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Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis

Istvan Mucsi[1–3], Miklos Zsolt Molnar[1,2,4], Csaba Ambrus[2,4], Lilla Szeifert[1], Agnes Zsofia Kovacs[1], Rezső Zoller[1], Szabolcs Barótfi[1], Adam Remport[5] and Marta Novak[1,6]

[1]Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary, [2]First Department of Internal Medicine, Semmelweis University, Budapest, Hungary, [3]Division of Nephrology, Faculty of Medicine, University of Toronto, Toronto, Canada, [4]Semmelweis University – Fresenius Medical Care Dialysis Center, Budapest, Hungary, [5]Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary and [6]Sleep Research Laboratory, Department of Psychiatry, University of Toronto, Toronto, Canada

Abstract

Background. In a cross-sectional study, we analysed the complex relationship between restless legs syndrome (RLS), insomnia and specific insomnia symptoms and health-related quality of life (QoL) in patients on maintenance dialysis.

Methods. Data were obtained from 333 patients on chronic maintenance dialysis. To assess the prevalence of RLS, we used the RLS Questionnaire (RLSQ). The Athens Insomnia Scale (AIS) was used to assess insomnia and QoL was measured with the Kidney Disease Quality-of-Life Questionnaire.

Results. The prevalence of RLS was 14%. The number of comorbid conditions was significantly higher in patients with *vs* without RLS (median: three *vs* two; $P < 0.05$). RLS patients were twice as likely to have significant insomnia as patients without RLS (35% *vs* 16%; $P < 0.05$). Furthermore, RLS was associated with impaired overall sleep quality (median AIS score: 8 *vs* 4; $P < 0.01$) and poorer QoL. RLS was a significant and independent predictor of several of the QoL domains after statistical adjustment for clinical and socio-demographic covariables. Importantly, this association remained significant even after adjusting for sleep quality.

Conclusions. RLS is associated with poor sleep, increased odds for insomnia and impaired QoL in patients on maintenance dialysis. Based on the present results, we suggest that both sleep-related and sleep-independent factors may confer the effect of RLS on QoL.

Keywords: insomnia; maintenance dialysis; quality of life; restless legs syndrome

Introduction

Restless legs syndrome (RLS) is a movement disorder characterized by an urge to move the legs that is often hard to resist and is usually, but not always, associated with disagreeable leg sensations. The symptoms tend to occur during inactivity and may interfere with sleep. RLS can occur in an idiopathic form or secondary to other conditions, such as pregnancy, iron deficiency and end-stage renal failure [1]. Recently, it has been suggested that RLS is associated with increased mortality and impaired health-related quality of life (QoL) in patients on maintenance dialysis [2,3]. One of the factors that may mediate the potential effect of RLS on QoL is the impact of RLS on sleep. However, there are only a few papers that have assessed the relationship between RLS and sleep complaints or insomnia in the chronic kidney disease (CKD) population using non-validated instruments [4–6].

The prevalence of RLS is estimated to be between 5 and 15% in the general population [7]. Previous studies have shown a 12–62% prevalence in patients with end-stage renal disease (ESRD) [2,3,6,8,9]. These large variations could be attributed, in part, to the heterogeneity of the study populations and also to differences in the definitions of RLS and the tools used to diagnose the syndrome. Clinical diagnostic criteria for RLS have been established by the International RLS Study Group (IRLSSG) and were modified recently [1]. The four minimal criteria of the

Correspondence and offprint requests to: Marta Novak, MD, Toronto Western Hospital, UHN, 399 Bathurst St, Toronto, ON M5T 2S8, Canada. Email: novis@hu.inter.net

disorder are:

(i) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
(ii) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.
(iii) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, for at least as long as the activity continues.
(iv) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

In the more recent papers that applied the IRLSSG diagnostic criteria, the prevalence of the disorder in the ESRD population was reported to be between 10 and 20%; however, the definitions of the disorder used in those reports were still quite variable [2,9]. Based on the IRLSSG criteria, a diagnostic questionnaire [RLS Questionnaire (RLSQ)] was developed by Allen and Earley [7,10]. The instrument may provide a relatively simple tool to detect RLS in a uniform and comparable manner.

In the general population, the prevalence of RLS increases with age, and women are more frequently affected than men. In a recent report, RLS was associated significantly with social status, worse somatic and mental health and diabetes [7,11]. Other potential correlates of RLS in both the general population and in patients with kidney disease are anaemia and iron deficiency [7]. In patients with ESRD, under-dialysis, iron deficiency and vitamin deficiency may predispose to the disorder [2,12].

Validated instruments to detect specific sleep disorders were used rarely in the earlier surveys assessing sleep complaints in patients with ESRD. A simple, easy-to-administer questionnaire, the Athens Insomnia Scale (AIS), based on the International Classification of Diseases criteria, recently has been established as a useful instrument to measure insomnia in epidemiological studies [13]. In this work, the AIS was used to assess the association of clinically significant insomnia and of specific insomnia symptoms and RLS.

In this study, we assessed the prevalence and correlates of RLS, and also the association of RLS with insomnia and specific sleep complaints using standard validated questionnaires in a sample of patients on maintenance dialysis. We also analysed the relationship between RLS and health-related QoL using the Kidney Disease Quality-of-Life Questionnaire (KDQoL).

Subjects and methods

Sample of patients and data collection

All prevalent patients on maintenance dialysis ($n = 257$) who were not listed on the transplant waiting list in four Fresenius Medical Care, Hungary and dialysis centres in Budapest, Hungary were asked to complete a battery of questionnaires, including the RLS Diagnostic Scale [7], the AIS [13] and the KDQoL [14]. In addition, waitlisted patients in all nine dialysis units in Budapest ($n = 214$), who were enrolled in a cross-sectional study aiming to study sleep and mood disorders and also health-related QoL (TransQoL–HU Study), completed a similar battery including these questionnaires. Data were collected between August 2002 and February 2003.

Demographic information and details concerning the medical history were collected at enrolment when information was obtained about age, gender, level of education, aetiology of ESRD, the presence or absence of diabetes and other comorbidities. The patients completed a battery of validated questionnaires during the dialysis sessions or while waiting for their treatment.

Dialysis-related data were extracted from the medical records and included single pool Kt/V (spKt/V) and 'vintage', i.e. time elapsed since starting dialysis treatment. Patients were asked to report if they suffered from any of the following comorbid conditions: heart disease, vascular disorder, bone disease, lung disorder, eye disorder, paraesthesias, diabetes mellitus or other conditions. The self-reported comorbidity score was calculated by summing the number of comorbid conditions reported by the patients.

The study was approved by the Ethics Committee of Semmelweis University. Before enrolment, the patients received detailed written and verbal information regarding the aims and protocol of the study.

Assessment of RLS

Symptoms of RLS were identified by using the RLSQ, a patient-completed instrument that has been shown to be a reliable screening tool for RLS [10]. The RLSQ was also used in a recent epidemiological survey [7]. The patients were asked to complete the first part of the questionnaire that included the diagnostic questions. The result was considered positive only if the patient met all the diagnostic criteria. If the questionnaire was not filled completely or the patient did not follow the instructions, the scale was not scored and the information was considered missing.

Assessment of insomnia

The AIS was used to assess sleep complaints and to identify possible cases of clinically significant insomnia. The AIS consists of eight items. The first five items cover night-time symptoms of insomnia (difficulty initiating sleep, difficulty maintaining sleep and early morning awakening) and three items probe daytime consequences of disturbed sleep (well-being, functioning capacity and daytime sleepiness). A recent publication suggested that a cut-off score of 10 provides acceptable sensitivity and specificity based on a prevalence of insomnia of ~10% [13]. The Hungarian version of the AIS was prepared following recommended procedures. Internal consistency of the Hungarian version of the AIS was excellent (Cronbach alpha = 0.86) and test–retest validation showed a good overall reproducibility ($r = 0.716$) [15].

The AIS was used to assess individual sleep complaints, to measure overall sleep quality and also to identify cases of potentially significant insomnia using a cut-off of 10

suggested by Soldatos *et al*. [13]. Night-time insomnia symptoms were classified as difficulty initiating sleep, difficulty maintaining sleep or early awakening.

Health-related QoL

The KDQoL questionnaire was used to assess health-related QoL. The KDQoL–SF includes both the 36-item Short-Form Health Survey (SF-36) general measures (eight domains) and 11 domains specific to patients with kidney disease. The KDQoL has been translated into many languages and has been used extensively in dialysis patients, most recently in the multicontinental DOPPS study [16]. The Hungarian version of the KDQoL has been prepared by the FACIT translation group, which followed the FACIT translation methodology [17]. The internal consistency of the individual sub-scales and test–retest reliability was similar to the original tool and to other translations. The questionnaire was scored according to the scoring manual. On all scales, the possible scores range from 0 to 100; higher scores indicate better functioning or better QoL.

Statistical analysis

Statistical analysis was carried out using the SPSS 10.0 software. Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test and categorical variables were analysed with the chi-square test or the Fisher exact test, as appropriate. Analysis of variance testing with Bonferroni correction for multiple comparisons was used to analyse the relationship between continuous and categorical variables. Univariate analysis was performed using the Pearson or Spearman correlation analysis, as appropriate. For multivariate analysis, linear or logistic regression was used.

Results

Patients' characteristics are shown in Table 1. Twenty-nine per cent of the 471 patients approached refused to participate or did not fill in the questionnaires completely (non-participants). The final study population, therefore, consisted of 333 individuals. Non-participants were significantly older (64 ± 14 *vs* 54 ± 15 years; $P < 0.001$), the proportion of women was higher (54% *vs* 42%; $P < 0.05$) and they were less likely to be on the waiting list. Other socio-demographic and clinical parameters (education, albumin, haemoglobin, ferritin, spKt/V and ESRD vintage) were similar between the two groups.

Mean age in the study population was 54 ± 15 years, 58% were males and the prevalence of diabetes was 22%. Median time since starting dialysis was 34 months (range: 3–239 months). The most prevalent underlying kidney disease was chronic glomerulonephritis (30%). The prevalence of other kidney diseases was diabetic nephropathy 22%, chronic pyelonephritis and tubular interstitial disease 18%, autosomal dominant polycystic kidney disease 8% and hypertensive nephropathy 6%. Other or unknown underlying kidney disease accounted for 16% of cases.

RLS was identified in 45 patients (14%). Most of the socio-demographic characteristics and the clinical parameters were similar between the groups with *vs* without the condition (Table 1). Specifically, the distribution of gender and the level of education were similar in the group with *vs* without RLS. Mean age in the two groups was similar. RLS was not associated with the presence of anaemia, iron deficiency (assessed by serum ferritin) or lower serum albumin.

Patients with RLS had somewhat higher median intact parathyroid hormone (iPTH; $P < 0.05$); however, the proportion of clinically significant secondary hyperparathyroidism (iPTH >300 pg/ml) was not different between the two groups. The mean spKt/V and also the proportion of patients with inadequate dialysis dose (spKt/V < 1.2) were similar in patients with *vs* without RLS, although the difference in the latter analysis approached statistical significance [39 *vs* 25%; odds ratio: 1.706; 95% confidence interval (CI): 0.985–2.954; $P = 0.058$].

Table 1. Patients' characteristics

	Total sample ($n = 333$)	RLS ($n = 45$)	No RLS ($n = 288$)	*P*-value
Male (%)	58	58	58	NS
Age (years)	54 ± 15	56 ± 14	53 ± 15	NS
Diabetes mellitus (%)	22	24	22	NS
Haemoglobin (g/l)	112 ± 15	110 ± 21	113 ± 15	NS
Anaemia (Hb <110 g/l) (%)	39	45	38	NS
Ferritin (μg/l) [median (range)]	489 (5–1185)	379 (11–957)	510 (5–1185)	NS
Iron deficiency (ferritin <100 μg/l)	11	10	12	NS
Phosphorus (mmol/l)	1.8 ± 0.56	1.95 ± 0.56	1.80 ± 0.56	NS
iPTH (pg/ml) [median (range)] (normal range: 10–65 pg/ml)	19.6 (1–1448)	32 (1–894)	17 (1–1448)	< 0.05
Serum albumin (g/dl)	40 ± 3.6	40 ± 3.7	40 ± 3.6	NS
Number of comorbid conditions [median (range)]	2 (0–7)	3 (0–7)	2 (0–7)	< 0.05
Kt/V	1.3 ± 0.24	1.3 ± 0.29	1.3 ± 0.22	NS
Kt/V < 1.2 (%)	27	39	25	0.058
ESRD time (months) [median (range)]	34 (3–239)	29 (3–117)	36 (3–239)	NS
Insomnia (AIS ≥ 10) (%)	19	35	16	< 0.05
AIS score [median (range)]	5 (0–22)	8 (1–18)	4 (0–22)	< 0.01

Hb, haemoglobin.

RLS was not associated with the presence of diabetes mellitus (Table 1). The number of self-reported comorbid conditions, however, was significantly higher in patients with RLS *vs* in individuals without this syndrome ($P < 0.05$; Table 1). The prevalence of RLS increased significantly with increasing number of self-reported comorbidities (Figure 1).

Logistic regression analysis was used to analyse the independent relationship between the presence of RLS and the main socio-demographic variables (age and gender) and the presence of diabetes mellitus. The variables that showed significant or marginal association with RLS in bivariate analysis (spKt/V, number of self-reported comorbid conditions and iPTH) were included in the model as independent variables. In this model, only poor dialysis dose (spKt/V <1.2) (odds ratio: 2.215; 95% CI: 1.052–4.663; $P = 0.036$), but none of the other variables, were associated significantly with the presence of RLS after statistical adjustment for the covariables.

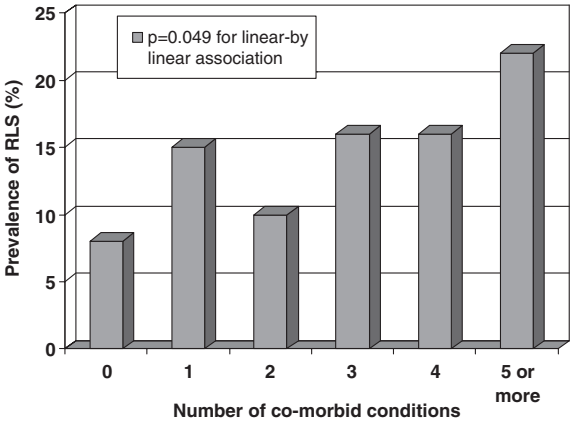

Fig. 1. Prevalence of RLS and number of comorbid conditions in dialysis patients.

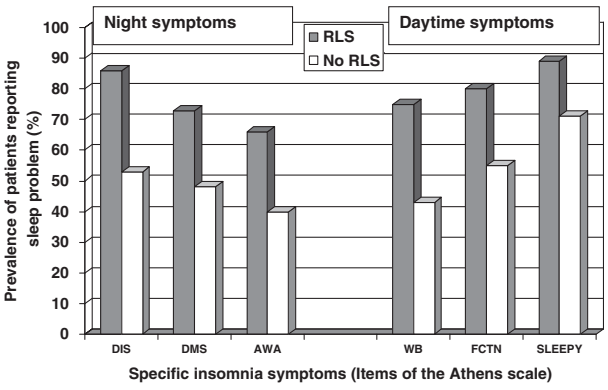

Fig. 2. Association of RLS with specific insomnia symptoms. DIS, difficulty initiating sleep; DMS, difficulty maintaining sleep; AWA, early awakening; WB, daytime well-being; FCTN, daytime functioning capacity; SLEEPY, daytime sleepiness. The prevalence of patients reporting these symptoms are significantly higher in the RLS *vs* the no RLS group ($P < 0.01$, chi-square test).

RLS, insomnia and specific sleep complaints

RLS patients were twice as likely to have significant insomnia as patients without RLS (35 *vs* 16%; $P < 0.05$; Table 1). Furthermore, patients with RLS had significantly higher AIS scores than patients without this syndrome (median: 8 *vs* 4; $P < 0.01$).

Patients with RLS more frequently reported the presence of the specific sleep problems assessed by the individual AIS items (Figure 2). Almost 90% of the patients with RLS reported problems with sleep initiation whereas only 50% of the patients without RLS had a similar complaint ($P < 0.01$). Similarly, more than two-thirds of the patients with RLS *vs* 40–45% of the patients without the condition reported problems with sleep fragmentation and early awakening ($P < 0.01$). Daytime consequences of poor sleep (impaired well-being or functioning capacity and sleepiness) were also significantly more frequent complaints in patients with *vs* without RLS ($P < 0.01$; Figure 2).

To assess the association of overall sleep quality and RLS, the proportion of patients with *vs* without the syndrome scoring in each of the quartiles of the AIS scores was also analysed (Figure 3). More than 40% of the RLS patients fell into the highest quartile (representing worse sleep), with only ~5% of them in the lowest quartile. The trend was completely the opposite in the group without RLS, with <20% of these patients scoring in the highest and >30% in the lowest quartile ($P < 0.01$). In multivariate regression models, the presence of RLS was the strongest significant independent predictor of the AIS score (Table 2) or the presence of insomnia (odds ratio: 2.804; 95% CI: 1.301–6.043; $P = 0.009$).

RLS and health-related QoL

The presence of RLS was associated with significantly worse QoL along most of the general and kidney

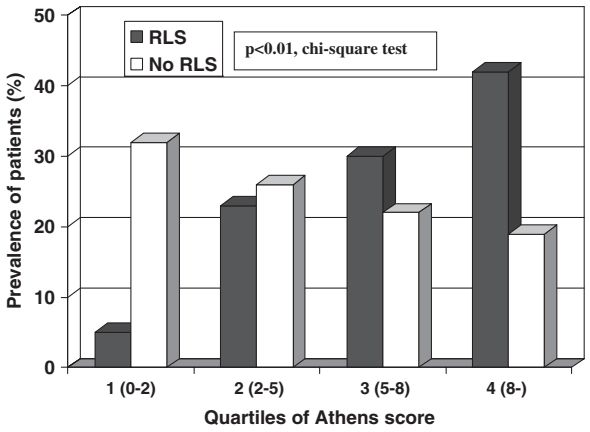

Fig. 3. RLS and overall sleep quality. The proportion of patients with RLS in each quartile of the AIS score is significantly different from the proportion of patients without RLS in the same quartile of the AIS score ($P < 0.01$, chi-square test).

disease-specific domains of the questionnaire, except the physical function ($P = 0.069$) and the energy/fatigue ($P = 0.137$) domains of the SF-36 instrument (Figure 4), although the QoL score of RLS patients tended to be lower than the score of patients without RLS even along these domains. In multivariate linear regression models, the presence of RLS was a significant and independent predictor of five out of the six QoL domains analysed (Table 3, left panel) after adjustment for the following covariables: age, gender, education, self-reported financial situation, serum albumin and number of self-reported comorbid conditions. Importantly, the independent association between RLS and QoL remained significant in four domains (emotional well-being, pain, symptoms, and problems of kidney disease and sleep), even after entering the AIS score in the model as an independent variable (Table 3, right side).

Table 2. Linear regression analysis of the predictors of the AIS score

	β	*t*	*P*-value
Age	0.124	2.186	0.030
Gender	0.149	2.504	0.013
Education	−0.052	−0.914	0.361
Serum albumin	−0.020	−0.344	0.731
Number of comorbid conditions	0.125	2.161	0.032
Presence of RLS	0.251	4.520	<0.001

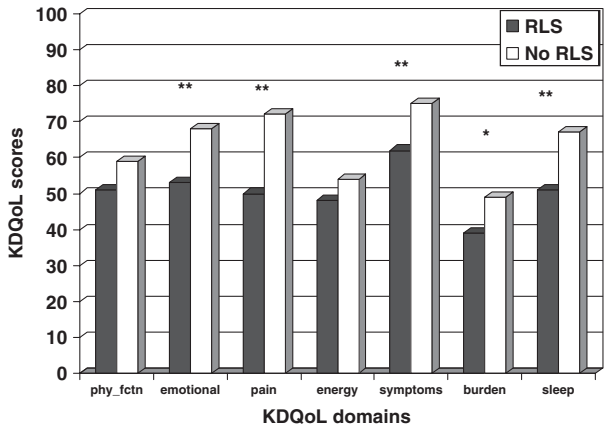

Fig. 4. RLS and health-related QoL. $*P < 0.05$; $**P < 0.01$ (Student's *t*-test). Phy-fctn, physical function; emotional, emotional well-being; pain, bodily pain; energy, energy/fatigue; symptoms, symptoms and problems list; burden, burden of kidney disease.

Discussion

Using the RLSQ instrument, we found that the prevalence of RLS was 14% in a sample of prevalent dialysis patients. Studies in recent years reported a 12–15% prevalence in ESRD populations using the IRLSSG criteria [3,9], although some studies found higher values [12]. The variable case definition used in some studies may, at least in part, be responsible for the observed differences. Employing uniform case definition by using standard diagnostic tools, such as the RLSQ, may facilitate research in this area.

The RLSQ was not completed or was completed only partially by a substantial proportion of patients. As the 'non-participant' group was somewhat older and there were more women in that group, the 'true' prevalence of RLS may be somewhat higher than observed. At the same time, we did not find an association between age or gender *vs* RLS; therefore, we suggest that the bias introduced by the relatively high number of 'non-participants' might not be too large. Although completion of all the questions requires some focusing and attention, we believe that the response rate can be improved substantially in an interview-like setting where the RLSQ is the main focus of the encounter. In this study, the RLSQ was given as part of a larger battery of questionnaires and this may be one explanation for the high proportion of non-participants.

Large epidemiological studies have identified several correlates of RLS in the general population: the

Table 3. Linear regression analysis of different QoL domains to assess the association with RLS independent of sleep. Shown in the cells of the table are the parameters of the independent variable: RLS present or not. Independent variables entered into the model: age, gender, education, self-reported financial situation, serum albumin, number of comorbid conditions, presence of RLS and ± AIS score

QoL domains	Parameters for RLS					
	AIS not in the model			AIS in the model		
	β	*t*	*P*-value	β	*t*	*P*-value
Physical function	−0.079	−1.627	0.105	−0.016	−0.340	0.734
Emotional well-being	−0.204	−3.647	<0.001	−0.123	−2.268	0.024
Pain	−0.224	−4.333	<0.001	−0.124	−2.484	0.014
Symptoms, problems list	−0.214	−4.078	<0.001	−0.142	−2.855	0.005
Burden of kidney disease	−0.128	−2.231	0.027	−0.046	−0.803	0.423
Sleep	−0.257	−4.750	<0.001	−0.111	−2.604	0.010

prevalence of the condition was higher in the elderly and in women [11], but this was not seen in all studies. Some studies found an association between the presence of RLS and lower socio-economic status [18]. In our population, RLS was not associated with gender, age or education. Somatic or psychiatric comorbidity has also been associated with RLS in several reports [8,19]. Laboratory and clinical factors were reportedly associated with RLS in dialysis patients in recent studies [9,12]; however, none of those were found consistently to be associated with the syndrome across the studies. We found somewhat higher iPTH and higher number of self-reported comorbid conditions in patients with RLS compared with the group without the condition. Importantly, we also found a significant association between self-reported comorbidity and RLS in a large sample of kidney-transplanted patients [21]. Furthermore, inadequate dialysis dose was associated marginally with RLS in a multivariate logistic regression model. None of the other factors assessed, however, were associated independently with RLS in multivariate analysis. These findings might suggest that in dialysis patients uraemia is the most important, overwhelming risk factor for RLS and, therefore, the association of any other factor with the condition is difficult to detect. Furthermore, because of the relatively low prevalence of RLS, the statistical power of most studies (including ours) might have been inadequate to detect relatively subtle associations.

Anaemia and iron deficiency have been linked to RLS; however, more recent studies have failed to confirm those earlier findings [3,12]. In our study, RLS was not associated with serum haemoglobin level or the presence of iron deficiency (assessed by serum ferritin). The routine use of erythropoietin and relatively large doses of intravenous iron in this population may explain the lack of that expected association as suggested by others [20]. Notably, iron deficiency was a significant independent predictor of RLS in kidney-transplanted patients, in whom intravenous iron was not used routinely [21]. It is also possible that parameters used to assess peripheral iron stores might not reflect brain iron metabolism properly and it is brain and not peripheral iron that might be associated with RLS, as suggested by recent studies [22].

An association between RLS and insomnia in patients on maintenance dialysis has been suggested already by a few papers [4–6]. Ours is the first report, however, using standard, validated tools to assess these sleep problems in the dialysis population. We report here that patients with RLS are twice as likely to have clinically significant insomnia as dialysis patients without RLS. Furthermore, patients with RLS reported more frequent and more severe insomnia symptoms. Importantly, daytime consequences of disturbed sleep, assessed by the AIS, were also reported more frequently by RLS patients. These results are consistent with the notion that RLS interferes with sleep, resulting in impaired daytime well-being, increased daytime sleepiness and reduced mental and physical functioning capacity.

Unruh *et al*. [3] have reported recently that RLS was associated with significantly impaired health-related QoL. Using the KDQoL questionnaire, we confirmed and extended their findings. Similarly to their results, RLS in the present study was associated independently with impaired QoL along several domains of the SF-36 general questionnaire after adjustment for several demographic and clinical variables. In addition, we showed here that RLS was associated independently with impaired QoL also along kidney disease-related QoL domains. The difference along most of the domains analysed was quite substantial and was likely to be clinically significant. It has been suggested previously that a 5-point difference on the scales of the KDQoL corresponds to clinically important and perceivable differences in the QoL [16].

The use of the AIS allowed us to analyse the complex relationship between RLS, sleep and QoL in more detail. Importantly, we found that the association between RLS and impaired QoL was partly independent of insomnia or sleep quality (Table 3). These results suggest that RLS symptoms that are not exclusively related to sleep, specifically paraesthesias, discomfort and restlessness, may also have a significant negative impact on the QoL of patients suffering from the syndrome.

Our study is notable for the use of standard, validated tools to assess RLS and insomnia along with a widely used instrument to assess several domains of QoL in patients with CKD. The instruments we used to identify patients with RLS showed excellent sensitivity and specificity in an earlier study [10].

Several limitations of this report should also be noted. The cross-sectional design precludes any directional or causal conclusions. Furthermore, RLS is best diagnosed by an experienced clinician. However, the use of standard, validated questionnaires may still be necessary and useful in studies involving large numbers of patients. We did not have information on peripheral neuropathy, number of pregnancies in women and some other variables that could potentially be associated with RLS. Finally, the proportion of patients who did not complete the RLSQ was substantial in this study, but given the relatively minor differences between the 'participant' and 'non-participant' groups, it is unlikely that this introduced a systematic bias that would distort our conclusions.

In summary, we used the RLSQ for the first time to identify dialysis patients with RLS. The prevalence of RLS was 14%, comparable to recent reports in similar populations. RLS was associated independently with increased odds for clinically significant insomnia, impaired overall sleep quality and poorer QoL after statistical adjustment for clinical and socio-demographic covariables. Importantly, this association remained significant even after adjusting for sleep quality, suggesting that both sleep-related and sleep-independent factors may confer the effect of RLS on QoL.

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Conflict of interest statement. None declared.

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