poor sleep quality (AOR = 1.9–4.1, $P \leq 0.0002$), physician-diagnosed depression (AOR = 1.3–1.7, $P \leq 0.004$), and QoL mental and physical composite scores 3.1–8.6 points lower ($P < 0.0001$) than patients with no/mild pruritus. Pruritus in HD patients was

associated with a 17% higher mortality risk ($P < 0.0001$), which was no longer significant after adjusting for sleep quality measures.

Conclusions. The pruritus/mortality relationship may be substantially attributed to poor sleep quality. The many poor outcomes associated with pruritus underscore the need for better therapeutic agents to provide relief for the 40–50% of HD patients affected by pruritus.

Keywords: calcium; DOPPS; haemodialysis; itching; mortality; phosphorus; pruritus; quality of life; sleep quality

Introduction

A large number of patients receiving chronic dialysis therapy for end-stage renal disease (ESRD) suffer from pruritus [1–3]. Pruritus is an intrusive and distressing symptom that negatively affects quality of life (QoL) in uraemic patients [4,5]. The pathophysiological mechanism(s) of pruritus remain largely unknown, although several hypotheses have been proposed. Recent concepts invoke derangements of the immune system and changes in the opioidergic system [1,5]. Iron deficiency anaemia, inflammation, as well as metabolic disturbances such as hypercalcaemia, hyperphosphataemia and secondary hyperparathyroidism have been reported to be associated with pruritus [6–11]. Various proposed treatments have resulted in limited success in providing long-term relief from pruritus in haemodialysis (HD) patients [12–19].

The prevalence of uraemic pruritus varies substantially in published reports [1–3]. However, most studies have been performed with relatively small numbers of patients (<300). The Dialysis Outcomes and Practice

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Patterns Study (DOPPS) is an observational study of the relationships between HD practices and patient outcomes with detailed data collected from more than 29 000 HD patients at more than 300 randomly selected dialysis facilities in 12 countries. In the present study, data collected during the DOPPS phase I (1996–2001) and phase II (2002–2004) have been analysed for the prevalence of self-reported pruritus, associated factors, and the relationship of pruritus to QoL, sleep quality, depression, medication use and mortality in this large international cohort of haemodialysis patients.

Methods

Data sources

Pruritus was assessed using data collected from both DOPPS I (1996–2001) and DOPPS II (2002–2004). Adult haemodialysis patients were randomly selected for study participation from 308 dialysis facilities in DOPPS I ($n=17\,034$ patients from seven countries: France, Germany, Italy, Japan, Spain, the UK and the US), and from 322 dialysis facilities in DOPPS II ($n=12\,839$ patients from 12 countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the UK and the US). The total number of patients for whom pruritus data were available was 10 810 patients from 284 facilities in DOPPS I, and 10 265 from 317 facilities in DOPPS II. The DOPPS sampling plan and study methods have been described previously [20,21].

Statistical methods

The main variable of interest was the degree to which patients were bothered by itchy skin. Patients were asked to indicate the extent to which they were bothered by itchy skin during a 4-week period as: not at all bothered, or somewhat, moderately, very much or extremely bothered. Since somewhat bothered was intermediate between not at all bothered and moderately bothered, somewhat bothered was defined as mild itchiness for some analyses.

Logistic regression was used to examine the relationship of degree of pruritus with the likelihood of a patient having poor sleep quality, feeling washed out or drained, or having physician-diagnosed depression. In order to allow for a meaningful comparison of these results, these particular analyses were restricted to the DOPPS I sample of patients since sleep quality measures were not collected in DOPPS II. 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. These logistic models were adjusted for age, gender, black race, years with ESRD, single pool Kt/V, haemoglobin, serum albumin, country, depression (except 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, black race, country of residence, smoking status, white blood cell (WBC) count, hepatitis B or C infection, presence of ascites, years with ESRD, whether new to ESRD in prior 3 months, single pool Kt/V, haemoglobin concentration, serum albumin and ferritin level, serum calcium corrected for albumin levels, serum phosphorus levels and 13 summary comorbid conditions (aforedescribed). All logistical regression models used generalized estimating equations (GEE) to account for clustering at the facility level, assuming a compound symmetry covariance structure [22].

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, black race, years with ESRD, 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, black race, years with ESRD, single pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, physician-diagnosed depression and country. These models used a robust estimator [23] 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) [22].

Results

Characteristics are shown in Table 1 for prevalent patients from 12 countries in DOPPS I and II who reported being bothered by moderate to extreme pruritus *vs* not being bothered or being bothered little by itchiness of the skin during the 4 weeks prior to questionnaire completion. With this large patient sample, many factors are seen to differ significantly ($P < 0.05$) between these two groups. Notably, nearly 45% of patients with moderate to severe pruritus had poor sleep quality, which resulted in being awake at night, compared with 29% of patients with mild/no pruritus having this problem.

The degree of pruritus reported by cross sections of prevalent HD patients in DOPPS I and II is shown in Figure 1 in which there was a slightly lower

Table 1. Comparison of selected patient characteristics in haemodialysis patients who reported being 'moderately to extremely bothered by itchy skin' vs 'not bothered or somewhat bothered by itchy skin'

Characteristic	Patients moderately to extremely bothered by itchy skin (n = 5737)	Patients NOT bothered or somewhat bothered by itchy skin (n = 7563)	P-value
Mean age, years (\pm SD)	60.7 (\pm 14.49)	60.3 (\pm 14.64)	0.12
Male, %	60.3	56.4	<0.0001
Mean years with ESRD (\pm SD)	4.92 (\pm 5.43)	5.18 (\pm 5.83)	0.008
Coronary artery disease, %	40.8	37.8	0.0005
Congestive heart failure, %	29.1	25.4	<0.0001
Hypertension, %	76.7	74.3	0.002
Other cardiovascular disease, %	35.3	32.7	0.002
Cerebrovascular disease, %	16.3	14.1	0.0007
Diabetes, %	33.1	30.4	0.001
Peripheral vascular disease, %	24.4	21.2	<0.0001
Gastrointestinal bleeding in prior 12 months, %	6.5	5.1	0.0008
Lung disease, %	10.6	8.6	<0.0001
Neurological disorder, %	8.9	7.6	0.007
HIV, %	0.9	0.5	0.03
Recurrent cellulites, gangrene, %	7.8	6.1	0.0002
Physician-diagnosed depression, %	15.1	11.5	<0.0001
Awake at night, %	45.4	28.6	<0.0001
Ascites, %	1.4	0.9	0.007
Hepatitis C, %	10.0	8.6	0.006
Hepatitis B, %	2.4	2.5	0.61
Current smoker or stopped smoking within past year, %	20.6	17.3	<0.0001
Prior history of parathyroidectomy, %	6.1	6.9	0.08
Mean serum phosphorus, mg/dl (\pm SD)	5.82 (\pm 1.85)	5.57 (\pm 1.78)	<0.0001
Mean serum calcium (albumin-corrected), mg/dl (\pm SD)	9.59 (\pm 0.94)	9.55 (\pm 0.92)	0.01
Mean serum albumin, g/dl (\pm SD)	3.77 (\pm 0.45)	3.81 (\pm 0.45)	<0.0001

Values shown are based upon a prevalent cross section of haemodialysis patients participating either in DOPPS I or II; P-values are based upon univariate analyses.

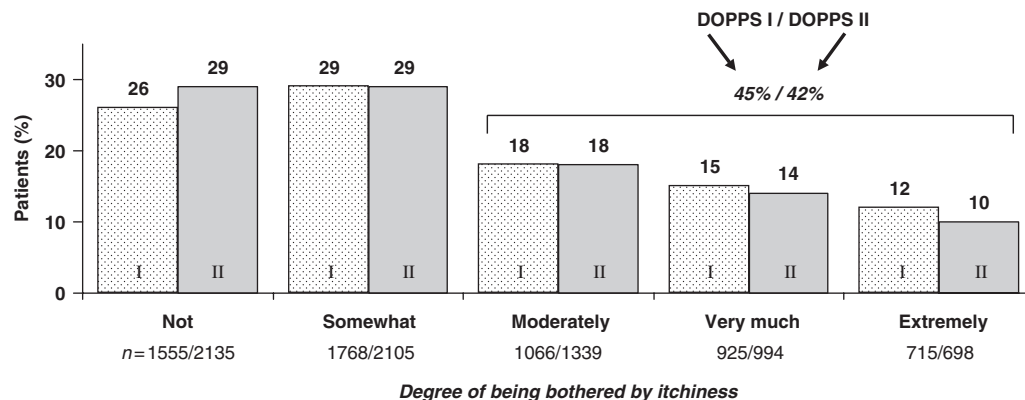


Fig. 1. Degree of pruritus among prevalent HD patients across 6-12 countries participating in DOPPS I (1996-1999) and DOPPS II (2002-2003). The extent to which HD patients were bothered by itchy skin during a 4-week period is shown based upon self-reported data collected from a prevalent cross-section of HD patients at 288 dialysis units participating in DOPPS I (1996-1999) from France, Germany, Japan, Spain, the UK and the US, and 320 dialysis units participating in DOPPS II (2002-2003) from the above six countries plus Australia, Belgium, Canada, Italy, New Zealand and Sweden.

percentage of patients having moderate to severe pruritus in DOPPS II (42%) compared with DOPPS I (45%) ($P=0.0002$). The percentage of dialysis unit patients reporting moderate to extreme pruritus varied from more than 70% of patients in some dialysis units to only 5-10% of patients in other dialysis units. Similarly, the percentage of HD patients having moderate to extreme pruritus substantially differed across some countries ranging

from 36% of patients in France to 50% in the UK (Table 2).

Characteristics associated with greater likelihood of pruritus in haemodialysis patients

A multivariate logistic model was used to determine the relationship of patient characteristics and

Table 2. Itchiness among prevalent haemodialysis patients, by country, in DOPPS I versus DOPPS II

Country	Percent of patients reporting moderate to extreme itchiness (pruritus)		P-value
	DOPPS I (1996–99)	DOPPS II (2002–03)	
France	38 (<i>n</i> = 503)	36 (<i>n</i> = 472)	0.62
Germany	48 (<i>n</i> = 426)	42 (<i>n</i> = 488)	0.10
Italy	–	40 (<i>n</i> = 514)	–
Japan	46 (<i>n</i> = 1973)	43 (<i>n</i> = 1555)	0.08
Spain	46 (<i>n</i> = 445)	40 (<i>n</i> = 553)	0.06
United Kingdom	48 (<i>n</i> = 414)	50 (<i>n</i> = 462)	0.53
United States	44 (<i>n</i> = 2268)	40 (<i>n</i> = 1444)	0.006
Australia/New Zealand	–	48 (<i>n</i> = 430)	–
Belgium	–	38 (<i>n</i> = 443)	–
Canada	–	43 (<i>n</i> = 464)	–
Sweden	–	40 (<i>n</i> = 446)	–

Based upon prevalent cross sections of haemodialysis patients in each country who completed a study patient questionnaire. In DOPPS I, prevalent cross sectional data in non-US countries were from 1998 or 1999, and in the US from 1996 to 1998. In DOPPS II, prevalent cross-sectional data were from 2002 to 2003. Data were not collected in Australia, Belgium, Canada, New Zealand and Sweden in DOPPS I, and DOPPS I pruritus data in Italy were not usable due to a translation error. Pruritus was defined as a patient being moderately to extremely bothered by itchy skin. The *P*-value shown indicates whether there was a significant difference in a country's level of pruritus in DOPPS I vs DOPPS II in countries having values for both study phases.

laboratory values with the likelihood of patients having moderate to extreme pruritus vs mild/no pruritus in the combined DOPPS I and II study sample (Table 3). Patients had a significantly higher odds of having moderate to extreme pruritus if they were male, had lung disease, congestive heart failure, neurological disease, higher serum calcium (albumin-corrected) or serum phosphorus levels, lower serum albumin concentrations, or had the following inflammatory or liver-related conditions: ascites, hepatitis C or >6700 white blood cells/ml. Higher calcium phosphorus product concentrations were also found to be associated with patients having moderate to extreme symptoms of itchiness, especially patients with a calcium phosphorus product >80 mg²/dl². These patients had a 1.5 times greater odds of pruritus (*P* < 0.0001) compared with patients having a calcium phosphorus product concentration of 50–60 mg²/dl² (data not shown). In contrast, patients were less likely to have moderate to extreme pruritus if they had a high serum ferritin concentration (≥400 vs 100–400 ng/ml), were relatively new to ESRD (3 months or less), or had lived with ESRD >10 years (AOR = 0.80, *P* = 0.0002 vs having ESRD 1–5 years). After adjusting for all the factors in Table 3, patients in the UK and Japan were significantly more likely and patients in Belgium less likely (AOR = 0.78, *P* = 0.03) to have moderate to extreme symptoms of itchiness compared with patients in the US.

Table 3. Association of selected factors with the likelihood of having moderate to extreme pruritus in haemodialysis patients

Characteristic	AOR of having [moderate to extreme pruritus] vs [mild/no pruritus] (<i>P</i> -value)
Male (vs female)	1.10 (0.005)
Time with ESRD, ≤3 months (vs 1.0–5.0 years)	0.82 (<0.0001)
Time with ESRD, 3–12 months (vs 1.0–5.0 years)	0.91 (0.06)
Time with ESRD, 5.01–10 years (vs 1.0–5.0 years)	1.00 (0.92)
Time with ESRD, >10 years (vs 1.0–5.0 years)	0.80 (0.0002)
Ascites (vs no)	1.85 (<0.0001)
Hepatitis C (vs no)	1.29 (<0.0001)
WBC count, 5400–6700 WBC/ml (vs < 5400)	1.03 (0.55)
WBC count, 6701–8400 WBC/ml (vs < 5400)	1.12 (0.01)
WBC count, >8400 WBC/ml (vs < 5400)	1.20 (0.0002)
Serum phosphorus, <3.5 (vs 3.5–5.49) mg/dl	1.0 (0.97)
Serum phosphorus, 5.5–6.7 (vs 3.5–5.49) mg/dl	1.21 (<0.0001)
Serum phosphorus, >6.7 mg/dl (vs 3.5–5.49) mg/dl	1.37 (<0.0001)
Serum calcium ^{alb} , <8.4 (vs 8.4–9.5) mg/dl	1.00 (0.98)
Serum calcium ^{alb} , 9.51–10.2 (vs 8.4–9.5) mg/dl	1.04 (0.41)
Serum calcium ^{alb} , >10.2 (vs 8.4–9.5) mg/dl	1.22 (<0.0001)
Serum ferritin, <100 ng/ml (vs 100–399 ng/ml)	1.03 (0.48)
Serum ferritin, 400–800 ng/ml (vs 100–399 ng/ml)	0.89 (0.007)
Serum ferritin, >800 ng/ml (vs 100–399 ng/ml)	0.83 (0.0007)
Belgium (vs US)	0.75 (0.007)
Japan (vs US)	1.18 (0.01)
United Kingdom (vs US)	1.47 (<0.0001)
Current smoker or stopped smoking within prior year (vs non-smoker or stopped smoking >1 year)	1.15 (0.0009)
Lung disease (vs no)	1.15 (0.01)
Neurological disease (vs no)	1.13 (0.04)
Congestive heart failure (vs no)	1.09 (0.03)
Serum albumin, <3.0 g/dl (vs 3.51–4.0 g/dl)	1.17 (0.03)
Serum albumin, 3.0–3.5 g/dl (vs 3.51–4.0 g/dl)	1.13 (0.004)
Serum albumin, >4.0 g/dl (vs 3.51–4.0 g/dl)	1.00 (0.95)
Age, per 10 years older	1.04 (0.002) ^a

Results are based upon DOPPS I and II data (*n* = 18 801) from a logistic regression analysis adjusted for all factors listed plus the non-significant factors: black race, 10 summary comorbid conditions (coronary artery disease, other cardiovascular disease, cerebrovascular disease, hypertension, diabetes, peripheral vascular disease, cancer, recurrent cellulites/gangrene, GI bleeding in prior 12 months and HIV/AIDS), hepatitis B and country. Each model accounted for facility clustering effects. AOR = adjusted odds ratio.

^aFactors for which the AOR of having moderate to extreme pruritus differed significantly (*P* < 0.05) between DOPPS I and II. Serum phosphorus (AOR = 1.08 per 1 mg/dl higher, *P* < 0.0001) and albumin corrected serum calcium (calcium^{alb}, AOR = 1.07 per 1 mg/dl higher, *P* = 0.0005) were each significant in the logistic model when tested as continuous variables in place of the corresponding categorical variables shown in the table.

Three factors strongly differed between DOPPS I and II in their relationship with pruritus. Patients with higher haemoglobin or single pool Kt/V > 1.5 (vs < 1.2) had significantly lower odds of having moderate to extreme pruritus in DOPPS I (*P* ≤ 0.004), whereas in

DOPPS II, haemoglobin and Kt/V did not show any significant relationship with pruritus ($P > 0.75$). Furthermore, regarding anaemia control, the likelihood of pruritus was found not to be significantly related to the use or weekly dose of recombinant human erythropoietin when modelled with or without adjustments for patient haemoglobin levels. Younger patients exhibited a significantly lower odds of having moderate to extreme pruritus in DOPPS II ($P \leq 0.001$), but this relationship was not significant in DOPPS I ($P = 0.20-0.33$). Several other factors were investigated to test their relationship with uraemic pruritus. Among these, serum aluminium levels ($P > 0.76$) and having had a prior parathyroidectomy ($P = 0.37$) were not significantly associated with moderate to extreme pruritus. Although hepatitis C consistently displayed a strong relationship with pruritus, hepatitis B failed to show a significant association with pruritus. In addition, moderate to extreme pruritus was found not to be significantly associated with serum parathyroid hormone levels, serum creatinine, body mass index, percent transferrin saturation, percent neutrophils, neutrophil count, dialyser membrane type or flux of the dialyser (high flux *vs* low flux), dialysis session length, black *vs* white race and sevelamer *vs* calcium-containing phosphate binders. Furthermore, no significant relationship was seen between the odds of having uraemic pruritus and whether or not patients had residual renal function (>200 ml urine output/day) when performed separately for patients on dialysis <3 months or <1 year ($P > 0.4$ in each case).

Relationship of pruritus to patient outcomes

Several patient outcomes, including mortality and different aspects of QoL, were examined to determine their relationship to degree of itchiness in HD patients. As shown in Figure 2A and B, as the extent of being bothered by pruritus increased, HD patients displayed increasingly lower mental and physical composite summary scores. In fact, patients not bothered by itchiness had MCS and PCS scores that were 8.6 and 6.4 points, respectively, higher than scores among patients extremely 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 ($P < 0.001$) and a 1.3–1.7 times higher odds of physician-diagnosed depression ($P < 0.001$) compared with patients not bothered by pruritus (Figure 3A and B).

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 1.4–4.0 higher odds ($P < 0.0002$) of being awake at night, feeling sleepy during the day, or not having enough sleep than did patients not bothered by itchy skin (Figure 4). 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 13% higher mortality risk ($P = 0.01$) compared with patients not bothered by pruritus in DOPPS I, a 21% higher mortality risk ($P = 0.0003$) in DOPPS II (Figure 5), and a 17% higher mortality risk ($P < 0.0001$) in DOPPS I and II combined. This analysis was adjusted for patient demographics, 13 comorbidity classes, physician-diagnosed depression, years on dialysis, country, dialysis dose, patient laboratory values for serum albumin, albumin-corrected calcium, serum phosphorus and haemoglobin. However, when the analysis was further adjusted for the three sleep variables collected in DOPPS I and which are described in Figure 4, then the relationship between pruritus and mortality was greatly diminished and no longer significant (Figure 5). This latter result suggests that the higher mortality risk associated with pruritus in HD patients may be explained in large part by pruritus leading to sleep disturbances, which ultimately are associated with increased mortality risk. 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.

Adjustment for poor sleep quality also greatly attenuated the relationship between pruritus severity and mean MCS and PCS scores shown in Figure 2. These results provide additional support for the possible mechanism of pruritus influencing patient sleep quality, which in turn is related to greater patient mortality risk and lower QoL summary scores.

Specific medication use among HD patients with pruritus

In DOPPS I and II, for the 42–45% of patients with moderate to extreme pruritus, 33.1% were prescribed a sleeping pill, 14.8% an antihistamine, 14.4% a benzodiazepine, and 8.4% an antidepressant. Sleeping pills were reported to have been taken by 30% of HD patients with moderate to extreme pruritus who had poor sleep quality. Compared with patients not bothered or bothered little by itchy skin, patients with moderate to extreme pruritus had 2.1-fold higher odds of taking an antihistamine, 1.5-fold higher odds of taking an antidepressant, 1.4-fold higher odds of taking a sleeping pill, and a 1.2 times greater likelihood of taking a benzodiazepine ($P < 0.001$) (data not shown).

Discussion

The present study provides the first international description of self-reported uraemic pruritus in

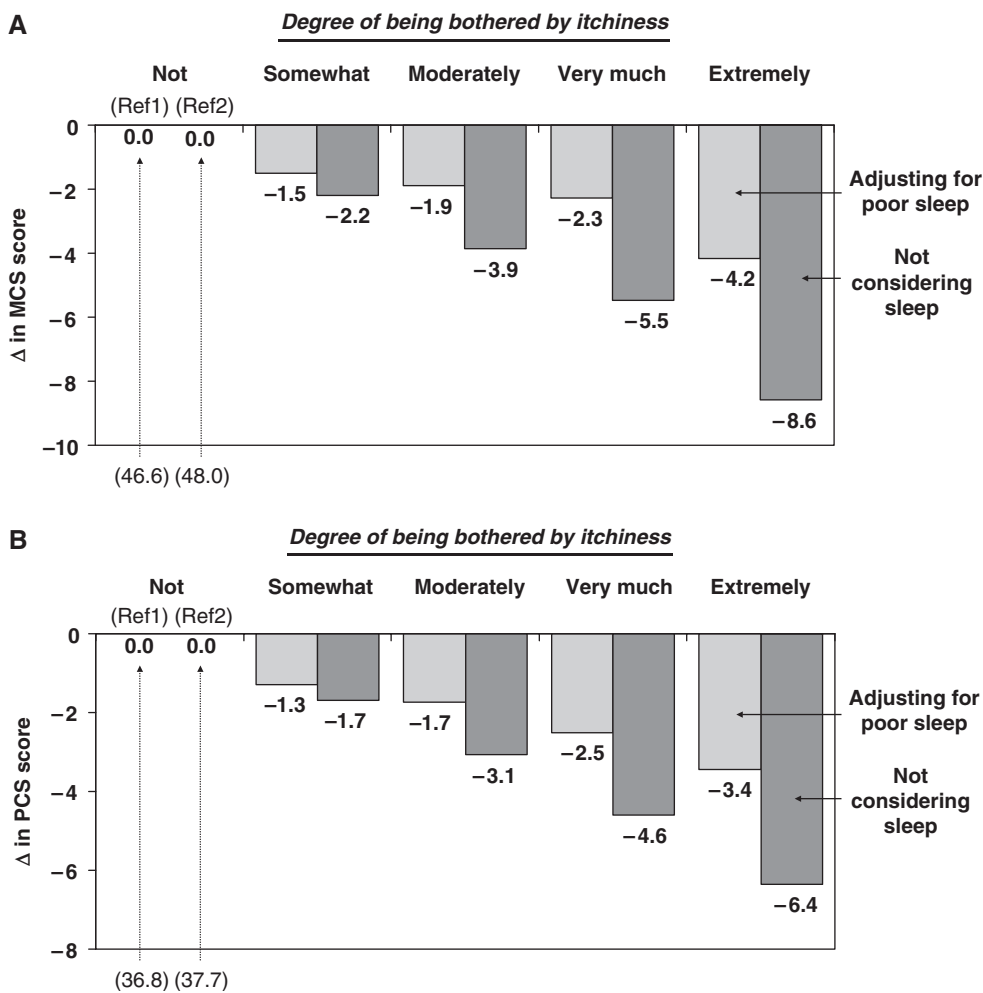


Fig. 2. (A) Relationship of QoL mental composite summary (MCS) score with the degree of patient-reported pruritus, with and without adjustments for sleep quality. Mixed linear regression was used to determine the relationship between degree of patient-reported pruritus and MCS scores in models with or without adjustments for patient sleep quality. Adjustments for sleep quality included whether a patient was bothered by being awake at night, sleepy during the day, not receiving enough sleep or feeling drained. Each model was adjusted for age, gender, black race, years with ESRD, single pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, physician-diagnosed depression, country and accounted for facility clustering effects. Analyses were restricted to patients in DOPPS I ($n = 9659$) since sleep quality data were not collected in DOPPS II. Results indicate the magnitude of the difference between the mean MCS value for a given pruritus category and the mean MCS value of the reference group. In the models with and without adjustment for sleep quality, the mean value for the reference group was 46.6 and 48.0, respectively. Each categorical mean value significantly differed from the mean value of the corresponding reference group with a $P < 0.0001$. **(B) Relationship of QoL physical composite summary (PCS) score with the degree of patient-reported pruritus, with and without adjustments for sleep quality.** Mixed linear regression was used to determine the relationship between degree of patient-reported pruritus and PCS scores in models with and without adjustments for patient sleep quality. Each model adjusted for age, gender, black race, years with ESRD, single pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, physician-diagnosed depression and country, and accounted for facility clustering effects. Additional adjustments for sleep quality included whether a patient was bothered by being awake at night, sleepy during the day, not receiving enough sleep or feeling drained. Analysis was restricted to patients in DOPPS I ($n = 9659$) since sleep quality data were not collected in DOPPS II. Results indicate the magnitude of the difference between the mean value for a given pruritus category and the mean PCS value of the reference group, which was 36.8 and 37.7, respectively for models without vs with adjustments for sleep quality. Each categorical mean value significantly differed from the mean value of the corresponding reference group with a $P < 0.0001$.

HD patients from 12 countries. With numerous patient characteristics, comorbidities, QoL measures, mortality and laboratory data reported for more than 18 000 HD patients participating in DOPPS I and II, this represents the largest international sample for evaluating the relationship of uraemic pruritus with many different patient characteristics and outcomes. Moderate to extreme pruritus was reported by 36–50% of HD patients in Australia, Belgium, Canada, France,

Germany, Italy, Japan, New Zealand, Spain, Sweden, the UK and the US. A high prevalence of uraemic pruritus has been reported in a number of single or multi-centre studies in which 22–86% of patients have reported being bothered by pruritus [1–3]. In the present study, wide variation in the percentage of facility patients with moderate to extreme pruritus was reported across DOPPS, ranging from 5% to 75% of facility patients in 314 DOPPS II dialysis units.

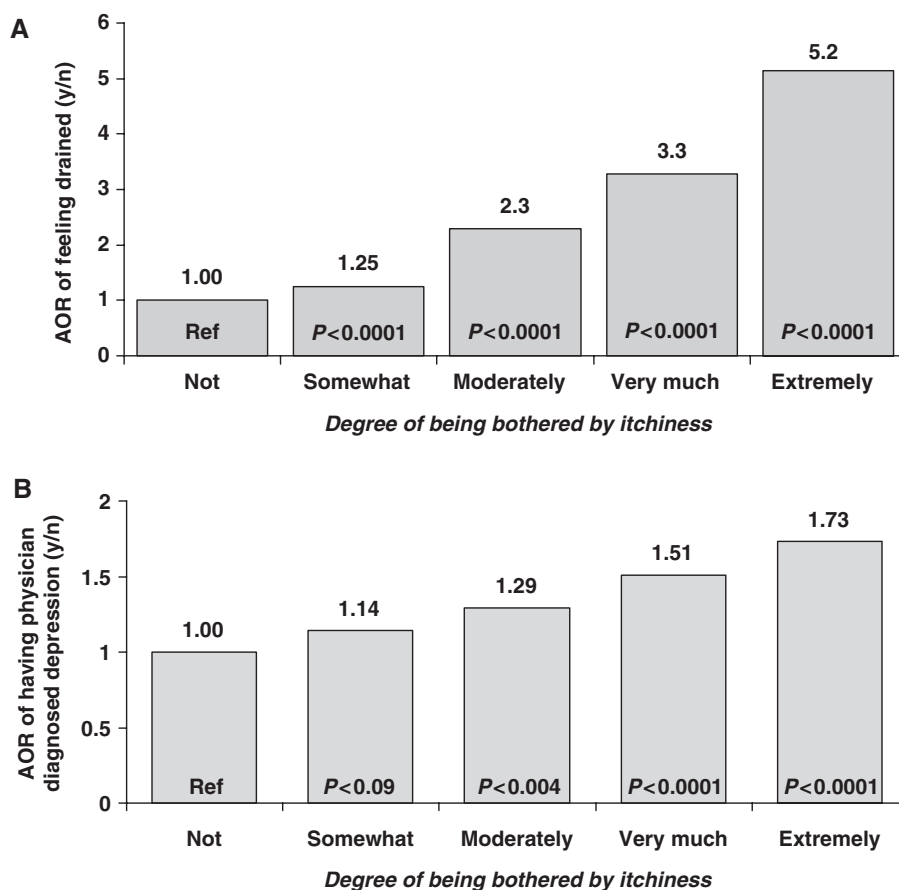


Fig. 3. (A) Association of degree of pruritus with adjusted odds of 'feeling drained'. Logistic regression was used to model the odds of 'feeling drained' (yes vs no). The model was adjusted for age, gender, black race, single pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, depression, years with ESRD, country and accounted for facility clustering effects. Analysis was restricted to DOPPS I, excluding Italy due to a translation error ($n = 9964$). **(B) Association of degree of pruritus with adjusted odds of HD patients having a physician diagnosis of depression.** Logistic regression was used to model the odds of having a physician diagnosis of depression (yes vs no). The model was adjusted for the same factors indicated in (A), except depression and feeling drained. Analysis was restricted to DOPPS I, excluding Italy ($n = 10\ 510$).

Approximately 30% of study patients did not complete a patient questionnaire which provides the information regarding self-reported pruritus. These 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.

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. However, these authors did not observe the significant relationship between pruritus and MCS scores that is seen in the present study.

Since episodes of uraemic pruritus have been reported to occur more often at night [24], 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.* [24] 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. The current investigation found that 45% of patients with moderate to extreme pruritus were bothered by being kept awake at night, and patients with extreme pruritus had a 2.2–4.0 times greater adjusted odds ratio of not having enough sleep, being sleepy during the day or 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 17% higher mortality risk ($P < 0.0001$) 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. It is especially important to emphasize that this finding concerning the sleep quality

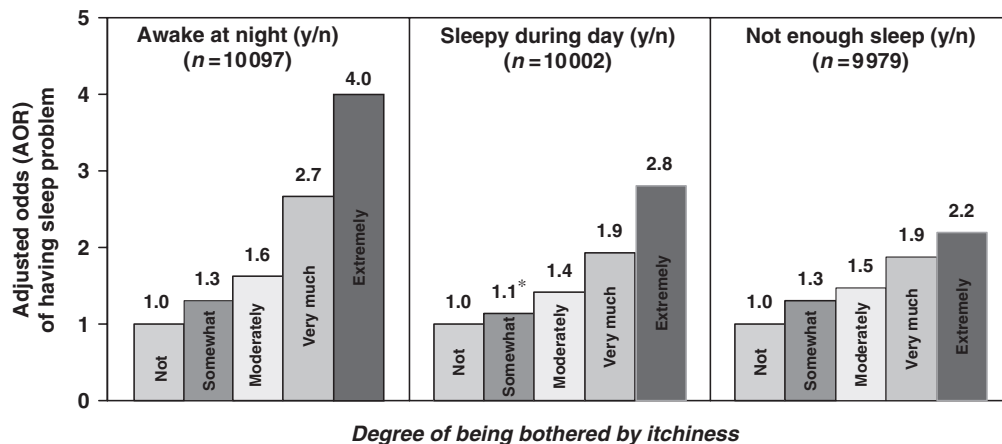


Fig. 4. Relationship of degree of pruritus with adjusted odds of HD patients being awake at night, sleepy during the day or not having enough sleep (yes vs no). Logistic regression, using DOPPS I data, was used for analysing the likelihood of each sleep quality indicator, adjusting for age, gender, black race, years with ESRD, single pool Kt/V, haemoglobin, serum albumin, 13 comorbidity classes, depression, country, and accounting for facility clustering effects. For each model, all comparisons with the reference group ('Not') were significant at $P \leq 0.0002$, except for the bar '*' having a $P = 0.09$.

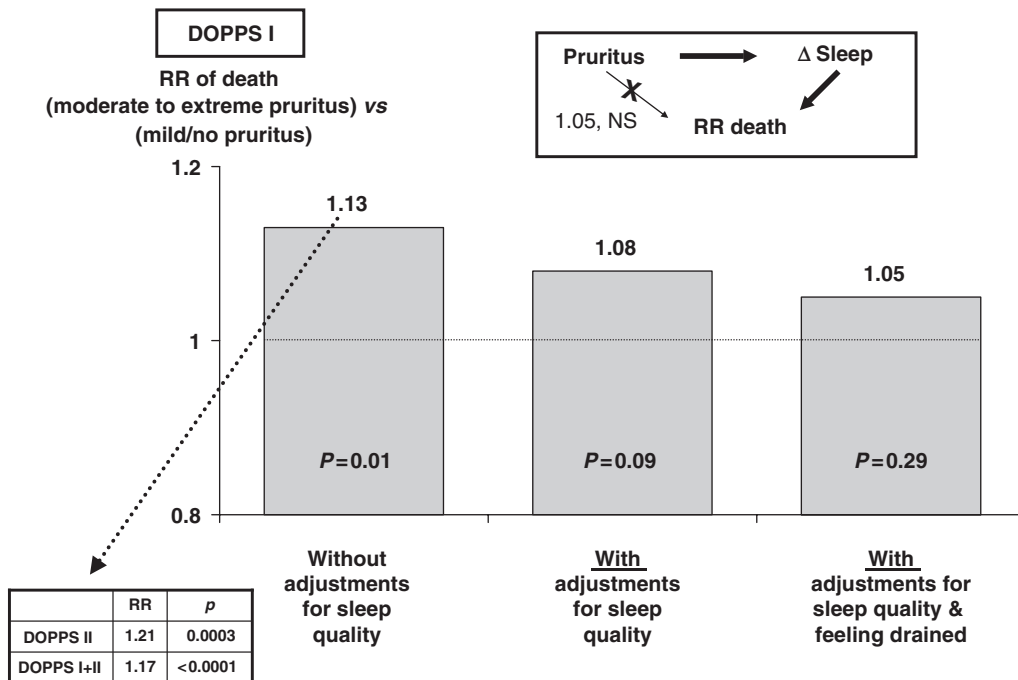


Fig. 5. Relative risk (RR) of mortality for HD patients with moderate to extreme pruritus vs mild/no pruritus with or without adjustments for sleep quality and feeling drained (DOPPS I). RR of mortality for patients with moderate to extreme pruritus versus mild/no pruritus was assessed using Cox survival models adjusted for age, black race, gender, single pool Kt/V, 13 comorbidity classes, physician-diagnosed depression, years on dialysis, country and baseline serum concentrations of haemoglobin, serum albumin, serum phosphorus, and albumin-corrected serum calcium ($n = 10\,267$). The Cox model adjusted for sleep quality included additional adjustments for being awake at night, problems in getting enough sleep, and being sleepy during the day. The Cox model adjusted for sleep quality and feeling drained included all of the above adjustments plus feeling drained. All models accounted for facility clustering effects, and were based on data collected in DOPPS I (1996–2001) in which sleep quality data were collected. Adjustments for sleep quality were not available in DOPPS II. Therefore, the RR of death with adjustments for sleep quality could only be modeled with DOPPS I data.

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 predominating characteristic of the pathway lying between uraemic pruritus and mortality risk.

The current study suggests a large opportunity for a clinical trial to test the extent of improved health outcomes, and sleep quality through novel drug treatment of pruritus and/or improved treatment of poor sleep quality in pruritic patients. Clinical trials that have tested various drugs for treatment of pruritus typically have not measured longer term outcomes such as improvements in patient QoL, sleep quality or survival. However, it is noteworthy that in a recent clinical trial by Kuypers *et al.* [16], of the 21 HD patients treated with tacrolimus for 6 weeks sleep medication use fell from 24% to 0% ($P=0.02$), and patient nervousness declined from 86% to 33% ($P=0.001$) during the 6-week drug trial which showed a large reduction in pruritic symptoms among the 21 trial subjects.

Across the 12 countries in DOPPS, it is seen that only 30% of pruritic patients who had poor sleep quality were prescribed sleeping pills, highlighting an opportunity for possibly improving patient outcomes through greater use of medication to address poor sleep quality in patients with pruritus. However, the efficacy of various sleep medications in alleviating poor sleep quality in uraemic pruritus has not been well-delineated. Other recent work from the DOPPS by Saran *et al.* [25] has shown significantly higher mortality risk, and poorer QoL scores for HD patients bothered by poor quality sleep. However, the causal pathways accounting for this relationship between poor sleep quality and mortality require elucidation.

Currently, a poor understanding exists regarding the mechanisms underlying the development of pruritus in haemodialysis patients. Two concepts, the 'immuno-hypothesis' and the 'opioid hypothesis,' have been raised as possible mechanisms for the pathogenesis of uraemic pruritus [1,5]. In the immuno-hypothesis, it is postulated that uraemic pruritus is a manifestation of a derangement of the immune system that results in an elevated systemic pro-inflammatory response. In support of this hypothesis, certain immunomodulators (e.g. ultraviolet B exposure, use of tacrolimus or thalidomide), which decrease generation of pro-inflammatory cytokines, have been shown to provide relief of uraemic pruritus [16,18,19]. Furthermore, after kidney transplantation and immunosuppression via cyclosporine, patients rarely experience uraemic pruritus, and cyclosporine has been described in one case study as providing relief from uraemic pruritus for a haemodialysis patient [25–27]. In addition, Kimmel *et al.* [28] have shown that HD patients with pruritus exhibit a significantly higher proportion of Th1 cells, and higher serum C-reactive protein (CRP) and interleukin (IL)-6 levels, providing support for the role of micro-inflammation in the pathogenesis of uraemic pruritus. In the current study, a number of patient characteristics thought to be associated with inflammation or immune function were found to be significant predictors of moderate to extreme uraemic pruritus. These include having a WBC count >6700 WBC/ml, hepatitis C or ascites. The observed relationship of pruritus with hepatitis C

and ascites in haemodialysis patients is consistent with prior studies that have reported a more frequent occurrence of pruritus in non-ESRD patients having chronic hepatic obstruction [29,30]. In addition, Mamianetti *et al.* [11] have found significantly higher serum bile acid levels in haemodialysis and pre-dialysis patients with pruritus. An interesting observation in the present study was a strong relationship of uraemic pruritus with hepatitis C but not with hepatitis B, raising the question of whether the pathogenesis of pruritus may differ for patients with hepatitis C vs hepatitis B. Patients with lower serum albumin values also were significantly more likely to have moderate to extreme pruritus, with lower serum albumin values generally being recognized as an indication of either poorer nutritional status or inflammation. In addition, lung disease was related to uraemic pruritus with borderline statistical significance. However, patients with higher serum ferritin values (>800 ng/ml) were less likely to have uraemic pruritus even though such high ferritin levels often are considered to be associated with inflammation, and no significant relationship was seen between pruritus and neutrophil count or neutrophil percentage.

There have been several studies reported in haemodialysis patients indicating a significant relationship of uraemic pruritus with higher serum calcium and phosphorus levels [6,31]. 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 (>80 mg²/dl²) with uraemic pruritus. The mechanism of this relationship between serum calcium and serum phosphorus with uraemic pruritus is not understood at the present time. However, Momose *et al.* [31] recently described abnormal distribution of calcium ions in the skin of haemodialysis patients with uraemic pruritus. These authors found significantly higher calcium ion deposition in the extracellular fluid and cytoplasm of basal cells, in the extracellular fluid, cytoplasm, and nuclei of spinous cells. These cells lie in the deepest layer of the epidermis, suggesting a disrupted calcium ion gradient in the skin that may be involved in the development and/or maintenance of uraemic pruritus. Regarding dialysis dose, earlier work of Hiroshige *et al.* [9] showed that increasing dialysis dose leads to an improvement in uraemic pruritus in haemodialysis patients, and is supported by our results with DOPPS I data but not DOPPS II data in which this relationship was not significant ($P > 0.75$). This inconsistency in the association of the Kt/V and pruritus raises concerns regarding the importance of this relationship. Finally, the present study observed a significantly lower likelihood of uraemic pruritus in patients with >10 years of ESRD. The reason for this finding is not clear at the present time, and may be seen in our analyses due to the larger sample size whereas the lack of relationship between ESRD vintage and pruritus cited in many previous studies

may be due to the much smaller samples used in these previous studies.

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. These observations suggest that there are additional factors that have not been measured in our extensive analyses, which play a substantial role in the pathogenesis or maintenance of uraemic pruritus in haemodialysis patients. Furthermore, the likelihood of haemodialysis patients having moderate to extreme pruritus was substantially higher in the UK and Japan compared with most other countries after adjustment for patient characteristics. What is particularly intriguing is that the higher prevalence of self-reported uraemic pruritus in the UK and Japan also is 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, for example in the UK, is due to conditions which patients carry with them from the pre-ESRD period into ESRD, and may not be substantially due to haemodialysis treatment effects *per se*, at least in patients incident to ESRD. These differences were not explained by residual renal function differences in new ESRD patients. The relatively high prevalence of uraemic pruritus, even among patients new to ESRD, suggests that pruritus is common in chronic kidney disease patients prior to stage 5. 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 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. For example, is the observed relationship between low serum albumin and higher odds of uraemic pruritus due to poorer nutrition or greater inflammation represented by low serum albumin, or is it due to some other unaccounted illness that the patient may have which leads to pruritus and to lower serum albumin? Although the issue of causality must be kept in mind when interpreting the results from patient-based

observational studies, an important strength of the current study is the description of a consistent pattern of relationships between two separate data collections (DOPPS I vs II), and across 12 countries.

In summary, this large international investigation provides further evidence of the common occurrence of uraemic pruritus in haemodialysis patients. Pruritus is associated with a 17% higher mortality risk, which appears to be mediated in large part through disturbances in sleep quality. There have been a number of recent clinical trials providing some early promising results for relief of pruritus in haemodialysis patients with agents such as gabapentin [17], tacrolimus [16] and the κ -opioid receptor agonist, nalfurafine [32]. Hopefully, further testing will continue to be positive and yield broadly available therapeutic remedies to help dialysis patients manage uraemic pruritus more effectively and lead to improvements in long-term outcomes for these patients.

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References

1. Mettang T, Pauli-Magnus C, Alschner DM. Uraemic pruritus—new perspectives and insights from recent trials. *Nephrol Dial Transplant* 2002; 17: 1558–1563
2. Merkus MP, Jager KJ, Dekker FW, de Haan RJ, Boeschoten EW, Krediet RT. Physical symptoms and quality of life in patients on chronic dialysis: results of The Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). *Nephrol Dial Transplant* 1999; 14: 1163–1170
3. Nakai S, Shinzato T, Sanaka T *et al.* An overview of dialysis treatment in Japan (as of Dec. 31, 1999). *Jpn Soc Dial Ther* 2001; 34: 1121–1147
4. Curtin RB, Bultman DC, Thomas-Hawkins C, Walters BAJ, Schatell D. Hemodialysis patients' symptom experiences: effects on physical and mental functioning. *Nephrol Nursing J* 2002; 29: 562–574
5. Biro T, Ko MC, Bromm B, Wei ET *et al.* How best to fight that nasty itch - from new insights into the neuroimmunological, neuroendocrine, and neurophysiological bases of pruritus to novel therapeutic approaches. *Exp Dermatol* 2005; 14: 225–240
6. Blachley JD, Blankenship M, Menter A, Parker III T, Knoche JP. Uremic pruritus: skin divalent ion content and response to ultraviolet phototherapy. *Am J Kidney Dis* 1985; 5: 237–241
7. Cho YL, Liu HN, Huang TP, Tarn DC. Uremic pruritus: roles of parathyroid hormone and substance P. *J Am Acad Dermatol* 1997; 36: 538–543
8. Chou FF, Ho JC, Huang SC, Sheen-Chen SM. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg* 2000; 190: 65–70
9. Hiroshige K, Kabashima N, Takasugi M, Kuroiwa A. Optimal dialysis improves uremic pruritus. *Am J Kidney Dis* 1995; 25: 413–419
10. Virga G, Visentin I, La Milia V, Bonadonna A. Inflammation and pruritus in haemodialysis patients. *Nephrol Dial Transplant* 2002; 17: 2164–2169

11. Mamiianetti A, Tripodi V, Vescina C *et al.* Serum bile acids and pruritus in hemodialysis patients. *Clin Nephrol* 2000; 53: 194–198
12. Targ DC, Cho YL, Liu HN, Huang TP. Hemodialysis-related pruritus: a double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron* 1996; 72: 617–622
13. Weisshaar E, Dunker N, Gollnick H. Topical capsaicin therapy in humans with hemodialysis-related pruritus. *Neurosci Lett* 2003; 345: 192–194
14. Kyriazis J, Glotsos J. Dialysate calcium concentration of <1.25 mmol/l: is it effective in suppressing uremic pruritus? *Nephron* 2000; 84: 85–86
15. Pauli-Magnus C, Mikus G, Alscher DM *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; 11: 514–519
16. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus (UP) in patients on chronic dialysis therapy. *Nephrol Dial Transplant* 2004; 19: 1895–1901
17. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 2004; 19: 3137–3139
18. Gilchrist BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanisms of action. *Ann Intern Med* 1979; 91: 17–21
19. Hsu MM, Yang CC. Uraemic pruritus responsive to broadband ultraviolet (UV) B therapy does not readily respond to narrowband UVB therapy. *Br J Dermatol* 2003; 149: 888–889
20. Young EW, Goodkin DA, Mapes DL *et al.* The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. *Kidney Int* 2000; 57 [Suppl 74]: S74–S81
21. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner M, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study: design, data elements, and methodology. *Am J Kidney Dis* 2004; 44 [Suppl 2]: S7–S15
22. SAS Institute, Inc. *SAS/STAT user's guide*. Version 8. Volume 2: 1452. SAS Institute, Cary, NC: 2002
23. Klein J, Moeschberger M. *Survival Analysis Techniques for Censored and Truncated Data*. Springer, New York, NY: 1997; 416–418
24. Yosipovitch G, Zucker I, Boner G, Gafter U, Shapira Y, David M. A questionnaire for the assessment of pruritus: validation in uremic patients. *Acta Derm Venereol* 2001; 81: 108–111
25. Saran R, Elder S, Akizawa T *et al.* Sleep quality in hemodialysis (HD) patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS) [abstract]. *Nephrol Dial Transplant* 2005; 20 [Suppl 5]: v326–v327
26. Fusaro M, Munaretto G, Spinello M, Gallieni M. Regression of uraemic pruritus by cyclosporin in a haemodialysis patient. *Nephrol Dial Transplant* 2004; 19: 1338–1339
27. Altmeyer P, Kachel HG, Schafer G, Fassbinder W. Normalisierung der urämischen hautveränderungen nach nieren-transplantation. *Hautarzt* 1986; 37: 217–221
28. Kimmel M, Alscher DM, Dunst R *et al.* The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transplant* 2006; 21: 749–755
29. Bergasa NV. Pruritus in chronic liver disease: mechanisms and treatment. *Curr Gastroenterol Rep* 2004; 6: 10–16
30. Hung KY, Shyu RS, Tsai TJ, Chen WY. Viral hepatitis infection should be considered for evaluating uremic pruritus in continuous ambulatory peritoneal dialysis patients. *Blood Purif* 1998; 16: 147–153
31. Momose A, Kudo S, Sato M *et al.* Calcium ions are abnormally distributed in the skin of haemodialysis patients with uremic pruritus. *Nephrol Dial Transplant* 2004; 19: 2061–2066
32. Wikström B, Gellert R, Ladefoged SD *et al.* K-opioid system in uremic pruritus: Multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005; 16: 3742–3747

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