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Restless legs syndrome in end stage renal disease patients undergoing hemodialysis

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Abstract

Background: The prevalence of Restless legs syndrome (RLS) in End Stage Renal Disease (ESRD) patients is higher than that in the general population. However, the associations of RLS within the ESRD population are inconsistent and RLS is usually neglected in dialysis centers, although it impairs the life quality among ESRD patients. We aim to investigate the prevalence of RLS in patients with ESRD undergoing maintenance hemodialysis and evaluate the risk factors of developing RLS and the effect of RLS on quality of life among ESRD patients.

Methods: ESRD patients undergoing maintenance hemodialysis in Shanghai General Hospital dialysis unit from July 2016 to October 2016 were enrolled in the study. RLS was diagnosed according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG). IRLSSG Severity Scale was used to evaluate the severity of RLS. Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality, and Hospital Anxiety and Depression Scale (HADS) was used to estimate anxiety and depression. Serologic and historic variables were analyzed to determine predictors of RLS in the ESRD population.

Results: A total of 137 ESRD patients were enrolled. The prevalence of RLS among the ESRD patients was 20.44%. The risk of RLS was increased significantly in females (OR = 2.729, $p = 0.032$) and daily alcohol drinkers (OR = 4.716, $p = 0.022$). RLS increased the risks of sleep disorders (25/28, 89.3% vs 73/109, 67.0%, $p = 0.02$) and sedative hypnotics intake (7/28, 25.0% vs 10/109, 9.2%, $p = 0.047$) and impaired the sleep quality (7/109 vs 11/28, $p = 0.001$) according to PSQI sum scores.

Conclusion: A high RLS prevalence among the ESRD patients undergoing hemodialysis was confirmed. ESRD patients who are women and drinking alcohol have a higher risk of RLS. The sleep quality was significantly impaired and sleeping medication use was more common among the ESRD patients with RLS.

Keywords: RLS, ESRD, Female, Alcohol intake, Sleep disorder

Background

Restless legs syndrome (RLS) is a common neurological disorder, which can be primary or associated with other conditions. RLS symptoms are characterized by the uncomfortable or abnormal sensations inside the legs or arms, associated with an urge to move the limbs. The symptoms usually occur at rest and at night, and can be temporarily relieved by movement [1]. RLS has an adverse impact on the quality of life and can be associated with mood disorders such as anxiety and depression [2].

In the general population, the prevalence of RLS ranges from 3 to 9%, depending on the age and gender [3]. However, the prevalence of RLS in End Stage Renal Disease (ESRD) characterized as permanent loss of renal function requiring renal replacement therapy or dialysis, is 6.6–70%, which is much higher than the general population [4].

RLS in ESRD patients has been variably reported to be associated with female gender [5, 6], duration of dialysis [4, 7], diabetes mellitus [4, 8–10], iron deficiency anemia [4, 10, 11], parathyroid hormone [12], increased body mass index (BMI) [13], and increased homocysteine [14]. However, results are very inconsistent. [10, 15].

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The occurrence of RLS among the ESRD patients impairs quality of life compared with the ESRD patients without RLS, possibly due to the poor sleep quality, insomnia or depression [9, 16]. Therefore, further studies are needed to determine the prevalence, risk factors and impact of RLS in ESRD patients.

The aim of the study was to investigate the prevalence of RLS in patients with ESRD undergoing maintenance hemodialysis in Shanghai General Hospital, China. We also aimed to evaluate the risk factors of developing RLS and to investigate the effect of RLS on quality of life among ESRD patients.

Methods

Study subjects

All ESRD patients undergoing long-term hemodialysis in the Shanghai General Hospital dialysis unit from July 2016 to October 2016 were approached for our study. Patients will be excluded when they were less than 3 months with hemodialysis duration, less than 18 years old, pregnant, Parkinson's disease, type 1 diabetes mellitus and peripheral neuropathy. The protocol was approved by the ethics committee of Shanghai General Hospital, and written informed consents were obtained.

Study design

Of the 161 ESRD patients enrolled in our study, 24 patients were excluded, including two patients with the less than 3 months of hemodialysis duration, twenty-one patients declined to participate, and one patient had type 1 diabetes mellitus, leaving 137 patients.

All the patients are diagnosed with the detailed history and International Restless Legs Syndrome Study Group (IRLSSG) scale which were carried out by neurologists through face-to-face interviews. The demographic questionnaire included gender, age, height, weight, cause of ESRD, hemodialysis data, other diseases, medication history, family history, personal history, etc. Furthermore, every participant was requested to complete the Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS).

The PSQI is used to evaluate the sleep quality of ESRD patients in seven parts: subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, presence of sleep disturbances, use of hypnotic-sedative medication and daytime dysfunction [17]. Participants with PSQI total scores of ≥5 were considered to have sleep disorders in our study.

The HADS consists of two subscales (HADS-A and HADS-D), which are composed of seven anxiety items and seven depression items respectively. The four options of every item were scored 0–3. The total subscale scores of 8–10 indicate doubtful anxiety or depression and sores of 11 or more indicate definite anxiety or depression [18].

The presence of RLS was assessed using the minimum diagnostic criteria recommended by the International Restless Legs Syndrome Study Group (IRLSSG), which consists of four questions: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and (4) 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 [1]. Participants with four "yes" replied to the four aforementioned questions were diagnosed with RLS. RLS participants completed the IRLSSG Severity Scale with 10 questions for evaluating severity of the RLS symptoms [19]. Patients were classified into four groups with mild (0–10 scores), moderate (11–20 scores), severe (21–30 scores) and very severe (31–40 scores) RLS.

Laboratory blood tests included blood urea nitrogen (BUN), pre-dialysis creatinine, post-dialysis creatinine, albumin, alkaline phosphatase (AKP), calcium, phosphate, hemoglobin, serum iron, ferritin, transferrin, total iron binding capacity (TIBC) and parathyroid hormone (PTH), which were tested within a week of the interview.

Statistical analysis

The data were analyzed via SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). T-test or Mann-Whitney U test was used for continuous variables and Chi-square test was used for categorical variables. The continuous data are presented as mean and standard deviation (normal distribution) or median and quartiles (non-normal distribution). Multivariate analysis was performed by binary logistic regression analysis, which allows adjustment for confounding factors, and all variables that had $p < 0.1$ in univariate analysis were used as independent variables. $p < 0.05$ was considered statistically significant.

Results

The data of 137 patients were analyzed in our study. There were 74 males (54%) and 63 females (46%). The mean age was 55.47 ± 12.76 years old. The mean duration of hemodialysis was 98.35 ± 71.66 months. The causes of ESRD included chronic glomerulonephritis ($n = 89$, 65.0%), hypertensive nephrosclerosis ($n = 17$, 12.4%), diabetic nephropathy ($n = 6$, 4.4%), polycystic kidney disease ($n = 8$, 5.8%), drug induced nephropathy ($n = 5$, 3.6%), vascular kidney disease ($n = 6$, 4.4%), autoimmune nephritis

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(n = 2, 1.5%), and unknown etiology (n = 4, 2.9%). RLS was found in 28 patients (20.44%). Only one of them had been previously diagnosed with RLS and received *pramipexole* treatment. There were 6 patients with mild RLS, 15 patients with moderate RLS, 7 patients with severe RLS and no patients with very severe RLS, based on the IRLSSG rating scale.

Demographic data and routine laboratory blood test data are summarized in Table 1 and Table 2. According to the univariate analyses, BUN (p = 0.014) and serum iron (p = 0.034) were significantly higher in RLS positive group. Female sex (p = 0.08), post-dialysis systolic pressure (p = 0.053) and alcohol intake (p = 0.069) seems to be the risk factors of RLS, but without statistically significance. Age, body mass index (BMI), weeks on hemodialysis, frequency of hemodialysis, dialysis solution temperature,

diabetes mellitus Type 2, family history of RLS, smoking, tea intake, coffee intake and other routine laboratory blood test data including creatinine, albumin, alkaline phosphatase (AKP), calcium, phosphate, hemoglobin, ferritin, transferrin, total iron binding capacity (TIBC), parathyroid hormone (PTH), URR, and Kt/v, showed no relationship with RLS (P Value > 0.05).

All variables that had $p < 0.1$ in univariate analysis, including BUN (p = 0.014), serum iron (p = 0.034), female (p = 0.08), post-dialysis systolic pressure (p = 0.053) and alcohol intake (p = 0.069), were included in multivariable regression analysis to identify independent risk factors of RLS among ESRD patients. We found that only female sex (OR 2.729, 95% CI 1.087–6.849, p = 0.032) and daily alcohol intake (OR 4.716, 95% CI 1.247–17.837, p = 0.022) were significantly independent risk factors.

Table 1 The demographic data of the ESRD patients with and without RLS

Variables		Patients with ESRD, N (%)		
		RLS −(n = 109)	RLS +(n = 28)	p value
Female		46 (42.2%)	17 (58.8%)	0.08
Age (year)		55.83 ± 13.20	54.04 ± 10.40	0.505
Educational Attainment	< Middle school	7 (6.4%)	4 (23.5%)	
	Middle school or vocational	70 (64.2%)	16 (57.1%)	
	High school or higher	32 (29.4%)	8 (28.6%)	0.548
BMI (kg/m2)	Underweight (< 18.5)	18 (16.5%)	6 (21.4%)	
	Normal Range (18.5-23.9)	67 (61.5%)	18 (64.3%)	
	Overweight (24.0-27.9)	20 (18.3%)	3 (10.7%)	
	Obese (≥28.0)	4 (3.7%)	1 (3.6%)	0.346
Duration of Hemodialysis (week)		90 (25-132)	113.5 (39-159.75)	0.224
Frequency of Hemodialysis	3 times/week	102 (93.6%)	25 (89.3%)	0.438
Dialysis Solution Temperature	36 ℃	52 (47.7%)	14 (50.0%)	
	36.5 ℃	46 (42.2%)	10 (35.7%)	
	37 ℃	11 (10.1%)	4 (15.3%)	0.991
Pre-dialysis Systolic Pressure (mmHg)		131.51 ± 20.44	125.36 ± 21.21	0.161
Pre-dialysis Diastolic Pressure (mmHg)		78.97 ± 11.46	77.86 ± 12.80	0.655
Post-dialysis Systolic Pressure (mmHg)		122.89 ± 19.88	115 ± 15.46	0.053
Post-dialysis Diastolic Pressure (mmHg)		74.60 ± 11.71	72.32 ± 11.43	0.358
Diabetes Mellitus		28 (25.7%)	9 (32.1%)	0.734
Hypertension		89 (81.7%)	24 (86.0%)	0.783
Family history	non	94 (86.2%)	22 (78.6%)	
	Hypertension	10 (9.2%)	3 (10.7%)	
	Polycystic kidney	2 (1.8%)	3 (10.7%)	
	Diabetes mellitus	3 (2.8%)	0 (0%)	0.151
Smoking	Daily and regularly	28 (25.7%)	9 (32.1%)	0.493
Alcohol intake	Daily and regularly	7 (6.4%)	5 (17.9%)	0.069
Tea intake	Daily and regularly	43 (39.4%)	9 (32.1%)	0.477
Coffee intake	Daily and regularly	18 (16.5%)	6 (21.4%)	0.58

Abbreviations: *ESRD* end stage renal disease, *RLS* restless legs syndrome, *RLS-* without RLS, *RLS+* with RLS, *BMI* body mass index

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Table 2 Laboratory blood test of the ESRD patients with and without RLS

Variables		Patients with ESRD, N (%)		
		RLS − (n = 109)	RLS + (n = 28)	p value
Blood Urea Nitrogen	mmol/L	27.48 (23.31-31.35)	29.33 (27.3-34.2)	0.014
Pre-dialysis Creatinine	mg/dl	1037 (874.5-1204.5)	1053 (900-1193.5)	0.852
Pro-dialysis Creatinine	mg/dl	350 (276-418)	327 (247-462)	0.378
D-value of Creatinine	mg/dl	685 (559.5-791.5)	699 (641.25-805.75)	0.370
Calcium	mg/dL	2.31 ± 0.26	2.32 ± 0.26	0.744
Phosphorus	mg/dL	1.90 ± 0.47	2.11 ± 0.70	0.155
Ca*P product	mg2/dL^2	4.41 ± 1.30	4.92 ± 1.75	0.157
Albumin	g/dL	39.24 ± 4.24	39.70 ± 6.29	0.650
Alkaline Phosphatase	U/L	73 (54-93.5)	75 (61-98.75)	0.523
Hemoglobin	g/L	100.13 ± 15.54	105.43 ± 22.1	0.240
Serum Iron	μmol/L	13.2 (9.45-16.3)	15.41 (12.5-18.0)	0.034
Ferritin	μg/L	194 (68.85-335.3)	122.5 (53.8-232.99)	0.371
Transferrin	g/L	2.11 (1.83-2.36)	2.14 (1.78-2.45)	0.953
TIBC	μmol/L	47.02 ± 8.49	48.51 ± 9.67	0.424
Parathyroid Hormone	pg/mL	203.9 (65.91-472.1)	258.3 (62.95-574.1)	0.522
Kt/V		1.53 ± 0.61	1.49 ± 0.34	0.783
URR	%	70.19 ± 8.15	70.27 ± 8.05	0.967

Abbreviations: *ESRD* end stage renal disease, *RLS* restless legs syndrome, *RLS-* without RLS, *RLS+* with RLS, *Ca*P product* calcium phosphorus product, *TIBC* total iron-binding capacity, *Kt/V* is a number used to quantify hemodialysis (K, dialyzer clearance of urea; t, dialysis time; V, volume of distribution of urea, approximately equal to patient's total body water); URR, urea reduction ratio

We also compared sleep quality, depression, anxiety and medications between ESRD patients with RLS and those without RLS (Table 3). RLS patients had significantly higher proportion of sleep disorders (89.3% vs 67.0%, *p* = 0.02) and lower sleep quality (11 vs 7, *p* = 0.001) according to PSQI total scores. The proportion of sedative hypnotics intake (25.0% vs 9.2%, *p* = 0.047) was significantly increased in the patients with RLS.

Discussion

The prevalence of RLS among the ESRD patients varies widely in different studies. It was 15.8% in Iran, 22% in Japan, 25.3% in Taiwan, 26.6% in Greek, and 52.6% in Brazil [4, 5, 7, 20, 21]. However, it has not been studied about the prevalence in mainland China. The discrepancy of RLS prevalence among ESRD patients might be influenced by racial heterogeneity, demographic difference [10], diagnostic criteria of RLS [22], differences in dialysis techniques, and methods of study. In our study, all the patients were long-term residence in Shanghai of China.

Table 3 Sleep quality, depression, anxiety and medications between RLS- and RLS+

		Patients with ESRD, N (%)		
		RLS- (n = 109)	RLS+ (n = 28)	P- value
PSQI		7 (4-10)	11 (5.25-13)	0.001
Sleep disorder		73 (67.0%)	25 (89.3%)	0.020
HADS-D		5 (1-9)	3 (1-7)	0.622
Depression	No symptom	70 (64.2%)	22 (78.6%)	0.251
	Suspicious	20 (18.3%)	1 (3.6%)	
	Confirmed	19 (17.4%)	5 (17.9%)	
HADS-A		2 (0-4)	3 (1-6.5)	0.151
Anxiety	No symptom	99 (91%)	25 (89.3%)	0.773
	Suspicious	6 (5.5%)	1 (3.6%)	
	Confirmed	4 (3.7%)	2 (7.1%)	
Medications	Anti-anemia Medicine	85 (78.0%)	23 (82.1%)	0.631
	Sedative hypnotics	10 (9.2%)	7 (25.0%)	0.047

Abbreviations: *ESRD* end stage renal disease, *RLS* restless legs syndrome, *RLS-* without RLS, *RLS+* with RLS, *PSQI* Pittsburgh Sleep Quality Index, *HADS-D* Hospital Anxiety and Depression Scale of Depression, *HADS-A* HADS-Anxiety

RLS diagnosis was made according to the 4 minimum diagnostic criteria of IRLSSG. Our prevalence of RLS among ESRD patients (20.44%) was similar to some large scale studies [4, 5, 10] and significantly higher than among the general Chinese population (7.2%) [23].

Our result reveals that RLS is more common in female ESRD patients (OR = 2.729, *p* = 0.032), similar to some other studies [5, 8, 24]. In general population studies, RLS is consistently more common in females [23, 25], although one German study found this was explained by previous pregnancies, such that null-parous women had similar RLS rates as men [25, 26]. The high level of estrogen during pregnancy could trigger RLS [27]. Interestingly, the concentration of estrogen level is usually high in advanced kidney failure, potentially explaining this [28].

In our study, the ratio of alcohol intake among RLS patients was higher than patients without RLS, which was not significant (*p* = 0.069) in univariate analysis but was significant (*p* = 0.022) in the multivariable backward logistic regression model. Regular alcohol intake increased the risk of developing RLS by 4.72 times in our ESRD patients. One study demonstrated that alcohol intake raised the risk of developing RLS in the general population [29]. However, a potentially protective effect of alcohol on the risk of RLS was found in several studies [30, 31]. These contradictory conclusions can be argued that moderate drinking could reduce the risk of RLS while excessive alcohol consumption could produce and aggravate RLS symptoms [32]. Therefore, additional studies are needed to clarify the role of alcohol in ESRD patients with RLS.

In contrast to some studies [4, 8–10], we found no significant association between diabetes mellitus type 2 and RLS among ESRD patients. It is not clear whether diabetes mellitus itself or diabetic peripheral neuropathy is the dominant risk factor [33]. Some other studies found that there are no correlationship between diabetes mellitus and the occurrence of RLS in ESRD patients [34, 35]. While a multicenter study in Taiwan showed that having type 2 diabetes is associated with RLS [4].

No significant association was found between iron deficiency and anemia, or iron deficiency and RLS among ESRD patients in our study. Iron-Deficiency Anemia (IDA) and the relevant blood parameters were reported as significant risk factors of RLS among the patients with ESRD [4, 10, 11]. Furthermore, the symptoms of RLS have improved with high-dose iron dextran therapy among the ESRD patients, which also suggested that IDA could induce RLS [36] . Other studies showed no relationship between IDA and RLS in ESRD patients [5, 8, 12].

In our study, we didn't find any difference between two groups regarding to Parathyroid hormone (PTH). Previous studies show mixed results. One previous study found PTH levels to be lower in the ESRD patients with RLS than those without RLS [12]. On the contrary, recent studies indicated that PTH was an independent risk factor [5, 37], which is supported by the finding that parathyroidectomy improved RLS in ESRD patients in one study [20]. Nevertheless, some studies suggested that there is no association between PTH and RLS in the ESRD patients [4, 10, 14]. Therefore, further large studies are needed to clarify the relationship between PTH and RLS in ESRD patients.

In our study, we found no statistical difference of BMI between ESRD patients with RLS and those without RLS ($p = 0.346$), which was similar to some other studies of RLS among patient with ESRD. In contrast to the results of our study, some studies indicated that the increasing BMI led to significantly higher odds of developing RLS both in patients with ESRD and in general population [30, 38].

Our study found no significant association between RLS and the duration of hemodialysis, blood pressure on hemodialysis, smoking, tea or coffee intake and blood markers in multivariable backward logistic regression analysis, similar to some previous studies [10, 15, 34, 38].

Previous studies indicated that ESRD patients with RLS suffered from poorer sleep quality than those without RLS [4, 14, 39]. Our study also found significant associations between RLS and sleep-related problems, including prolonged sleep latency, night awakening, shorten sleep duration and sleeping medication use. And also, RLS had an association with impairment of sleep quality among the ESRD patients. Sleep disorders occurred more frequently and sleep quality was poorer among ESRD patients with RLS than those without RLS.

Moreover, ESRD patients with RLS were more likely to require sedative hypnotics to improve their sleep quality.

Depression prevalence in hemodialysis patients was reported to be 15–30%, depending on the method of depression assessment and demographics [40]. The incidence of anxiety in hemodialysis patients ranged from 12 to 52% [41]. In our study, the incidence of confirmed depression in ESRD patients with RLS of 17.4% was similar to the previous studies. However, there was no significant difference in depression between ESRD patients with RLS and without RLS. The incidence of confirmed anxiety in ESRD patients with RLS (7.1%) in our study was lower than those in other studies, and no significant difference of anxiety existed between ESRD patients with RLS and without RLS. Due to the face-to-face interviews in the public area, patients were likely to have misgivings about giving the real answers to the HADS questionnaire. This may be responsible for the irrelevancy between RLS and depression/anxiety.

Several limitations of this study should be noted. Firstly, the cross-sectional design and descriptive nature do not allow for conclusions about the direction of theses relationships. Secondly, this is a single-center study with comparatively small number of participants, which decreases the statistical power. Thirdly, we didn't make formal evaluations to look for peripheral neuropathy. Lastly, in our present study, we only included hemodialysis patients and did not include peritoneal dialysis patients, which partially limits the comparison with previous studies.

Conclusion

Our study confirmed a high incidence of RLS among the ESRD patients undergoing maintenance hemodialysis. Among ESRD patients, the risk of RLS was significantly increased in females and alcohol users. The sleep quality was significantly impaired and sleeping medication use was more frequent among the ESRD patients with RLS. High prevalence of RLS among ESRD patients suggests the need for clinicians to improve awareness and recognition of RLS among ESRD patients. Although the risk factors of RLS among ESRD patients were identified by many studies, the results are still disputable. Therefore, more multicenter studies are needed to confirm the various risk or protective factors in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LXW, ZJF, QMY and NLY collected and analyzed data, and drafted the manuscript. LXY, ZJF and QMY participated in the acquisition and interpretation of data, and were involved in revising the manuscript. KSH, WO and YHL helped to revise the manuscript. YQ and WYC made contributions to supervision in data collection and management and revising the manuscript. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai General Hospital. All patients provided written informed consent to participate. A copy of the written consent is available for review by the Editor of this journal.

Consent for publication

Not applicable

Competing interests

Yun-Cheng Wu is an Editorial Board Member of BMC Neurology. Other authors declare that they have no competing interests.

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References

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome D, epidemiology workshop at the National Institutes of H, international restless legs syndrome study G. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4(2):101–19.
2. Abetz L, Allen R, Follet A, Washburn T, Earley C, Kirsch J, Knight H. Evaluating the quality of life of patients with restless legs syndrome. Clin Ther. 2004;26(6):925–35.
3. Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. Lancet Neurol. 2005;4(8):465–75.
4. Lin CH, Wu VC, Li WY, Sy HN, Wu SL, Chang CC, Chiu PF, Lion HH, Lin CY, Chang HW, Lin SY, Wu KD, Chen YM, Wu RM. Restless legs syndrome in end-stage renal disease: a multicenter study in Taiwan. Eur J Neurol. 2013; 20(7):1025–31.
5. Stefanidis I, Vainas A, Dardiotis E, Giannaki CD, Gourli P, Papadopoulou D, Vakianis P, Patsidis E, Eleftheriadis T, Liakopoulos V, Pournaras S, Sakkas GK, Zintzaras E, Hadjigeorgiou GM. Restless legs syndrome in hemodialysis patients: an epidemiologic survey in Greece. Sleep Med. 2013;14(12):1381–6.
6. La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML, Centofanti F, Carretta E, Plazzi G, Coli L, Montagna P, Stefoni S. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. Nephrol Dial Transplant. 2011;26(6):1976–83.
7. Beladi-Mousavi SS, Jafarizade M, Shayanpour S, Bahadoram M, Moosavian SM, Houshmand G. Restless legs syndrome: associated risk factors in hemodialysis patients. Nephrourol Mon. 2015;7(6):e31967.
8. Rafie S, Jafari M, Azizi M, Bahadoram M, Jafari S. Restless legs syndrome in hemodialysis patients. Saudi J Kidney Dis Transpl. 2016;27(2):326–30.
9. Yildiz D, Kahvecioglu S, Buyukkoyuncu N, Kilic AK, Yildiz A, Gul CB, Seferoglu M, Tufan F. Restless-legs syndrome and insomnia in hemodialysis patients. Ren Fail. 2016;38(2):194–7.
10. Mao S, Shen H, Huang S, Zhang A. Restless legs syndrome in dialysis patients: a meta-analysis. Sleep Med. 2014;15(12):1532–8.
11. Kavanagh D, Siddiqui S, Geddes CC. Restless legs syndrome in patients on dialysis. Am J Kidney Dis. 2004;43(5):763–71.
12. Collado-Seidel V, Kohnen R, Samtleben W, Hillebrand GF, Oertel WH, Trenkwalder C. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. Am J Kidney Dis. 1998;31(2):324–8.
13. Zadeh Saraji N, Hami M, Boostani R, Mojahedi MJ. Restless leg syndrome in chronic hemodialysis patients in Mashhad hemodialysis centers. J Renal Inj Prev. 2017;6(2):137–41.
14. Gade K, Blaschke S, Rodenbeck A, Becker A, Anderson-Schmidt H, Cohrs S. Uremic restless legs syndrome (RLS) and sleep quality in patients with end-stage renal disease on hemodialysis: potential role of homocysteine and parathyroid hormone. Kidney Blood Press Res. 2013;37(4–5):458–63.
15. Chu L, Chu E, Dogra G, Chakera A. Restless legs syndrome: an underappreciated and distressing problem for haemodialysis patients. Intern Med J. 2014;44(10):1030–3.
16. Giannaki CD, Sakkas GK, Karatzaferi C, Hadjigeorgiou GM, Lavdas E, Liakopoulos V, Tsianas N, Koukoulis GN, Koutedakis Y, Stefanidis I. Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome. PLoS One. 2011;6(10):e25180.
17. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
19. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C. International restless legs syndrome study G. Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med. 2003;4(2):121–32.
20. Santos RS, Coelho FM, Silva BC, Graciolli FG, Dominguez WV, Menezes Montenegro FL, Jorgetti V, Moyses RM, Elias RM. Parathyroidectomy improves restless leg syndrome in patients on hemodialysis. PLoS One. 2016;11(5):e0155835.
21. Higuchi T, Abe M, Mizuno M, Yamazaki T, Suzuki H, Moriuchi M, Oikawa O, Okawa E, Ando H, Okada K. Association of restless legs syndrome with oxidative stress and inflammation in patients undergoing hemodialysis. Sleep Med. 2015;16(8):941–8.
22. Novak M, Winkelman JW, Unruh M. Restless legs syndrome in patients with chronic kidney disease. Semin Nephrol. 2015;35(4):347–58.
23. Li LH, Chen HB, Zhang LP, Wang ZW, Wang CP. A community-based investigation on restless legs syndrome in a town in China. Sleep Med. 2012;13(4):342–5.
24. Aritake-Okada S, Nakao T, Komada Y, Asaoka S, Sakuta K, Esaki S, Nomura T, Nakashima K, Matsuura M, Inoue Y. Prevalence and clinical characteristics of restless legs syndrome in chronic kidney disease patients. Sleep Med. 2011; 12(10):1031–3.
25. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med. 2004; 164(2):196–202.
26. Sun D, Shao H, Li C, Tao M. Sleep disturbance and correlates in menopausal women in Shanghai. J Psychosom Res. 2014;76(3):237–41.
27. Gupta R, Dhyani M, Kendzerska T, Pandi-Perumal SR, BaHammam AS, Srivanitchapoom P, Pandey S, Hallett M. Restless legs syndrome and pregnancy: prevalence, possible pathophysiological mechanisms and treatment. Acta Neurol Scand. 2016;133(5):320–9.
28. Lim VS, Fang VS. Restoration of plasma testosterone levels in uremic men with clomiphene citrate. J Clin Endocrinol Metab. 1976;43(6):1370–7.
29. Aldrich MS, Shipley JE. Alcohol use and periodic limb movements of sleep. Alcohol Clin Exp Res. 1993;17(1):192–6.
30. Batool-Anwar S, Li Y, De Vito K, Malhotra A, Winkelman J, Gao X. Lifestyle factors and risk of restless legs syndrome: prospective cohort study. J Clin Sleep Med. 2016;12(2):187–94.
31. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med. 2000;160(14):2137–41.
32. Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M, Gigli GL. Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. Nephrol Dial Transplant. 2006;21(1):184–90.

33. Trenkwalder C, Allen R, Hogl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases: a systematic review and new concept. Neurology. 2016;86(14):1336–43.
34. Bathla N, Ahmad S, Gupta R, Ahmad S. Prevalence and correlates of Willis-Ekbom's disease/restless legs syndrome in patients undergoing hemodialysis. Saudi J Kidney Dis Transpl. 2016;27(4):685–91.
35. Araujo SM, de Bruin VM, Nepomuceno LA, Maximo ML, Daher Ede F, Correia Ferrer DP, de Bruin PF. Restless legs syndrome in end-stage renal disease: clinical characteristics and associated comorbidities. Sleep Med. 2010;11(8): 785–90.
36. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. Am J Kidney Dis. 2004;43(4):663–70.
37. Schneider R, Karakas E, Bartsch DK, Schlosser K. The influence of parathyroidectomy on restless legs syndrome in patients with renal hyperparathyroidism. World J Surg. 2013;37(12):2866–71.
38. Wali SO, Alkhouli AF. Restless legs syndrome among Saudi end-stage renal disease patients on hemodialysis. Saudi Med J. 2015;36(2):204–10.
39. Plantinga L, Lee K, Inker LA, Saran R, Yee J, Gillespie B, Rolka D, Saydah S, Powe NR, Team CCS. Association of sleep-related problems with CKD in the United States, 2005-2008. Am J Kidney Dis. 2011;58(4):554–64.
40. Weisbord SD. Patient-centered Dialysis care: depression, pain, and quality of life. Semin Dial. 2016;29(2):158–64.
41. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis. 2007; 14(1):82–99.