The Prevalence of Restless Legs Syndrome across the Full Spectrum of Kidney Disease

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Study Objectives: Although restless legs syndrome (RLS) is common and well recognized as an important and potentially treatable cause of sleep disruption in end-stage renal disease (ESRD), few studies have evaluated the prevalence of RLS and its impact on sleep in the non-dialysis-dependent chronic kidney disease (CKD) population. The objectives of the study were to determine the prevalence of RLS across the full spectrum of kidney disease and to assess the impact of RLS on sleep quality and daytime function.

Methods: Five hundred patients were recruited from nephrology clinics and were stratified according to estimated glomerular filtration rate (eGFR): eGFR ≥ 60 mL/min/1.73m² (n = 127), CKD (eGFR < 60, not on dialysis, n = 242), and ESRD (on hemodialysis, n = 131). All subjects completed a sleep and medical history questionnaire, an RLS questionnaire, the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Scale (ESS).

Results: The prevalence of RLS did not differ among the three groups (18.9% [eGFR ≥ 60], 26% (CKD), and 26% (ESRD) p = 0.27). However, many symptoms of sleep disruption were more common in patients with RLS, and RLS was independently correlated with the PSQI score both in the full cohort (OR = 2.63, CI = 1.60-4.00, p < 0.001) and the CKD group (OR = 2.39, CI = 1.20-4.79, p = 0.014).

Conclusions: RLS is common in non-dialysis-dependent CKD patients and is an important source of sleep disruption.

Keywords: Restless legs syndrome, chronic kidney disease, end-stage renal disease, sleep quality, daytime sleepiness, prevalence

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous studies of Restless Legs Syndrome (RLS) in patients with kidney disease have focused on those with end-stage renal disease (ESRD). The objective of this study was to determine the prevalence of RLS and its impact of sleep quality and daytime function across the full spectrum of kidney disease.

Study Impact: Restless Legs Syndrome (RLS) is common in patients with non-dialysis-dependent chronic kidney disease (CKD) as well as those with ESRD. Furthermore, RLS is a significant source of sleep disruption in both of these patient populations and should be considered in any patient with kidney disease who reports poor sleep quality.

Restless legs syndrome (RLS) is common in end-stage renal disease (ESRD), affecting up to 62% of patients,^{1,2} which is substantially higher than the 5% to 15% prevalence rate in the general population.³⁻⁶ Although a number of studies have evaluated RLS in patients with ESRD,^{1,2,7} very few have investigated the prevalence of RLS in patients with chronic kidney disease (CKD) who are not dialysis-dependent and its impact on sleep and daytime function. Merlino et al. reported an increased prevalence of RLS in CKD patients (10.9% vs 3.3%) in a case-control study that was limited by a relatively small sample size (138 CKD patients).⁸ Aritake-Okada et al. conducted a larger study on 514 Japanese patients with CKD.⁹ Although they found a higher prevalence of RLS in CKD patients compared to their control group (3.5% vs 1.5%), this prevalence is very low compared to western countries and their findings may not be generalizable to non-Asian populations. Neither of these studies included patients with ESRD and consequently could not compare the prevalence of RLS across the full spectrum of kidney disease.

The coexistence of RLS in patients with CKD is likely to have clinical relevance. RLS has been associated with poor sleep and impaired daytime function both in the general population⁶ and patients with ESRD.¹⁰ Furthermore, RLS was associated with increased mortality in patients receiving treatment with chronic hemodialysis.¹¹ The non-dialysis-dependent CKD population is much larger than the ESRD population, and its prevalence is growing.¹² Establishing that the

prevalence of RLS is increased in patients with CKD could heighten the treating physician's awareness of this comorbidity and thereby provide an opportunity to potentially improve the quality of life and clinical outcomes in a relatively large group of patients.

The primary objective of the current study was to determine the prevalence of RLS across the full spectrum of kidney disease using the same methodology in patients with normal renal function, CKD, and ESRD. Our secondary objective was to assess the impact of RLS on sleep quality and daytime function. We hypothesized that the prevalence of RLS would increase progressively as kidney function decreased, and that RLS would have a negative impact on both sleep quality and daytime alertness in patients with CKD and ESRD.

METHODS

Patient Recruitment and Data Collection

Adult patients (≥ 18 years) were recruited from outpatient nephrology clinics and hemodialysis units in the Southern Alberta Renal Program in Calgary, Alberta from May 2008 to February 2012. Consecutive patients were invited to participate; all those who consented and were able to complete the questionnaires were included in the study. Some of the data have previously been published in a study that investigated the prevalence of sleep apnea and nocturnal hypoxia in CKD.¹³ The current study was designed to evaluate the prevalence and clinical significance of RLS in CKD with an expanded cohort of patients. The study was approved by the University of Calgary Conjoint Health Research Ethics Board. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

All patients completed a set of questionnaires administered either face-to-face or by telephone interview. First, a standardized questionnaire surveyed demographic information, sleep and medical history, and the use of medications, alcohol, caffeine, and cigarettes. Alcohol consumption was self-reported as the number of alcoholic drinks per week, and caffeine ingestion by the number of cups of coffee, tea, and cola per day. Cigarette smoking was defined as any current smoking habits. In addition, coexisting medical disorders were recorded, including hypertension, congestive heart failure, coronary artery disease (angina, myocardial infarction, and coronary artery bypass surgery), cerebrovascular disease (stroke or transient ischemic attack), diabetes, and chronic obstructive pulmonary disease (COPD). Second, the RLS Questionnaire devised by the International RLS Study Group (IRLSSG)⁶ was administered to determine the prevalence of RLS. Patients were given a positive diagnosis of RLS if they met the following four criteria: (1) an urge to move due to uncomfortable sensations in the legs, (2) uncomfortable sensations are relieved by movement, (3) symptoms worsen during rest or inactivity, and (4) symptoms worsen in the evening. In addition, each patient was asked about a family history of RLS. Third, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality, where a score > 5 indicated poor sleep quality.¹⁴ Fourth, the Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness, where a score > 10 indicated excess sleepiness.¹⁵

Questionnaire data was supplemented by review of each patient's medical record, which provided a measurement of hemoglobin level and estimated glomerular filtration rate (eGFR) within 1 month of the study visit. Patients were stratified according to their eGFR and classified into 3 groups based on the National Kidney Foundation Staging System: eGFR ≥ 60 mL/min/1.73m²; CKD, eGFR < 60 not on dialysis; and ESRD on conventional hemodialysis.¹⁶ eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.¹⁷

Statistical Analysis

Data are reported as mean $\pm$ standard deviation for continuous variables and median (range) for non-normally distributed variables. Parametric and nonparametric tests were used when appropriate. The Pearson chi-squared (χ^2) test was used for categorical comparisons, followed by a linear-by-linear association trend analysis to evaluate underlying trends. The unpaired

t-test or the Mann-Whitney U-Test was used for comparisons of continuous variables between 2 groups. Comparisons across 3 groups were done using either a one-way analysis of variance followed by a Tukey HSD post hoc test or the Kruskal-Wallis Test. The Jonckheere-Terpstra Test was used for trend analysis of non-normally distributed continuous variables.

Multivariable logistic regression analysis was performed to determine the association between severity of kidney disease and likelihood of RLS, controlling for traditional predictors of RLS including age, gender, anemia, diabetes, use of antidepressant medications, and a family history of RLS.

Determining the effect of RLS on sleep quality and daytime sleepiness was addressed by generating 2 multivariable logistic regression models with RLS as an independent variable and PSQI and ESS scores as the dependent variables. We controlled for potential confounding variables including age, gender, severity of kidney disease (as determined by the 3 study groups), sleep restriction (defined as spending < 6 h in bed at night), alcohol and caffeine intake, cigarette smoking, and comorbidities that could disrupt sleep (sleep apnea, congestive heart failure, cerebrovascular disease, and COPD). This analysis was repeated for the non-dialysis dependent CKD group alone. Both the Hosmer-Lemeshow goodness-of-fit test and the Omnibus test of model coefficients indicated an adequate fit of the data to the models. Odds ratios were reported along with 95% confidence intervals and p-values. All analyses were performed using the Statistical Package for Social Sciences 17.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Table 1 summarizes the demographic characteristics of the 500 patients we studied: 127 were eGFR ≥ 60 ; 242 had CKD (eGFR < 60); and 131 were ESRD patients. Patients in the eGFR ≥ 60 group were significantly younger than those with CKD and ESRD. Gender distribution was similar across the 3 study groups (40% female, 60% male). Median hemoglobin levels declined with increasing severity of kidney disease. Additionally, and as anticipated,¹⁸ the prevalence of hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease and diabetes increased as kidney function declined.

Overall, 24.2% of the cohort met the diagnostic criteria for RLS. Within the 3 study groups, the prevalence of RLS was 18.9% (eGFR ≥ 60), 26% (CKD), and 26% (ESRD). These differences were not statistically significant ($\chi^2 = 2.61$; $p = 0.271$), and the trend analysis was also nonsignificant ($p = 0.19$). The prevalence of RLS in the CKD group was significantly higher for women than for men (women 34.7%, men 25.6%; $\chi^2 = 6.15$; $p = 0.04$). Although women still had a higher prevalence of RLS among eGFR ≥ 60 and ESRD patients, this gender difference was not statistically significant.

Features of sleep disruption were reported more frequently by patients with, compared to those without, RLS (**Table 2**). Sleep latency was longer, and reports of feeling unrefreshed in the morning and of impaired memory and concentration during the daytime were more prevalent in those with RLS. The presence of poor sleep quality was also higher in this group, as reflected by the PSQI. Excessive daytime sleepiness (ESS > 10), on the other hand, was not significantly more prevalent in patients with RLS.

Table 1—Clinical profile of all patients

	eGFR ≥ 60 (n = 127)	CKD (n = 242)	ESRD (n = 131)	p-value
Age (years)	44.6 $\pm$ 14.8*	65.7 $\pm$ 12.5	64.3 $\pm$ 14.1	< 0.001
Gender (M/F)	72/55	147/95	80/51	0.71
BMI (kg/m ²)	28.6 $\pm$ 6.61	30.4 $\pm$ 7.82*	27.3 $\pm$ 6.43*	< 0.001
Hypertension (%)	50.4*	81.4	87.0	< 0.001
Congestive heart failure (%)	0	5.37	16.8	< 0.05
Coronary artery disease (%)	5.51	19	30.5	< 0.001
Cerebrovascular disease (%)	0	7.44	13.7	< 0.001
Diabetes (%)	11	38.8	55	< 0.001
COPD (%)	4.72	7.44	12.2	0.077
Antidepressant meds (%)	7.87	5.79	8.4	0.58
Alcohol Intake (drinks/week)	2.84 $\pm$ 5.01	1.92 $\pm$ 4.09	0.45 $\pm$ 1.42*	< 0.001
Caffeine intake (cups/day)	2.23 $\pm$ 2.01	2.66 $\pm$ 1.96*	2.13 $\pm$ 1.67*	0.031
Hemoglobin (g/L)	142 $\pm$ 16.1	130 $\pm$ 19	116 $\pm$ 12.7	< 0.001
Prevalence of RLS (%)	18.9	26	26	0.27

*Statistical significance. eGFR, estimated glomerular filtration rate (mL/min/1.73m²); CKD, chronic kidney disease; ESRD, end-stage renal disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease. Continuous variables are reported as mean $\pm$ standard deviation.

Table 2—Sleep characteristics of patients with and without RLS

	All Patients			CKD Patients		
	RLS (n = 121)	No RLS (n = 379)	p-value	RLS (n = 63)	No RLS (n = 179)	p-value
Sleep latency (min)	31.4 $\pm$ 33.2	21.3 $\pm$ 26.9	< 0.001	26 $\pm$ 26.6	18.9 $\pm$ 23.3	0.023
Leg movements during sleep (%)	42.1	18.2	< 0.001	33.3	14	0.001
Un-refreshing sleep (%)	48.8	37.7	0.031	50.8	35.2	0.029
Poor memory or concentration (%)	54.5	35.4	< 0.001	52.4	37.4	0.038
PSQI score > 5 (%)	67.8	45.4	< 0.001	57.1	39.7	0.016
ESS score > 10 (%)	28	19.8	0.054	27	19	0.181

RLS, restless legs syndrome; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale. Continuous variables are reported as mean $\pm$ standard deviation.

Finally, more patients with RLS reported a history of leg movements during sleep ($\chi^2 = 28.8$; $p < 0.001$). Similar findings were noted when the analysis was confined to the CKD group alone.

Multivariable logistic regression analysis revealed that increasing severity of kidney disease was not significantly associated with the presence of RLS when controlled for confounders (**Table 3**). Women were at higher risk of developing RLS (OR = 1.74, CI = 1.13-2.68, $p = 0.012$), as were patients with a positive family history of RLS (OR = 3.37, CI = 1.47-7.71, $p = 0.004$). Further, the comorbidities listed in **Table 1** were not associated with the prevalence of RLS, other than female gender.

Regression models were used to evaluate the association between RLS and the PSQI and ESS scores (**Table 4**). RLS was independently and positively associated with the PSQI score (OR = 2.63, CI = 1.60-4.00, $p < 0.001$) but not with the ESS score (OR = 1.49, CI = 0.853-2.6, $p = 0.16$), which further supports the observation that RLS does contribute to poor sleep quality but not to excessive daytime sleepiness. Some factors that were correlated with the ESS score were a previous diagnosis of sleep apnea (OR = 3.75, CI = 1.77-7.96, $p = 0.001$) and the presence of smoking, which was negatively correlated with the ESS score (OR = 0.51, CI = 0.273-0.951, $p = 0.034$). Factors linked to PSQI score were female gender (OR = 2.26, CI = 1.48-3.46, $p < 0.001$) and spending < 6 h in

Table 3—Multivariable logistic regression analysis for independent predictors of RLS

Predictors	OR	95% CI	p-value
Kidney function			
eGFR ≥ 60	1.00		
CKD	1.06	0.546-2.04	0.87
ESRD	0.922	0.429-1.98	0.84
Gender			
Male	1.00		
Female	1.74	1.13-2.68	0.012
Age	1.01	0.995-1.03	0.19
Family history of RLS	3.37	1.47-7.71	0.004
Anemia	1.43	0.877-2.33	0.15
Antidepressant meds	1.83	0.859-3.90	0.12
Diabetes	1.06	0.668-1.68	0.81

OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73m²); ESRD, end-stage renal disease; RLS, restless legs syndrome.

bed (OR = 4.29, CI = 1.09-16.9, $p = 0.038$). We repeated the logistic regression analysis in the CKD group alone, excluding both the eGFR ≥ 60 and ESRD groups, to evaluate the relationship between RLS and PSQI and ESS. As with the full cohort,

Table 4—Multivariable logistic regression analysis for independent predictors of poor sleep quality and excessive daytime sleepiness

Factor	Poor Sleep Quality (PSQI score > 5)			Excessive Daytime Sleepiness (ESS score > 10)		
	OR	95% CI	p-value	OR	95% CI	p-value
RLS	2.63	1.60-4.00	< 0.001	1.49	0.853-2.6	0.16
Kidney function						
eGFR ≥ 60	1.00			1.00		
CKD	0.679	0.388-1.19	0.18	0.763	0.391-1.49	0.43
ESRD	1.42	0.736-2.74	0.30	0.934	0.44-1.99	0.86
Gender						
Male	1.00			1.33	0.8-2.21	0.273
Female	2.26	1.48-3.46	< 0.001	1.00		
Age	0.997	0.983-1.01	0.74	0.996	0.978-1.01	0.65
Sleep restriction	4.29	1.09-16.9	0.038	2.23	0.84-7.88	0.161
Alcohol	1.02	0.975-1.07	0.38	0.949	0.88-1.02	0.175
Smoking	0.624	0.320-1.22	0.17	0.51	0.273-0.951	0.034
Caffeine	1.01	0.927-1.09	0.86	1.06	0.963-1.16	0.241
Sleep apnea	1.09	0.520-2.28	0.82	3.75	1.77-7.96	0.001
Congestive heart failure	1.19	0.483-2.91	0.71	0.798	0.26-2.45	0.694
Cerebrovascular disease	0.949	0.464-1.94	0.89	0.636	0.247-1.64	0.349
COPD	0.518	0.231-1.16	0.11	0.313	0.196-1.69	0.575

OR, odds ratio; CI, confidence interval; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73m²); ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease.

RLS in the CKD group was significantly associated with the PSQI score (OR = 2.39, CI = 1.20-4.79, $p = 0.014$), but not with ESS (OR = 1.89, CI = 0.792-4.48, $p = 0.15$).

DISCUSSION

We found that the prevalence of RLS was similar in patients with non-dialysis-dependent CKD and ESRD and was higher than what has previously been reported in the general population.^{3,19} Furthermore, patients with RLS had many more sleep-related symptoms than those without RLS, and RLS was an independent predictor of poor sleep quality as reflected by the PSQI scores. We believe that RLS is a common and clinically relevant sleep disorder in patients with CKD and ESRD.

Our observation of a high and similar prevalence of RLS in patients with early, non-dialysis-dependent CKD and ESRD supports the hypothesis that RLS is associated with kidney disease, but departs from it in that RLS was not correlated with the severity of kidney disease. This may indicate that RLS develops relatively early in the natural history of CKD and remains stable with progressive loss of kidney function. Up to now, RLS has been most strongly associated with ESRD among the renal disease population, which is also consistent with anecdotal evidence from clinical practice.² This may reflect the paucity of studies that have formally evaluated the prevalence of RLS in patients with CKD. Alternatively, it is possible that RLS symptoms become more severe, and consequently more clinically apparent, as renal disease progresses. Unfortunately, our study cannot address this, as we did not measure the severity of RLS symptoms.

RLS was associated with many symptoms of sleep disruption and sleep loss in patients with kidney disease, namely increased sleep latency, feeling unrefreshed upon awakening, and

impaired memory and concentration during the daytime. Furthermore, in our multivariable analysis, RLS was strongly associated with poor sleep quality, reflected by the PSQI score. This supports the clinical importance of RLS in this patient population. The pathogenesis of these sleep-related complaints can be attributed to the difficulty initiating sleep that is characteristically associated with RLS and the difficulty maintaining sleep that is often associated with periodic limb movement disorder (PLMD). Although we did not confirm the presence of this disorder by polysomnography, many patients with RLS (42.1%) reported a history of leg movements during sleep, which supports a diagnosis of PLMD.

Our study did not find excessive daytime sleepiness (reflected by the ESS) to be more prevalent in patients with RLS, nor was daytime sleepiness independently associated with RLS in our multivariate analysis. This finding concurs with previous research in which patients with RLS did not report excessive sleepiness, despite having chronic sleep loss.²⁰ Gamaldo et al. observed that individuals with RLS had a higher level of daytime alertness than sleep deprived controls, and suggested that RLS-linked abnormalities in the dopaminergic activating system played a role in enhancing arousal.²¹ This may explain why patients with RLS in our study had poorer sleep quality but not excessive daytime sleepiness. It is also possible that some of our older, medically disabled patients may have slept voluntarily during the daytime and thereby not experienced involuntary sleepiness.

We chose to recruit patients with eGFR ≥ 60 as our control group in the belief that this would be the best way to control for the potential impact of non-renal factors on our outcome measurements. In some respects this was appropriate since all patients in the study were recruited from the same specialty clinics that were attended by the same healthcare providers. However, in other re-

spects, patients with $\text{eGFR} \geq 60$ had significant limitations as a control group since they were a referred population with several comorbidities who had a renal abnormality. It would have been interesting to measure the prevalence of RLS using the same methodology in a healthy, community-based population. It is likely that the prevalence of RLS would have been lower, which may have impacted the outcome of our multivariate analysis.

Our study does have other limitations which should be addressed. First, reliance on self-reported data has its shortcomings, as misinterpretation of interview questions and errors in recall may result in inaccurate findings. However, the diagnosis of RLS is based on a clinical interview which we attempted to re-create by having all patients complete the questionnaires either face to face or by telephone. Second, some data such as total sleep duration, sleep efficiency, number of awakenings, and the presence of PLMD would have been more reliably collected by objective monitoring with polysomnography. This would have been costly and more inconvenient for patients which would have reduced our sample size or prolonged the time taken to complete the study. Third, additional measurements such as the IRLSSG rating scale²² that quantifies the severity of RLS symptoms would have enabled us to compare the severity of RLS across the full spectrum of kidney disease. Finally, information from iron studies were not collected, which would have been valuable as iron deficiency is a risk factor for RLS, especially among the elderly.²³ The presence of anemia was recorded and served as an indirect indicator of absolute iron deficiency, in which there is insufficient iron for hemoglobin production.

Despite these limitations, the present study has established that RLS is common and a significant cause of sleep-related symptoms in patients with non-dialysis-dependent CKD and not just in patients with ESRD. Healthcare providers should be aware of this and consider RLS in any patient with kidney disease who reports poor sleep quality. Further research is required to determine whether the severity of RLS changes in individual patients as kidney disease progresses and how detection and treatment of RLS alters clinical outcomes in this patient population.

ABBREVIATIONS

RLS, restless legs syndrome
ESRD, end-stage renal disease
CKD, chronic kidney disease
COPD, chronic obstructive pulmonary disease
IRLSSG, International RLS Study Group
PSQI, Pittsburgh Sleep Quality Index
ESS, Epworth Sleepiness Scale
eGFR, estimated glomerular filtration rate
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
PLMD, periodic limb movement disorder

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