

INVESTIGATIVE REPORT

Uraemic Pruritus Markedly Affects the Quality of Life and Depressive Symptoms in Haemodialysis Patients with End-stage Renal Disease

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Little is known about the influence of uraemic pruritus on patients' wellbeing. The aim of our study was to evaluate the impact of uraemic pruritus on quality of life and depressive symptoms in patients with end-stage renal disease. A total of 200 haemodialysis patients were included into the study. The prevalence of uraemic pruritus was 38%. Patients with uraemic pruritus had significantly lower quality of life according to SF-36 questionnaire compared to the remaining of analysed subjects. Among patients with uraemic pruritus, 64.5% individuals also showed impaired skin-related quality of life evaluated with Dermatology Life Quality Index. The quality of life impairment correlated with uraemic pruritus intensity assessed with VAS and the 4-item itch questionnaire. Depression level significantly correlated with quality of life and severity of depressive symptoms was significantly associated with uraemic pruritus intensity. Our study underscores that uraemic pruritus should be regarded as an important health problem among haemodialysis patients. Key words: uraemic pruritus; quality of life; depression.

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End stage renal disease (ESRD) is a growing public health problem with increasing prevalence worldwide (1, 2). In recent years many attempts have been made to improve the survival of haemodialysis (HD) patients with ESRD (1). However, numerous studies indicated that this group of patients still has significantly impaired health-related quality of life (HRQoL), which might be even lower than in patients with leukaemia, colon or breast cancer. Thus, a need for improvement of HRQoL in chronic HD patients with ESRD has been strongly emphasised (1–7).

Uraemic pruritus (UP), i.e. a chronic pruritus caused by renal failure, is bothersome and often persistent complication of renal disease in HD patients with the prevalence ranging from 20% to 70% (8–13). Variations of the frequency of UP reported in various studies likely result from different study populations as well as sub-

jective and complex nature of pruritus (8). However, a global cross-sectional study reported that moderate and severe UP was present in 42% of HD patients (3). The aetiology of UP is complex and remains not fully elucidated. It usually occurs about 3–6 months after the start of HD, and some authors showed positive relationship with the HD duration (8–11). However, in some subjects UP may be present even before haemodialysis (12).

Despite the high prevalence of UP, there are only few studies dealing with the impact of UP on the wellbeing of HD patients with ESRD. Some previous reports showed that UP has been associated with sleep disturbances, depression, impairment of HRQoL and increased mortality risk (3–6). To corroborate and extend these data, we aimed to investigate the impact of UP and its intensity on the wellbeing of patients with ESRD undergoing HD in Poland in a cross-sectional study using validated questionnaires.

MATERIAL AND METHODS

Study population

A total of 200 adult patients, 76 (38%) women and 124 (62%) men, with ESRD undergoing regular HD were recruited into the study. All patients underwent a detailed physical examination. The demographic and clinical data, including: age, gender, underlying renal disease, type and duration of HD and presence of pruritus were collected by a single investigator (dermatologist). The exclusion criteria included other possible causes of pruritus, such as: skin diseases or haematological diseases. The age of patients ranged from 22 to 88 years (mean 59.05 years). The underlying renal diseases were as follows: diabetic nephropathy (29%), chronic glomerulonephritis (15%), polycystic kidney disease (11%), hypertensive nephropathy (8.5%), other cause (17.5%), and unknown cause (19%). The patients underwent HD 3 times/week for about 5 h each time; 148 patients (74%) used polysulfone dialyzer and 52 patients (26%) used haemofan dialyzer. The mean duration of HD was 142.6 weeks. All patients provided their written informed consent prior to the enrolment to the study. The study was approved by the local ethics committee (KB-378/2004).

Assessment of uraemic pruritus

Intensity of UP was evaluated with 2 different methods: the visual analogue scale (VAS) and the validated 4-item Itch Questionnaire that had been previously developed and used by our group in various studies on pruritus (14–20). Using VAS, patients were asked to mark on the 10-cm long horizontal line the mean intensity of pruritus which they experienced within 7 days prior to the time of examination. The scores ranged

from 0 (no itch) to 10 points (worst imaginable itch) (14). The 4-item Itch Questionnaire consisted of evaluations of localisation of pruritus (1–3 points), severity (1–5 points), frequency (1–5 points), as well as sleep disturbances due to itching (0–6 points) within 7 days prior to the examination; scoring ranges from 3 (mild pruritus) to 19 points (maximal pruritus) (15, 18).

Assessment of quality of life and depression symptoms

HRQoL was evaluated with 2 different questionnaires: (i) a generic instrument – the 36-item Short Form Health Survey (SF-36) (21), and (ii) a dermatological-specific questionnaire – the Dermatology Life Quality Index (DLQI) (22, 23). Both questionnaires have their validated Polish versions (23, 24). However, these questionnaires were not validated in patients on dialysis, which may represent a limitation of our study. The SF-36 questionnaire consisted of questions concerning physical and mental health within the period of the last 4 weeks. Thirty-six items of SF-36 are related to 8 different dimensions: physical functioning (PF), role limitation-physical functioning (RP), bodily pain (BP), general health perception (GH), vitality (V), social functioning (SF), role limitation-emotional functioning (RE) and mental health (MH). The eight-dimension scores range from 0 to 100 points, with a lower score indicating lower level of functioning and worse HRQoL (21). The DLQI is one of the most commonly used instruments for assessment of HRQoL in dermatology, as it is self-explanatory and easy-handled by patients. The DLQI score ranges from 0 to 30 points with higher score indicating more decreased HRQoL. According to the classification of DLQI score proposed by Hongbo et al. (25), patients with score of 0 to 1 points have normal quality of life (QoL), with scores 2–5 points slightly, 6–10 points severely, 11–20 points very severely and 20–30 extremely severely impaired HRQoL. Prevalence and severity of depression was assessed with Beck's Depression Inventory (BDI) (26, 27). Each item of BDI is presented in multiple choice formats, evaluated from 0 to 3 points. A total scoring above 10 points may suggest clinically relevant depression. All questionnaires were distributed among patients shortly before HD after thorough instructions about how to complete them and were fulfilled by the patients alone, without any help of the investigator.

Statistical analysis

The statistical analysis was performed using software Statistica v.6.0 (Statsoft, Krakow, Poland). The means, maximal and minimal values and standard deviations were calculated. The Student's *t* test or Mann-Whitney's *U* test were used where appropriate to compare continuous variables. The significance of differences between categorical variables was determined by Pearson's Chi-square test. The relationships between continuous variables of interest were assessed by Spearman's rank correlation test. Statistical significance was set at $p < 0.05$.

Sample size was determined with the assumption of 10% confidence interval at 99% confidence level using a web-based calculator (<http://www.surveysystem.com/sscalc.htm>). According to calculation, a sample of at least 166 patients or more would fulfill our requirements.

RESULTS

Prevalence, intensity and clinical characteristics of uraemic pruritus

Out of 200 HD patients, 76 participants (38%) had UP; 26 (34.2%) women and 50 (65.8%) men (Table I). The

intensity of pruritus evaluated with the VAS ranged from 1 to 10 points (mean 5.1 ± 2.5 points); the mean intensity of pruritus in women was 5.8 ± 2.7 points, and in men 4.7 ± 2.3 points. According to VAS, mild pruritus ($> 0 - < 4$ points) was observed in 25 (33%) patients, moderate pruritus ($\geq 4 - < 7$ points) in 28 (36.8%) patients, and severe or very severe pruritus ($\geq 7 - 10$ points) in 23 (30.2%) patients (14). The intensity of pruritus evaluated with the 4-item Itch Questionnaire ranged from 3 to 19 (mean intensity: 8.2 ± 4.5 points); the mean intensity of pruritus in women was 8.9 ± 5.2 points and in men 7.9 ± 4.1 points. A significant, strong correlation was observed between the results of the pruritus intensity obtained using VAS and the 4-Item Itch Questionnaire ($R = 0.61$; $p < 0.001$) (Fig. S1¹). The differences in prevalence or intensity of pruritus between genders were not statistically significant. As mentioned in Methods, some clinical aspects of UP were assessed with the 4-item Itch Questionnaire. Among HD patients with UP, 21.1% ($n = 16$) had generalised pruritus, 42.1% ($n = 32$) reported itch in two or more localisations, and 36.8% ($n = 28$) had itch in one body area, such as: trunk ($n = 15$), lower extremities ($n = 9$), upper extremities ($n = 3$) or scalp ($n = 1$). Ten (13.2%) patients reported no scratching due to itch; 46.2% patients ($n = 35$) reported scratching due to itch, but without visible excoriations, 34.2% patients ($n = 26$) noted persistent itch relieved by scratching with visible scratch marks, whereas in 5.2% patients ($n = 4$) itch could not be relieved by scratching. One

Table I. Results of the 4-item Itch Questionnaire

Pruritus feature	Patients <i>n</i> (%)
Distribution	
Pruritus at single location	28 (36.8)
Pruritus at multiple locations	32 (42.1)
Generalized pruritus	16 (21.1)
Severity	
Pruritus without the need to scratch	10 (13.2)
Pruritus with the need to scratch but without excoriations	35 (46.1)
Pruritus unrelieved by scratching but without excoriations	4 (5.2)
Pruritus accompanied by excoriations	26 (34.2)
Totally restless	1 (1.3)
Frequency ^a	
1 point	37 (48.7)
2 points	7 (9.2)
3 points	6 (7.9)
4 points	3 (3.9)
Continuous pruritus	23 (30.2)
Sleep disturbances	
None	49 (64.5)
1 episode of awakening due to pruritus (last 24 h)	8 (10.5)
2 episodes of awakening due to pruritus (last 24 h)	5 (6.6)
≥ 3 episodes of awakening due to pruritus (last 24 h)	14 (18.4)

^aEach long itch episode > 10 min or 4 short itch episodes < 10 min were scored as 1 point.

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patient reported, that he was totally restless because of itch. Furthermore, 35.5% patients ($n=27$) reported sleep disturbances due to itch. None of the analysed demographic and clinical parameters, including age, gender, underlying renal disease, type and duration of dialysis influenced the presence, intensity and clinical characteristics of pruritus (data not shown).

The impact of uraemic pruritus on quality of life

Results from SF-36 and DLQI are given in Tables II and III. A total of 198 patients completed the SF-36 questionnaire. According to SF-36, HD patients with UP had significantly lower total score of SF-36 indicating decreased HRQoL compared to patients without UP (93.0 ± 20.4 vs. 99.6 ± 19.9 points, $p=0.03$) (Table II). Separate analysis of each dimension of SF-36 revealed a significantly lower scoring of general health perception in patients with UP compared to patients without pruritus. There was no significant difference in total scoring of SF-36 between female and male patients with UP; however, women with UP had significantly lower score of vitality and social functioning compared to men. In addition, women with UP had significantly lower scoring of general health perception, social functioning and role limitation due to emotional problems compared to female patients without UP. Male patients with UP had significantly lower score only in the general health perception compared to men without UP (Table II). We found significant negative correlations between the total SF-36 scoring and intensity of pruritus assessed with both the VAS and the 4-item Itch Questionnaire ($R=-0.35$; $p=0.002$; $R=-0.43$, $p<0.001$, respectively) (Fig. S2¹).

To further assess the impact of pruritus on HRQoL in HD patients, we used the DLQI. All 76 HD patients with UP, 26 women and 50 men, completed the DLQI questionnaire. The DLQI score ranged from 1 to 14 points (1–14 in women, 1–10 in men). The mean score of DLQI was 3.6 ± 3.4 points (4.4 ± 4.4 points in women and 3.2 ± 2.8 points in men). There was no significant difference of DLQI score between female and male patients with UP. Based on the classification of DLQI

score (24), 49 (64.5%) patients with UP demonstrated some degree of HRQoL impairment: 31 (40.8%) slightly impaired, 14 (18.4%) severely impaired, and 4 (5.3%) very severely impaired HRQoL; 27 (35.5%) patients with UP had normal HRQoL according to the DLQI (Table III).

Comparing female and male patients with UP, 73.1% women and 60% of men had decreased skin-related QoL – this difference was not statistically significant. Among women with UP, 46.2% ($n=12$) had slightly, 11.5% ($n=3$) severely and 15.4% ($n=4$) very severely impaired QoL; whereas 38% ($n=19$) men had slightly and 22% ($n=11$) severely impaired QoL. Significantly more female patients with UP had very severely decreased QoL compared to male subjects with UP ($p=0.006$) (Table III). There were significant, positive correlations between the DLQI score and intensity of pruritus assessed with both the VAS and the 4-item Itch Questionnaire ($R=0.56$, $p<0.0001$; $R=0.48$, $p<0.0001$, respectively). Moreover, there was significant, negative correlation between SF-36 score and DLQI score in HD patients with UP ($R=-0.29$, $p=0.01$).

The impact of uraemic pruritus on depressive symptoms

A total of 198 patients completed BDI. Mean BDI score in HD patients with UP was slightly higher (5.8 ± 5.9 points) than in patients without UP (5.5 ± 6.3 points) ($p>0.05$). Almost every sixth HD patient (16.6%) (17.6% with UP and 16.1% without UP) got more than 10 points in BDI which might suggest clinically relevant depression. There was no significant difference in BDI scoring and prevalence of clinically relevant depression between HD patients with and without UP ($p>0.05$). Comparing HD women ($n=26$) and men ($n=48$) with UP, the mean BDI score was higher in female patients (7.07 ± 5.4 points) compared to male counterparts (5.1 ± 6.0 points), however, this difference was not statistically significant ($p>0.05$). Similarly, HD women without UP had higher mean BDI score (6.4 ± 6.3 points) compared to men without UP (4.8 ± 6.2), but again this difference was not statistically relevant ($p>0.05$). Finally, we observed significant

Table II. Evaluation of health-related quality of life with SF-36 in haemodialysis patients with and without uraemic pruritus (UP)

	Patients ($n=198$)			Women ($n=75$)			Men ($n=123$)		
	UP (+) $n=75$	UP (-) $n=123$	p	UP (+) $n=26$	UP (-) $n=49$	p	UP (+) $n=49$	UP (-) $n=74$	p
Physical functioning	50.3	56.0	0.19	46	50.8	0.52	52.6	59.5	0.2
Role limitation-physical functioning	58.0	69.5	0.12	48	70.9	0.06	63.2	68.6	0.6
Bodily pain	63.5	69.4	0.21	58.7	62.6	0.61	65.9	73.9	0.17
General health perception	32.6	42.7	0.0003	32.5	43	0.02	32.6	42.5	0.006
Vitality	46.5	50.8	0.29	38	49.2	0.08	51.0	51.8	0.88
Social functioning	71.6	78.0	0.16	62	77.5	0.04	76.8	78.3	0.72
Role limitation-emotional functioning	76.9	85.9	0.08	66.7	85.7	0.03	82.3	86.0	0.59
Mental health	61.9	64.5	0.39	55.7	61.8	0.31	65.1	66.3	0.68

Bold figures indicate $p<0.05$.

Table III. Evaluation of skin-related quality of life using DLQI in hemodialysis patients with uraemic pruritus. Interpretation according to Hongbo et al. (25)

DLQI score	Impairment of health-related quality of life due to uraemic pruritus	All patients <i>n</i> = 76 <i>n</i> (%)	Women <i>n</i> = 26 <i>n</i> (%)	Men <i>n</i> = 50 <i>n</i> (%)	<i>p</i>
0–1	Normal health-related quality of life	27 (35.5)	7 (26.9)	20 (40)	0.26
2–5	Slightly impaired health-related quality of life	31 (40.8)	12 (46.2)	19 (38)	0.49
6–10	Severely impaired health-related quality of life	14 (18.4)	3 (11.5)	11 (22)	0.27
11–20	Very severely impaired health-related quality of life	4 (5.3)	4 (15.4)	0	0.006
21–30	Extremely severely impaired health-related quality of life	0	0	0	–

correlation between BDI scoring and intensity of itch assessed with the 4-item itch questionnaire ($R=0.29$, $p=0.01$) (Fig. S3¹), but we failed to find such correlation between BDI score and VAS.

Interestingly, there was significant, negative correlation between BDI scoring and total SF-36 scoring in all HD patients ($R=-0.7$, $p<0.0001$). This correlation was found both in HD patients with UP ($R=-0.69$, $p<0.0001$) and HD patients without UP ($R=-0.68$, $p<0.0001$). We did not observe any significant correlation between BDI score and DLQI score ($p>0.05$).

DISCUSSION

The prevalence of UP in our study population was 38% which is more or less in accordance with previous reports (3, 8–12). We did not find any associations between presence or intensity of UP and some sociodemographic data, such as age, gender, underlying renal disease, presence of other co-morbidities or duration of HD. These results may suggest that above mentioned factors likely do not play a significant role in the pathogenesis of UP. It must, however, be underlined, that we have not studied other parameters of potential relevance, such as uraemic xerosis or some laboratory findings. It would be of interest to prove whether these factors are of importance for UP and how they may modulate HRQoL.

The intensity of UP in the study population was assessed by using 2 different instruments: VAS and validated 4-item Itch Questionnaire (15–19). A potential limitation of our study could be that we have measured only a mean pruritus within one week. In any future studies it should be recommended to assess several VAS-scores, including strongest and weakest itch experience, as it may give better information about itch-intensity. The significant, strong correlation between results obtained with 2 instruments used in our study confirmed that 4-item Itch Questionnaire may be regarded as a useful and reliable tool for the assessment of UP intensity in HD patients with ESDR. Moreover, the 4-item Itch Questionnaire provides the investigators with some clinical features of UP. In the current study approximately 20% of the patients suffered from generalised pruritus and 35.5% individuals had sleep disturbance

due to itch. The trunk was the most common site of pruritus. The certain discrepancy in clinical features of UP between individuals may reflect its complex nature.

Based on our study it could be suggested that both presence and severity of UP may negatively affect the well-being of HD patients with ESRD. We have used SF-36 and DLQI as questionnaires which were previously used in patients with itchy dermatoses. By using such questionnaires it was possible to compare the influence of UP on QoL with other dermatological conditions. However, it would also be interesting to apply a questionnaire specifically designed for patients with kidney diseases, e.g. KDQOL. Lack of its usage could be regarded as a limitation of our study and further studies should be performed in the future to confirm that our results are reproducible using a kidney disease specific instruments to assess QoL in dialysis patients.

The overall HRQoL impairment was evaluated using a generic, multidimensional questionnaire: SF-36 (23). It was demonstrated that HD patients with ESDR had significantly more decreased physical functioning and vitality compared to controls (28–30). To establish the impact of UP on HRQoL of HD patients, we compared SF-36 score of individuals suffering from UP to SF-36 score of subjects without UP that serve as a control group. It should be pointed out that there were no significant differences in age or presence of other co-morbidities that frequently occur in HD patients with ESRD, such as diabetes, arterial hypertension, malignancies, hepatitis C or B, connective tissue diseases between HD patients with UP and those without UP. Therefore, it seems that the above-mentioned parameters did not significantly alter the potential influence of UP on HRQoL. Our results may indicate that UP significantly affects the general health perception in HD patients. Previously, Curtin et al. (31) showed that UP markedly impaired the physical functioning domain in HD patients, although the influence of UP on this dimension seems to be difficult to explain. Interestingly, female HD patients suffering from UP had significantly higher impairment in social functioning and emotional functioning compared to female patients without UP. Moreover, UP had significantly higher negative effect on vitality and social functioning in HD female patients compared to HD male patients. These results may indicate that UP seems

to more prominently affect the HRQoL in HD female patients compared to HD male patients with ESRD, especially in social functioning, vitality, and emotional functioning. These results remain in accordance with some observations that women have more complaints of pruritus compared to men that could be associated with some hormonal and psychological differences (32).

We further aimed to assess the impact of UP on skin-related QoL in HD patients with ESRD, using a dermatology-oriented QoL questionnaire (DLQI) (21, 22). DLQI has been commonly used to assess the QoL impairment in many chronic itchy skin diseases (17, 33, 34). We observed significant positive correlation between UP intensity and DLQI score. Interestingly, the DLQI deterioration in pruritic HD patients with ESRD was lower than in patients with other chronic itchy skin diseases (33). These results may indicate that the itch contributes less to QoL deterioration in HD patients than in patients with chronic itchy dermatoses or may suggest certain limitation in the use of this questionnaire in HD patients. However, the significant correlation between SF-36 score and DLQI score was found. The impact of UP on DLQI was also more prominent in women; significantly more female HD patients had very severely affected skin-related QoL compared to male HD patients. UP impaired QoL through low self-esteem, bad feelings, physical limitation and daily activity. Previously, Szepietowski et al. (20), demonstrated using DLQI that uraemic xerosis affected QoL in HD patients. The mechanism of UP is unclear, however, some previous studies indicated that uraemic xerosis aggravated UP, as there was a positive correlation between these two variables. The authors suggested that the intensity of xerosis may compromise the skin-related QoL mainly indirectly, by aggravation of associated UP (20).

The prevalence of depression in ESRD patients on HD is relatively high and ranges between 5–30%. Depression was related with poorer adherence to dialysis and nutrition, poorer QoL and higher mortality rate (35). Therefore, the treatment of depression provides an additional opportunity to improve the QoL in HD patients (1). In the current study the prevalence of clinically suspected depression was 16.6%. However, it must be underlined that BDI as many other depression scales is not a diagnostic tool and the diagnosis of depression should be confirmed by thorough psychiatric examination. Furthermore, patients with high BDI scoring frequently do not have true depression, but rather a reduced mood, which in HD subjects might be linked with their poor health status. Nonetheless, the observed percentage was high, especially considering that the severity of depressive symptoms negatively affected QoL. Although previous studies showed relationships between UP and the presence of depression (3), we did not find such association in our group of patients. How-

ever, we observed the significant correlation between the intensity of UP and severity of depressive symptoms.

The results of current study remain in accordance with some previous reports showing the negative influence of UP on QoL, both on mental and physical composites (3, 5). Patients under HD suffering from UP more likely felt drained, had poor sleep quality and depression (3, 5). In addition, severe UP was demonstrated to be an independent predictor of poor outcome, associated with higher mortality risk that was largely attributed to poor sleep quality (3–6). The special QoL instruments have been validated by Yosipovitch et al. (36) and recently by Mathur et al. (13) in patients with UP. It should be stressed that generic and disease-specific instruments provide different information regarding HRQoL impairment: measure of general health or certain aspects of HRQoL (1).

Based on our results it seems that both presence and intensity of UP might significantly worsen the well-being, QoL and depressive symptoms in HD patients with ESRD. Therefore, we believe that this study contributes to the novel perspective on UP as severe complication in HD patients with ESRD. Furthermore, this study emphasises the need for diagnosis and effective treatment of UP in order to improve QoL in HD patients with ESRD.

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