ORIGINAL ARTICLE

ASSOCIATION OF BONE MINERAL PROFILE WITH RESTLESS LEG SYNDROME IN PATIENTS WITH END STAGE RENAL DISEASE.

Sajid Sultan, Kiran Nasir, Ruqaya Qureshi, Murtaza Dhrolia, Aasim Ahmad
The Kidney Centre Postgraduate Training Institute Karachi-Pakistan

Background: Restless leg syndrome (RLS) is one of the problem hemodialysis patients may encounter. This study was done to find out the association of restless legs syndrome (RLS) in end stage renal disease patients with serum calcium, phosphorus and parathyroid hormone levels. **Methods:** This cross-sectional observational study was done at The Kidney Centre, postgraduate Training Institute Karachi, Pakistan from Jan to June 2020. One hundred and twelve patients on three per week hemodialysis for more than three months at our hemodialysis centre were face to face interviewed as per International Restless Legs Syndrome Study Group criteria (IRLSSG) for the presence of RLS symptoms. Their demographic data and laboratory values were recorded from history chart and computer records. The bone mineral profile in this study includes serum calcium (corrected for albumin), serum phosphate levels and serum intact Parathyroid hormone (iPTH) levels. Statistical analyses were done by using SPSS-21. **Results:** In our study, 38.4% patients had RLS. Serum phosphorus levels were significantly higher in patients with RLS as compared to those who didn't have RLS. No significant association of serum calcium and Parathyroid hormone (PTH) levels with RLS was found. **Conclusion:** There is a high prevalence of RLS in ESRD patients as compared to general population. Serum phosphorus levels need to be observed and corrected along with maintenance of calcium and PTH levels to improve symptoms of RLS in these patients.

Keyword: Restless leg syndrome; Bone Mineral profile; Hemodialysis; End stage renal disease

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INTRODUCTION

Patients with End stage renal disease (ESRD) are those who require either dialysis or renal transplant for their survival. Dialysis dependent patients treated with different dialysis modalities like hemodialysis or peritoneal dialysis may suffer from mental and physical complications. The patient may suffer from complications related to their primary disease, adverse effect of medications and complications associated with dialysis. Restless leg syndrome (RLS) is one of the problem hemodialysis patients may encounter. Restless syndrome (RLS) is "characterized by a distressing irresistible urge to move the legs that are brought on by rest (sitting or lying down)".[1]

It is sensorimotor disorder that has multiple effects on sleep and daily life activities. Patients often describe it in their own way of perception such as "Creepy-Crawly legs" and others.[2] It is a common medical condition that causes uncomfortable urge to move the legs. These urges happen in the evening and at night and can keep people from sleeping well. These may be lessened or relieved by movement. Considering the etiology, the disease is classified into primary and secondary forms. Most of the patients have primary idiopathic disease, in which a positive family history is present in nearly 40% of the cases.[3, 4] Secondary Restless Leg Syndrome may be present in different conditions like pregnancy or other medical conditions such as renal insufficiency, iron deficiency anemia, Parkinson's disease, and diabetic neuropathy.[5] The use of certain medications, including selective serotonin reuptake inhibitors, lithium, dopamine antagonists, and caffeine can also increase the prevalence of RLS in some patients.[6]

Prevalence of RLS is between 3.5–10% in adults in the general population. A significantly higher prevalence of RLS ranging from 12–62% has been reported in patients with end-stage renal disease.[7] 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 and insomnia.[8] In hemodialysis patients, RLS may raise some serious concern to the patients by its impact on their overall general health, body aches, fatigability and reduction of the physical activities. RLS has an adverse impact on mental health status of the hemodialysis patients leading to mood disorders such as anxiety and depression.[9]The comorbidities of sleep quality and sleep pattern disturbances and stressed mental health can cause severe consequences for HD patients.[10]

In Pakistan where there is a huge burden of ESRD,[11] multiple factors have been linked with the

etiology of RLS in hemodialysis population, Bone mineral metabolic derangements might be one of them, however, no study has been done till date to research the association of bone mineral profile (calcium, phosphorus and PTH) with RLS in Pakistani hemodialysis population. Disorders of calcium and phosphorus metabolism are a common complication of chronic kidney disease (CKD). In CKD, kidneys are unable to maintain proper level of calcium, phosphate, and parathyroid hormone (PTH) in the blood. There is a secondary hyperparathyroidism in CKD patients with low serum calcium and elevated serum phosphorus levels.[12]

By stage 3 CKD, that is a 50% decline in kidney function, around 60% of patients have an increased PTH level. This stimulates the nephrons to excrete phosphorus and stimulates bones to release calcium, leading to an ongoing bone resorption, remodeling, and redistribution.[13] These abnormalities in calcium phosphorus metabolism are suspected to be the causative or associative factor for RLS in dialysis patients; therefore, further studies are needed to determine the prevalence, risk factors and impact of RLS and its association in ESRD patients. Our study's objective is to evaluate the frequency of restless legs syndrome (RLS) in end stage renal disease patients and its association with serum calcium, phosphorus and parathyroid hormone levels.

MATERIAL AND METHODS

A cross sectional study was done in hemodialysis patients at The Kidney Centre Post Graduate Training Institute Karachi. After getting approval from the ethical review committee of the hospital, data was collected from 112 diagnosed cases of ESRD patients. Inclusion criteria of the study included the patients of both genders, of age over 18 years undergoing maintenance hemodialysis with frequency of hemodialysis three per week, each hemodialysis session lasting for four hours, in our centre for more than 3 months. An informed consent was taken from the patient or his/her next kin after explaining the purpose of the study. The patients with known psychiatric disorders, patients who refused informed consent and patients with skin diseases prior to development of RLS were excluded from the study. The diagnostic criteria for RLS includes four major questions based on International Restless Leg Syndrome Study Group Criteria (IRLSSG), i.e., (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. (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day. The patients were asked by the primary investigator about these four symptoms. Only patients endorsing all four questions were considered to have RLS.[2] Pruritus or pain as isolated symptoms, without circadian characteristic and without relief with movement was not considered as RLS. Demographic and clinical data was extracted from the history chart and computer records. The bone mineral profile in this study includes serum calcium (corrected for albumin), serum phosphate levels and serum intact Parathyroid hormone (iPTH) levels. Normal laboratory values for serum calcium levels are 8.6-10.2 mg/dl and for serum phosphorus are 2.5–4.5 mg/dl. Serum iPTH levels in normal non-CKD individuals are 10-55 pg/ml, but in ESRD population it is increased by 5-9 times of the upper normal limit as compared to normal individuals. In our study iPTH levels higher than 450 pg/ml will be considered as high. Medications in use recorded were: erythropoietin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, calcium channel blockers, vasodilators, pain relieving medications, diuretics, and statins.

Data was entered and analyzed in IBM SPSS version 21. Cleaning and coding of the data was done prior to analysis. Continuous variables were expressed in mean±std and median with inter quartile range, while frequencies and percentages were obtained for categorical variables. Association of categorical variables was assessed by Chi square or fisher's exact test. To observe the mean difference of normally distributed lab parameters of patients with and without RLM, Independent student t test was executed, while Man Whitney u test was used for skewed variables. Significance level (p-value) was set as ≤ 0.05.

RESULTS

The total number of patients recruited for the study was 112. There were 70 males (62.5%) and 42(37.5%) female patients. The most prevalent cause of renal failure was DM, 40 (35.7%) in our population and the most common comorbid condition was hypertension 88 (78.6%). 43 patients (38.4%) had symptoms of RLS. Out of the 112 study patients, 41(36.6%) were using pain relieving medications like gabapentin. Table-1

Age was not different between groups of RLS positive and RLS negative (p=0.454). The overall mean age in our patients in years was 51.4±14.6. Similarly, there was no difference between duration of hemodialysis between those two groups. (p=0.535), as total duration of hemodialysis in years was 3 years. iPTH was lower in RLS positive

patients (236) as compared to the RLS negative patients (270), although p-value is not significant (p=0.392). Similarly, the mean calcium was also different in both groups, as patients with RLS had mean calcium of 8.9±0.5 as compared to RLS negative patients which had slightly higher calcium with mean 9.1±0.7, although P value is insignificant (p=0.075). On the other hand, serum phosphorus levels were significantly different in both groups. (p=0.042). The RLS positive patients had higher phosphate levels (4.5) as compared to RLS negative patients (4.3). Table-2.

Table-1: Comparison of demographic features of RLS and non RLS patients

Variables		RLS		Total	*p*-value
		Yes: 43 (38.4%)	No: 69 (61.6%)		
Gender	Male	23(53.5%)	47(68.1%)	70(62.5%)	0.120
	Female	20(46.5%)	22(31.9%)	42(37.5%)	
Pain relieving Medications	Yes	19(44.2%)	17(24.6%)	41(36.6%)	
	No	24(55.8%)	52(75.4%)	71(63.4%)	0.001
Cause of renal failure	DM	21(48.8%)	19(27.5%)	40(35.7%)	
	GN	4(9.3 %)	5(7.2)	9(8%)	
	CIN	1(2.3%)	1(1.4%)	2(1.8%)	0.168
	ADPKD	0	1(1.4%)	1(0.9%)	
	Renal Stones	1(2.3%)	7(10.1%)	8(7.1%)	
	Unknown	16(37.2%)	36(52.2%)	52(46.4%)	
Comorbidities	Hypertension				
	Yes	36(83.7%)	52(75.4%)	88(78.6%)	0.294
	No	7(16.3%)	17(24.6%)	24(21.4%)	
	IHD				
	Yes	2(4.7%)	8(11.6%)	10(8.9%)	0.312
	No	41(95.3%)	61(88.4%)	102(91.1%)	
Calcimimetics	Yes	6(14%)	7(10.1%)	13(11.6%)	0.557
	No	37(86%)	62(89.9)	99(88.4%)	
Statins	Yes	25(58.1%)	43(62.3%)	68(60.7%)	0.660
	No	18(41.9%)	26(37.7%)	44(39.3%)	
Vasodilators	Yes	17(39.5%)	21(30.4%)	38(33.9%)	0.323
	No	26(60.5%)	48(69.6%)	74(66.1%)	
Calcium channel blockers	Yes	16(37.2%)	30(43.5%)	46(41.1%)	0.512
	No	27(62.8%)	39(56.5%)	66(58.9%)	
Beta Blockers	Yes	27(62.8%)	41(59.4%)	68(60.7%)	0.722
	No	16(37.2%)	28(40.6%)	44(39.3%)	
ACEi\ARBs	Yes	7(16.3%)	5(7.2%)	12(10.7%)	0.207
	No	36(83.7)	64(92.8%)	100(89.3%)	

Table-2: Comparison of Calcium, Phosphorus and iPTH levels in RLS and non RLS patients.

Variables	RLS positive patients mean±std, median, (25^{th} quartile-75^{th} quartile)	RLS negative patients mean±std, median, (25^{th} quartile-75^{th} quartile)	Total mean±std, median (25^{th} quartile-75^{th} quartile)	*p* value
Age(in years)	52.7 ±14.1	50.5±14.9	51. ±14.6	0.454
Calcium (mg/dl)	8.9±0.5	9.1±0.7	9.0 ±0.6	0.075
Phosphorus (mg/dl)	4.5 (3.7- 6)	4.3 (3.4–4.8)	4.4 (3.5–5.2	0.042
iPTH(pg/ml)	236 (150- 369)	270 (172–462.5)	267.5 (172–449.5)	0.392
Years of hemodialysis	3 (2–5)	4 (1.5–5)	3 (2–5)	0.535

DISCUSSION

Globally, Chronic Kidney Disease (CKD) is one of the leading causes of death and disability. In 1990, CKD was the 27th leading cause of death which increased by time and became 18th leading cause of death in 2010.[14] In 2013, around 1 million people died because of CKD related causes.[15] Pakistan is having a high load of CKD and ESRD patients. The overall CKD prevalence among Pakistani adults was 21.2% in a systematic review done in South Asian population.[16]

Abnormal mineral metabolism starts early in the course of CKD and ESRD, and is usually accompanied by profound changes such as bone disease, musculoskeletal symptoms and growth retardation.[17] The pathophysiology of both idiopathic and secondary RLS is still a subject of discussion. A limited number of studies have been conducted to find out the pathophysiology of RLS in uremic patients.

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.[9] In a

multicenter study done in Pakistan it was 12%.[18] In another study in Pakistan it was 64% in ESRD patients.[19]

Patients with RLS often ignore their symptoms and very few of them consult their physician, may be due to their disease burden or hemodialysis busy schedules, particularly when symptoms are not severe. This is the reason of delayed diagnosis and treatment. RLS has no specific diagnostic test and hence, it is diagnosed on clinical basis based on the four essential criteria. In our study the prevalence of RLS was 38.4% in ESRD dialysis patients. The prevalence varies with different patient characteristics, diagnostic criteria, and sample sizes. It also varies with the duration of hemodialysis delivered to the patients. In a study from Pakistan by Abideen ZU *et.al*,[20] longer duration and greater number of HD sessions were significantly associated with RLS. These variations of the prevalence in different studies may be multifactorial as discussed.

Previous studies showed no significant association of RLS with age of the patients.[21,22] In our study we had similar results. Just like age, gender was not associated with RLS in our study. Diabetes mellitus was the major cause of ESRD in our study and 19 patients, i.e., 44.2% out of the total RLS positive patients were diabetics.

It is hypothesized that calcium/phosphate imbalance could be involved in the pathophysiology of RLS. In a recent Iran based systemic review and meta-analysis it concluded that serum phosphorus levels were higher in patients with RLS compared to the patient who did not have RLS.[23] Our study is the first study in Pakistan to measure the association of bone mineral chemistry, i.e., serum calcium, serum phosphorus and serum iPTH with the prevalence of RLS in hemodialysis population. In our study there was a significant association of serum phosphorus level with RLS as it was high in the RLS positive patient as compared to RLS negative patients. This is similar to the results of above-mentioned Iran based study by Mansourain *et.al*.[23] Serum calcium was low in our RLS positive patients though insignificant and similar was the case of PTH levels. There was no significant association of patients taking pain medications with absence or presence of RLS.

There were few limitations in our study. Patients need to be examined for the presence of the other causes of neuropathies like diabetic neuropathy. FGF 23 and vitamin D levels were not done because of financial constraints. FGF-23 is a stable biomarker of disordered phosphate metabolism and for this reason may also be associated with RLS.[24] Furthermore, the severity as well as the impact of RLS was not assessed in this study.

CONCLUSIONS

Serum phosphorus levels had a significant association with the presence of RLS in ESRD hemodialysis patients. Aggressive and timely treatment is needed in ESRD dialysis patients. Better control of serum phosphorus while maintaining normal serum calcium level will positively impact on overall health including RLS in this patient population. Further studies are needed for better understanding of RLS and factors associated with it.

AUTHORS' CONTRIBUTION

SS: Principal Investigator. Conception of idea, literature search, write-up KN: Conceptualization of study design. RQ: Co-Investigator and co-author.
MD, AA: Conceptualization of study design

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Address for Correspondence:
Sajid Sultan, C/o Sultan Agri Zone Village and Post Office Bherkund, Tehsil and District Mansehra-Pakistan
Cell: +92 333 557 6625
Email: ss.sajidsultan@gmail.com