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Association of Various Factors with Restless Leg Syndrome in Patients of Chronic Kidney Disease

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ABSTRACT

Objective: To explore the association of anemia, stage of chronic kidney disease, diabetes mellitus, age of the patient, and duration of chronic kidney disease/hemodialysis with restless leg syndrome in patients of chronic kidney disease.
Study Design: Cross-sectional study
Place and Duration of Study : Combined Military Hospital Sialkot, Pakistan from Jun to Dec 2022.
Methodology: A total of 250 patients were included in the study. Sampling was done using the nonprobability consecutive sampling technique. Patients' clinical evaluation was done for restless leg syndrome.
Results: Out of 250 patients, 176(70.4%) were males and 74(29.6%) were females with a mean age of 47.6±12 years. Restless leg syndrome was observed in 82(32.8%) patients with chronic kidney disease. The 59(72.0%) males and 23(28.0%) females had restless leg syndrome. No significant difference among gender, smoking, BMI, alcohol consumption, and restless leg syndrome was observed. Significant difference among age groups, diabetes, anemia, duration, and stages of chronic kidney disease with *p*-value <0.001 was observed.
Conclusions: Restless leg syndrome is prevalent in chronic kidney disease patients and is associated with anemia, stage of chronic kidney disease, duration of chronic kidney disease, diabetes mellitus, and age of the patient.

Keywords: CKD, Restless leg syndrome, risk factors, RLS prevalence

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INTRODUCTION

Restless leg syndrome (RLS) also known as Willis-Ekbom disease (WED) is one of the most unrecognized chronic motor-neurological disorders in renal failure patients.[1] In the general adult population, the prevalence of RLS is 3.5-10%.[2] However, in the case of End Stage Renal Disease (ESRD) which is the permanent renal dysfunction following dialysis or renal replacement therapy, the prevalence of RLS is significantly higher than that of the general population i.e., 6.6-70%.[3]

RLS is a strong urge to shake limbs,[4] due to the constant unpleasant sense of restlessness at rest or sleep, mostly during the night.[5,6] Having an overwhelming urge to move limbs; primarily legs, both men and women experience daily drowsiness and insomnia and tend to walk during the night. Thus, it highly affects the quality of life, interferes with their daily functioning, and can result in psychological disorders. The predominant effect of RLS is on legs and feet but a rare one can be on arms.[1,6,7] Complex environmental and genetic interactions determine RLS manifestations. Hence, the disease becomes an interesting model to find out gene expression via its interactions with the environment. In some patients, RLS diagnosis can be challenging, specifically in elder patients and pediatrics. As per a study, after some years of therapy with drugs especially when dopaminergic agents are used, effective treatment has been seen to achieve with difficulty. In addition to this, there lies an interesting example of genetics and environmental interaction in the pathophysiology of the disease, when the involvement of strong iron metabolism and iron's interaction with its factors of genes are considered.[8] RLS can happen at any age and is classified into two types primary (idiopathic) and secondary (symptomatic).[6,9] Primary RLS suggests a genetic predisposition because 40% of the cases present positive family history,[10] However, secondary RLS is associated with renal failure, diabetes, pregnancy, neuropathy, rheumatoid arthritis, and iron deficiency anemia.[7]

Symptoms of RLS include electrical sensations, throbbing, itching, crawling, and creeping1. Among many complications of chronic kidney disease (CKD), RLS is one of the complications in hemodialysis patients.[10] To improve the quality of life of RLS patients and to prevent muscular atrophy, early diagnosis is very essential, especially for those with

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end stage renal disease.[1] There have been variable reports on the association between RLS in ESRD patients, diabetes mellitus, duration of dialysis, iron deficiency anemia, higher body mass index (BMI), and higher parathyroid and female gender. Yet, the results are not consistent.[2] Due to non-consistency of results as well as paucity of local data available on RLS, further studies are needed to determine the consistent results of an association between various above-listed factors and RLS in patients with CKD.

This study aimed to investigate the association of various factors such as anemia, stage of CKD, diabetes mellitus, age of the patient, and duration of CKD/hemodialysis with restless leg syndrome in patients with chronic kidney disease in our local population.

METHODOLOGY

This was a cross-sectional study. The study was conducted at Combined Millitary Hospital, Sialkot for a duration of six months from June 2022 to December 2022. Institutional Review Board (IRB) (vide reference number ERC/02/2023) provided us the ethical clearance. After a thorough literature search, a sample size of 241 was calculated using a WHO calculator, keeping a 5% margin of error, 95% confidence level, and an expected prevalence of RLS in ESRD patients of 19.4%.[12] Sampling was done using the nonprobability consecutive sampling technique. 250 participants were included in this study.

Inclusion Criteria: Chronic Kidney Disease (CKD) patients ranging between 20-80 years of age and suffering from a disease for at least ≥ 3 months were included.

Exclusion Criteria: Patients suffering from Parkinson's disease, seizure disorder, Periodic leg movement of sleep, Epilepsy, Peripheral neuropathy, and pregnant patients were excluded.

The patients were notified about the study and informed consent was taken from each. A self-designed Proforma was made which consisted of a history of smoking and alcohol use, and demographic data such as age, gender, BMI, and duration of symptoms. Patients' clinical evaluation was done for RLS. Restless Leg Syndrome was labeled as per operational definition by National Institute of Neurological Disorder and Stroke, NIH i.e. a neurological disorder that causes unpleasant or uncomfortable sensations in your legs and an irresistible urge to move them based on a strong urge to move limbs which would be associated with unpleasant sensations, burning, pain, and tingling or numbness. Diabetic nephropathy, Iron deficiency anemia, chronic fatigue syndrome and any other clinical diagnosis were ruled out before labelling the patient as having RLS.

Data were entered in Microsoft excel and the following analysis was performed by using Statistical Package for Social Sciences (SPSS) 21.0.Mean and SD was calculated for age. Frequency and percentage were calculated and the Chi-Square test was applied for the comparison of RLS with different factors like BMI, age of the patient, alcohol consumption, smoking, anemia, diabetes mellitus, duration and stages of CKD, and gender. A p-value ≤0.05 was considered significant.

RESULTS

A total of 250 patients were included in the study. Out of which 176(70.4%) were males and 74(29.6%) were females. The mean age of the study participants was 47.6±12.0 years. The highest frequency of cases was noted among males and females in the age group 40-60 years as shown in Table-I below.

Table-I: Gender Distribution Among Age Groups (n=250)

Age Range	Males	Females	Total
20-40	65 (26.0%)	15 (6.0%)	80 (32.0%)
40-60	76 (30.4%)	44 (17.6%)	120 (48.0%)
>60	35 (14.0%)	15 (6.0%)	50 (20.0%)
Total	176 (70.4%)	74 (29.6%)	250 (100.0%)

The 41(16.4%) patients had normal weight while 110 (44%) cases were underweight. Overweight was seen in 99(39.6%) cases. CKD with <1-year duration was found in 96(38.4%) cases while 63(25.2%) and 91(36.4%) had a duration of disease 1-3 years and >3 years respectively. Among CKD patients, 30(12.0%) had alcohol consumption and 80(32.0%) were a smoker. RLS was observed in 82(32.8%) patients with CKD. The 59(72.0%) males and 23(28.0%) females had RLS. No significant difference among gender, smoking, BMI, alcohol consumption, and RLS (p=0.707, 0.945, 0.615, 0.947 respectively) was observed. Significant difference among age groups, diabetes, anemia, duration, and stages of CKD with p-value <0.001 was observed as shown in Table-II

Table-II: Association of Restless Leg Syndrome with Study Parameters (n=250)

Parameter(s)		Restless Leg Syndrome		*p*-Value
		Yes (n=82)	No (n=168)	
Gender	Males	59(72.0%)	117(69.6%)	0.707
	Females	23(28.0%)	51(30.4%)	
Age Group	20-40	12(14.6%)	68(40.5%)	<0.001
	40-60	46(56.1%)	74(44.0%)	
	>60	24(29.3%)	26(15.5%)	
Body Mass Index	18-24	15(18.3%)	26(15.5%)	0.615
	25-30	38(46.3%)	72(42.9%)	
	>30	29(35.4%)	70(41.7%)	
Smoking	Smokers	26(31.7%)	52(32.1%)	0.945
	Non-smokers	56(68.3%)	114(67.9%)	
Alcohol Consumption	Yes	10(12.2%)	20(11.9%)	0.947
	No	72(87.8%)	148(88.1%)	
Diabetes Mellitus	Diabetic	44(53.7%)	34(20.2%)	<0.001
	Non-Diabetic	38(46.3%)	134(79.8%)	
Anemia	Yes	54(65.9%)	42(25.0%)	<0.001
	No	28(34.1%)	126(75.0%)	
Duration of CKD	<1 Year	11(13.4%)	85(50.6%)	<0.001
	1-3 Year	28(34.1%)	35(20.8%)	
	>3 Years	43(52.4%)	48(28.6%)	
Stages of CKD	Stage 1	0(0%)	116(69.0%)	<0.001
	Stage 2-3	42(51.2%)	42(25.0%)	
	Stage 4-5	40(48.8%)	10(6.0%)	

CKD: Chronic Kidney Disease BMI: Body Mass Index* RLS: Restless Leg Syndrome**

DISCUSSION

In the present study, RLS was observed in 82(32.8%) patients with CKD. Chronic kidney disease affects nearly 13-19% of the world population. CKD is almost 21.2% of the adult population of Pakistan. However, the incidence is 43.6% and 10.5% at an age of ≥50 years and <30 years, respectively.[12] Many CKD patients suffer from a sensory-motor disorder, restless leg syndrome which affects the prognosis of chronic kidney disease patients, causing higher short-term mortality and lower survival. 2 to 3% of the general population is suffering from RLS.[13,14] In Pakistan, the prevalence of RLS in the dialysis population was 24%.[11] Siddique S *et al,* positively screened 29 ESRD patients for RLS with a calculated prevalence of 38.7% of RLS in ESRD patients.[12] Only the targeted chronic kidney disease patients were included in the present cohort. In the present study, RLS was observed in 82(32.8%) patients with CKD. As per the literature review, the incidence of RLS in various populations comes to be 13.3-36.7%.[12] Those researchers who have used IRLSSG criteria for RLS diagnosis also have reported a broad positivity range in results.

Riar SK et al, found more prevalence of RLS in CKD patients (n=124) as compared to 85 normal children (15.3 vs. 5.9 %;*p*= 0.04) and found no significant difference between RLS and CKD etiology, CKD duration, and CKD stage. Moreover, found that 26.3% of patients with CKD and RLS complained about RLS symptoms and only one of them was diagnosed with RLS before the study.[15] However, our study consisted of an age range between 20 to >60 years and found the greatest frequency of cases i.e. 48% in the males and females of the age group between 40 to 60 years. Also, a significant difference with the *p*-value <0.001 was observed among age groups, CKD duration, and CKD stages. The variation of values in our population may be due to differences in race, criteria of diagnosis, and heterogeneity our population such as age, gender. As per the literature, there has been an increased prevalence of RLS present only in iron deficiency and kidney disease, yet insufficient evidence or poor methodologies of some studies lie in the case of anemia (without iron deficiency) and cardiovascular disease and diabetes, respectively.16 Saraji NZ *et al,* reported a 55% prevalence of RLS including 59.4% males and 40.6% females. They found significantly higher dialysis duration ($p<0.05$) than the other group.[17] However, our study found that 59(71.9%) males and 23 (28.1%) females had RLS. The variation may be due to the number of participants. Also, Saraji NZ *et al,* stated

that the significant predictors of RLS have been the history of diabetes mellitus, hypertension, and smoking (p<0.05); whereas, in the present study, no significant difference between smoking and restless leg syndrome was observed (0.945), but a significant difference for diabetes was observed with the p-value of <0.001. RLS frequency is reported to be increased with advancing age. The mean age of the study in present participants was 47.68±12.26, while Becker PM *et al,* found the mean age of presentation of 50.7 years, which is in comparison.18 Siddique S et al, and Xiao et al, showed that females are more affected by RLS in comparison to males (42.9 Vs 37%), whereas no significant difference in gender (p=0.707) was found in the present study.[12]

Although relatively common, RLS remains undiagnosed as indicated by Becker PM *et al*, that 91% of RLS patients were not diagnosed previously.[18] Multiple studies have found the associated risk factors which can play a role in the development of RLS. Literature has revealed no significant differences in age, gender, dialysis shift, and a significant difference for alcohol consumption.[19,20] which is comparable with the present study that no statistically significant association between alcohol consumption (p=0.947) and smoking (p=0.945) to RLS was found. Also, in the present study, no statistical association of BMI (p=0.615) with RLS, while Saraji NZ *et al,* found a statistically significant association between BMI with RLS.[17]

LIMITATIONS OF THE STUDY

There were some limitations in the present study such as the relatively small sample size. This study lacked information on potential comorbidities such as anxiety, depression, insomnia, migraine, obesity, and pain. Further studies are required with the large sample size for the establishment of effective treatment and management of disease and improvement of the suffering of the RLS patients to increase their life span and quality of life.

CONCLUSION

RLS is prevalent in CKD patients and is associated with anemia, stage of chronic kidney disease, duration of CKD, diabetes mellitus, and age of the patient. Males are predisposed to develop RLS as compared to females.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AS & AM: Data acquisition, data analysis, critical review, approval of the final version to be published.

MQ & FI: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MW & RY: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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