https://doi.org/10.29309/TPMJ/2022.29.07.6359

The Professional Medical Journal
www.theprofesional.com
2022, Volume, 29 Issue, 07

ORIGINAL ARTICLE

Restless leg syndrome and associated factors in patients with end-stage renal disease on haemodialysis.

Muhammad Ali[1], Abdul Manan Junejo[2], Vinod Kumar[3], Ayesha Ejaz[4], Hina Iram[5], Shafique Ahmed[6]

Article Citation: Ali M, Junejo AM, Kumar V, Ejaz A, Iram H, Ahmed S. Restless leg syndrome and associated factors in patients with end-stage renal disease on haemodialysis. Professional Med J 2022; 29(7):975-980. https://doi.org/10.29309/TPMJ/2022.29.07.6359

ABSTRACT… Objective: To assess the frequency and the risk factors associated with restless leg syndrome (RLS) in patients suffering from end-stage renal disease (ESRD) on hemodialysis. **Study Design:** Cross-sectional Observational study. **Setting:** Department of Nephrology, Jinnah Postgraduate Medical Centre, Karachi, Pakistan. **Period:** 1st of January 2020 till 30th of June 2020. **Material & Methods:** We enrolled the patients in this study after written consent and were assessed for RLS according to the International RLS Study Group criteria. Serum samples were collected for hemoglobulin level, parathyroid hormone level, vitamin D, serum urea and creatinine, and serum ferritin. The sampling technique used was non-probability, variables were recorded as mean and standard deviation and frequency. **Results:** Ninety-four patients were included in this study; men comprised 65.95% of the patients, and women comprised 34.04%. The mean age in the study was 45.51±13.29 years. Diabetes mellitus was the most common cause (47.87%). The mean duration on the hemodialysis was 5.21 years, and the mean vitamin D level was 24.36 mg/dl. RLS was observed in 26 (27.65%) patients and was significantly associated with low vitamin D and time duration on hemodialysis. **Conclusion:** The RLS seems to be a common consequence of ESRD, and it has a significant impact on the ESRD patients' everyday lives and sleeping patterns. There is a definitive link between RLS and hemodialysis duration; however, more large multicenter studies are still needed to establish and investigate the etiology.

Key words: Anxiety, End-stage Renal Disease, Hemodialysis, Insomnia, Restless Leg Syndrome, Therapy.

INTRODUCTION

Restless leg syndrome (RLS), often called the Will–Ekbom illness is a neurologic somatosensory ailment characterized by degenerative alterations in motor and sensory brain areas, iron deficiency in particular.[1] Patients with RLS have pain in their legs or other portions of their bodies. The feelings of stiffness, wormier sensation, itching, swelling, numbness, soreness, burning, and agony are some of the symptoms, which cause people to move their limbs to relieve the pain.[1] Depending on the cause, RLS can be classed as primary or secondary.[1] RLS has been strongly linked to genetics: around 60% of patients have a strong genetic component related to the disease.[1]

Secondary RLS is associated mostly with end-stage renal disease (ESRD).[1] Therefore, it is critical to recognize the associated factors for RLS in Hemodialysis (HD) patients to provide the best possible therapy.[1] The fundamental explanation of the higher occurrence of RLS in HD patients, unfortunately, remains unknown.[1] Chronic kidney diseases are the ninth leading health problem and cause of death in the USA.[2] Hill et al. (2016) found in a meta-analysis and systematic review that global chronic kidney disease (CKD) prevalence is between 11% and 13%.[3] The prevalence of ESRD in Pakistan is 14.6 million, or 14.3% of the population.[4] Treatments for CKD patients include renal replacement therapy, renal transplantation, and dialysis, which may be either HD or peritoneal dialysis. Renal replacement therapy creates an economic and social burden, leading to anxiety and sleep disturbances. People with CKD are expected more to have dyslipidemia, as well as around half of patients with CKD, have hypertriglyceridemia.[5]

1. MBBS, FCPS, Assistant Professor Nephrology, Fazaia Ruth Pfau, Medical College,
2. MBBS, FCPS, Professor Nephrology, Jinnah Postgraduate Medical Centre
3. MBBS, FCPS, Assistant Professor, Sir Syed College of medical sciences, of Medical Sciences for Girls
4. MBBS, FCPS, Assistant Professor Nephrology, Jinnah Postgraduate Medical Centre
5. MBBS, Senior registrar Nephrology, Jinnah Postgraduate Medical Centre.
6. MBBS, Registrar Nephrology, Jinnah Postgraduate Medical Centre.

Correspondence Address:
Dr. Muhammad Ali
Department of Nephrology
Fazaia Ruth Pfau, Medical College,
maunar2002@gmail.com

Article received on: 15/01/2021
Accepted for publication: 17/01/2022

Though the total cholesterol and the low-density lipoprotein cholesterol (LDL-C) levels in this subgroup were either normal or high, high-density lipoprotein cholesterol (HDL-C) levels remained lower.[5]

RLS affects the quality of life in ESRD patients, compared to ESRD patients who do not have RLS, probably resulting from poor sleep patterns, insomnia, or sadness.[6,7] The symptoms of RLS, or Willis-Ekbom disease, are one of the reasons for insomnia; it is related to a neurological syndrome which is manifested as the bumpy or horrible sensation during rest and causes 50–80% of insomnia due to sleep disturbance, impacting patients' mental health and daily life.

In 2012, the International RLS Study Group produced the diagnostic criteria for RLS, which included five primary diagnostic criteria:

(I) Patients have a strong desire to move their legs due to unpleasant sensations and discomfort
(II). During periods of sitting, lying down, inactivity, or rest, this urge becomes stronger
(III). Exercises like stretching and walking provide alleviation.
(IV) As a result of increased inactivity, the desire for leg movement and the accompanying restlessness develops at night
(V). One of the primary causes of poor quality of life in the general population is RLS.

Sleep disturbances in HD patients can cause major problems with psychological health, overall health, body discomfort, exhaustion, and functional capacity. For hemodialysis patients, the coexistence of sleep problems and depression might have serious repercussions.[8] Even though precise mechanism is unspecified, the nonconfirmatory pathophysiological concepts for the uremic RLS include the distorted transferrin expression inside the choroid plexus, enhanced glutamate concentration inside thalamus, lessened opioid receptors, dopamine system dysfunction, calcium/phosphate discrepancy, and single nucleotide polymorphisms within BTBD9 and MEIS1 genes.[9] Nonpharmaceutical treatments comprise reducing the dialysis fluid temperature by 1 °C temperature and using home-based therapy such as massage techniques, contrast baths, and cardiovascular workouts.[9] Medical management, such as the dopamine agonists ropinirole and pramipexole, effectively lowers the effects.[9] Surgical therapies such as parathyroidectomy and renal transplantation, on the other hand, are recommended for individuals with the uremic RLS.[9] RLS patients, particularly those who have ESRD, need to be diagnosed early to avoid muscle atrophy and improve their quality of life.[9] Due to the concomitant discomfort and shortening of HD treatment, cardiac death is significant in uremic RLS patients.[9] RLS could be idiopathic or might be secondary to other conditions, for instance, pregnancy, rheumatoid arthritis, iron deficiency, diabetes mellitus, and uremia.

As a result, more research is needed to understand the frequency, factors associated, and consequences of the RLS in individuals with the disease. The purpose of this study is to assess the burden of RLS along with its associated risk factors in HD patients so that early recognition and management of correctable factors can be addressed to avoid RLS.

MATERIAL & METHODS

A cross-sectional, observational study was conducted at the Department of Nephrology, from January 1 to June 30, 2020, with approval of the institutional ethical board (letter-number F.81/2020-GEN/49235/JPMC). Patients were enrolled in the current study after written consent. All patients were examined according to the 2012 International RLS Study Group approved criteria for diagnosis of RLS. Serum samples were collected to determine Hb level, iPTH level, vitamin D, urea and creatinine, ferritin.

The sampling technique used was non-probability, and both male and female patients aged 14–85 years on HD were included. The study included the patients who were suffering from ESRD on HD, while patients who were suffering from Parkinson's disease, were pregnant, had arthritis, leg edema, myalgia, venous stasis, habitual foot tapping, and positional discomfort were excluded.

IBM SPSS package version 22 was used for statistical analysis. Age, gender, single pool Kt/V, urea reduction ratio, and other variables were recorded as mean and standard deviation [SD], while the sessions, years, type of access, and RLS were measured as frequency and percentages. The independent t-test was applied to determine the correlation of RLS with any variable factors.

RESULTS

We studied 94 patients; 65.95% were male, and 34.04% were female, with a mean age of 45.51±13.29. The main cause of CKD was diabetes mellitus (47.87%).

RLS was diagnosed in 27.65% (n=26) of the patients, of which 14 were male and 12 were female. There were 16 diabetics (Table-I).

	Frequency (%)	RLS+VE	RLS–VE
Males	62 (65.95%)	14	48
Females	32 (34.04%)	12	20
Diabetes Mellitus	45 (47.87%)	16	29
Others	49 (52.12%)	10	39

Table-I. Patients' genders and causes of ESRD Abbreviations: ESRD (End-stage renal disease), RLS (Restless leg syndrome), DM (Diabetes mellitus), +VE (Positive), -VE (Negative).

Most of the patients (61.70%) were undergoing three HD sessions per week, and 37.23% received two per week (the overall mean = 2.60±0.51).

In our study, we found that 51.06% of patients were on HD for more than five years, 23.40% were on it for three years, and 19.15% patients for four years, respectively (overall mean = 5.21±1.00). In our patients, the mean urea reduction ratio was 64.07, and the mean single pool Kt/V was 0.11 (Table-II).

Dialysis Sessions	
Sessions Per Week	**Number of Patients (%)**
One	1 (1.06%)
Two	35 (37.23%)
Three	58 (61.70%)
	Mean 2.60±0.51
Dialysis Duration	
Less than 6 months	2 (2.12%)
One year	1 (1.06%)
Two years	3 (3.19%)
Three years	22 (23.40%)
Four years	18 (19.15%)
>Five years	48 (51.06%)
	Mean 5.21±1.00 years
Dialysis Adequacy	
URR	Mean 64.07±4.40
SpKt/V	Mean 1.22±0.11

Table-II. Patient parameters of hemodialysis Abbreviations: URR (urea reduction ratio), SpKt/V (single pool Kt/v)

Patients' mean hemoglobulin was 9.27, mean iron was 91.50, the vitamin D deficiency was found with a mean value of 24.36, and mean creatinine was 7.95 mg/dL (Table-III).

We found a significant correlation between vitamin D deficiency and RLS (p = 0.001). RLS was also associated with the duration of hemodialysis (p=0.019). (Table-IV)

	Age	Uric Acid	Hb	Vit-D	PTH	Iron	T-Stat	Calcium	Albumin	Cr	URR	SpKt/V
Mean	45.51	8.16	9.27	24.36	578.72	91.50	36.55	8.11	3.33	7.95	64.07	1.22
SD	13.20	15.41	1.38	13.03	583.15	41.61	16.16	.82	.53	2.50	4.40	0.11

Table-III. Mean values of parameters

	URR	SpKt/v	year	Cause	HB	Vit-D	Gender	Iron	T-Stat	PTH	Calc	Cr
RLS	.01	.03	-.24*	.09	-.02	.34**	-.18	-.00	.13	.11	.01	.02
	.91	.71	.02	.35	.84	.00	.06	.96	.19	.27	.88	.82

Table-IV. Correlation of RLS with study parameters
*** Correlation is significant at the 0.05 level (2-tailed).**
**** Correlation is significant at the 0.01 level (2-tailed).**

DISCUSSION

RLS in the patients undergoing HD is being associated with low-spirited quality of life, high immunology and cardiac diseases, high blood pressure, sleep deprivation, daytime sleepiness, fatigue, and daytime function disorders. We found the prevalence of RLS to be 27.65% in patients on maintenance HD; 14 were male patients and 12 were found to be females, with a mean age of 45.51 years. This is in correspondence with the research done in Karachi at the Institute of Kidney Diseases where the prevalence of RLS was 26.7%.[10] Like our results, 26.6% RLS prevalence in ESRD patients was identified in a study conducted in Greece.[11] Giannaki et al. also had similar frequency results as ours (27.1%).[12] Furthermore, it was found in a study in Shanghai that out of 137 patients, 28 (20.44%) were experiencing RLS in ESRD patients enduring the HD.[13] Prevalence of the RLS in patients on HD varies in different regions of country and world, ranging from 15% to 60%. Iqra et al. (2018) found a much higher prevalence of RLS (64.8%) in Lahore.[14] Another study stated this frequency on a higher side with 35.8% of ESRD patients suffering from RLS with HD.[15] Whereas, in a study conducted in Saudi Arabia, it was found that there was 16.8% occurrence of RLS among chronic renal failure patients.[16] Such variation in prevalence may be due to the heterogeneity of the study populations and associated factors that could aggravate the RLS.

In our study, there was no significant relation between HD adequacy and Hb, frequency of hemodialysis, age, gender, calcium, phosphorous, iPTH, iron, and cause of ESRD. There was no significant association found to be related to the iron deficiency, anemia, or iron deficiency in relation with the RLS in ESRD patients in the literature[13] which was similar to ours because we also did not find any association between these risk factors. Moreover, the same disconnect of RLS with iron deficiency was seen in a study in Saudi Arabia.[17] While in contrast, Iqra et al. found a higher prevalence in female patients and found a relation to age.[14] Another study supported this narrative and found females suffering more than males from RLS.[18] The mean duration of HD in our patients (Table-II) was 5.212 years, with a frequency of 2.606 sessions per week**,** URR 64.074, and SpKt/V 1.225. We found a significant correlation between RLS and the duration of HD (Table-III). One reason for this may be that prolonged duration leads to the accumulation of middle molecules in a process similar to the accumulation of dialysis-related amyloids. A statistically significant correlation was found between the RLS and the duration of dialysis in a study done in 2020.[15] A longer duration of dialysis along with low HDL levels was associated with RLS in a study done in Baltimore.[19] Ul Abideen et al.[20], and Beladi-Mousavi[21] also reported similar findings. Opposing to this was seen in several studies done with no relation found.[13,22] In correspondence to this, a study in Italy concluded no association between the frequency of dialysis and RLS among the patients.[23] Further studies may be necessary to explain this phenomenon.

In our study, it was also found that RLS and Vitamin D had a significant relationship (Table-IV). These findings are also supported by Huzmeli et al.[24] There was a recent study done showing that patients with low vitamin D levels experience RLS more often proving the same point of view as discussed in the current study.[25] In similarity to this, Almeneessier et al. noticed Vitamin D as a profound propagating factor for RLS.[26] A meta-analysis was published reporting a significant correlation of serum Vitamin D levels with the RLS.[27] Vitamin D level deficiency causes muscle and bone pain, which may be associated with or aggravate symptoms of RLS. Oran et al. (2014) found that symptoms of RLS improved along with vitamin D deficiency and stated that there might be a possible correlation between the vitamin D deficiency and idiopathic type of RLS.[28]

There were limitations present in the current literature. To begin with, cross-sectional design and the observational nature of data made it impossible to draw inferences regarding the direction of these associations. Moreover, since this is a single-center study with limited patients, statistical power is reduced. Furthermore, we did not conduct systematic assessments to look for nerve damage. Finally, we only included

hemodialysis patients in this study and excluded the peritoneal dialysis patients, thereby limiting the comparability with other investigations.

CONCLUSION

RLS seems to be a common consequence of ESRD, and it has a significant impact on the ESRD patients' everyday lives and sleeping patterns. The RLS is linked to considerable morbidity and increased cardiovascular events, hence the early detection and adjustment of the related factors are critical for ESRD patients' long-term health. There is a definitive link between RLS and hemodialysis duration; however, larger multicenter studies are still needed to establish and investigate the etiology.

REFERENCES

1. Tsai LH, See LC, Chien CC, Chen CM, Chang SH. **Risk factors for restless legs syndrome in hemodialysis patients in Taiwan: A case–control study.** Medicine. 2019; 98(51). doi:10.1097/MD.0000000000018450

2. **Centers for disease control and prevention: Deaths and mortality.** (2017). Accessed: May 1, 2019: http://www.cdc.gov/nchs/fastats/deaths.htm.

3. Hill NR, Fatoba ST, Oke JL, et al. **Global prevalence of chronic kidney disease-a systematic review and meta-analysis.** PLoS One. 2016, 11:e0158765. doi:10.1371/journal.pone.0158765.

4. Bikbov B, Purcell CA, Levey AS, et al. **Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017.** Lancet. 2020, 395(10225):709–33. doi:10.1016/S0140-6736(20)30045-3

5. Qunibi WY. **Dyslipidemia in dialysis patients. In Seminars in dialysis.** 2015, 28(4):345-353. doi:10.1111/sdi.12375

6. Yildiz D, Kahvecioğlu S, Buyukkoyuncu N, et al. **Restless-legs syndrome and insomnia in hemodialysis patients.** Renal failure. 2016; 38(2):194-7. doi:10.3109/0886022X.2015.1111118

7. Giannaki CD, Sakkas GK, Karatzaferi C, et al. **Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome.** PLoS One. 2011; 6(10):e25180. doi:10.1371/journal.pone.0025180

8. Turk AC, Ozkurt S, Turgal E, Sahin F. **The association between the prevalence of restless leg syndrome, fatigue, and sleep quality in patients undergoing hemodialysis.** Saudi medical journal. 2018; 39(8):792. doi:10.15537/smj.2018.8.22398

9. Kambampati S, Wasim S, Kukkar V, Awad VM, Malik BH. **Restless leg syndrome in the setting of patients with end-stage renal disease on hemodialysis: A literature review.** Cureus. 2020; 12(8). doi:10.7759/cureus.9965

10. Yaseen M, Jarullah FA, Yaqoob S, Shakeel HA, Maqsood H, Naveed S. **Association of quality of life, anxiety, and depression with restless leg syndrome in the hemodialysis patients.** BMC Res Notes. 2021, 14(1):284. doi:10.1186/s13104-021-05701-w

11. Santos RS, Coelho FM, Silva BC, et al. **Parathyroidectomy improves restless leg syndrome in patients on hemodialysis.** PLoS One. 2016; 11(5):e0155835. doi:10.1371/journal.pone.0155835

12. Giannaki CD, Hadjigavriel M, Lazarou A, et al. **Restless legs syndrome is contributing to fatigue and low quality of life levels in hemodialysis patients.** World J Nephrol. 2017; 6(5):236-242. doi:10.5527/wjn.v6.i5.236

13. Lin XW, Zhang JF, Qiu MY, et al. **Restless legs syndrome in end stage renal disease patients undergoing hemodialysis.** BMC neurology. 2019; 19(1):1-7. doi:10.1186/s12883-019-1265-y

14. Sagheer I, Iqbal F, Zulfiqar A. **A cross-sectional research on restless legs syndrome (RLS) in the patients of end stage renal disease (ESRD) and its associated risk factors in the light of revised international RLS criteria.** Indo American J Pharm Sci. 2018; 5(5):4186–90. doi: 10.5281/zenodo.1252409

15. Raja J. **Burden of restless leg syndrome in patients with end stage renal disease undergoing maintenance hemodialysis** (Doctoral dissertation, University of Nairobi); 2020.

16. Turk AC, Ozkurt S, Turgal E, Sahin F. **The association between the prevalence of restless leg syndrome, fatigue, and sleep quality in patients undergoing hemodialysis.** Saudi medical journal. 2018; 39(8):792.

17. Rafie S, Jafari M, Azizi M, Bahadoram M, Jafari S. **Restless legs syndrome in hemodialysis patients.** Saudi Journal of Kidney Diseases and Transplantation. 2016; 27(2):326.

18. Einollahi B, Izadianmehr N. **Restless leg syndrome: A neglected diagnosis. Nephro-urology monthly.** 2014; 6(5). doi:10.5812/numonthly.22009

19. Tsai LH, See LC, Chien CC, Chen CM, Chang SH. **Risk factors for restless legs syndrome in hemodialysis patients in Taiwan: A case–control study.** Medicine. 2019 Dec; 98(51).

20. Abideen ZU, Mahmud SN, Mushtaq F, et al. **Association of hemodialysis inadequacy and duration with restless legs syndrome: A cross-sectional study.** Cureus. 2018; 10(5). doi:10.5812/numonthly.31967.

21. Beladi-Mousavi SS, Jafarizade M, Shayanpour S, Bahadoram M, Moosavian SM, Houshmand G. Restless legs syndrome: associated risk factors in hemodialysis patients. Nephro-urology monthly. 2015; 7(6). doi: 10.5812/numonthly.31967

22. Bathla N, Ahmad S, Gupta R, Ahmad S. **Prevalence and correlates of Willis-Ekbom's disease/restless legs syndrome in patients undergoing hemodialysis.** Saudi Journal of Kidney Diseases and Transplantation. 2016; 27(4):685. doi: 10.4103/1319-2442.185224

23. Capelli I, Pizza F, Ruggeri M, et al. **Time evolution of restless legs syndrome in haemodialysis patients.** Clinical Kidney Journal. 2021; 14(1):341-7. doi: 10.1093/ckj/sfz148

24. Hüzmeli C, Candan F, Timucin M, et al. **The relationship between restless leg syndrome and 25-hydroxy D vitamin in hemodialysis patients.** Age. 2018; 75(57.8):19–84. doi:10.5664/jcsm.7044

25. Liu HM, Chu M, Liu CF, Zhang T, Gu P. **Analysis of Serum Vitamin D Level and related factors in patients with restless legs syndrome.** Frontiers in neurology. 2021; 12:782565-. doi: 10.3389/fneur.2021.782565

26. Almeneessier AS, Alzahrani M, Alsafi A, Alotaibi R, Olaish AH, BaHammam AS. **Prevalence and predictors of restless legs syndrome in non-pregnant Saudi women of childbearing age.** Sleep and Breathing. 2020; 24(3):1107-13. doi: 10.1007/s11325-020-02054-9

27. Mansourian M, Rafie N, Khorvash F, Hadi A, Arab A. **Are serum vitamin D, calcium and phosphorous associated with restless leg syndrome? A systematic review and meta-analysis.** Sleep Medicine. 2020. doi: 10.1016/j.sleep.2020.08.022

28. Oran M, Unsal C, Albayrak Y, et al. **Possible association between vitamin D deficiency and restless legs syndrome.** Neuropsychiatric disease and treatment. 2014; 10:953. doi: 10.2147/NDT.S63599

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Ali	Conception.	
2	Abdul Manan Junejo	Conception.	
3	Vinod Kumar	Design.	
4	Ayesha Ejaz	Interpretation of data.	
5	Hina Iram	Interpretation of data.	
6	Shafique Ahmed	Analysis.	