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Original article

## Has Residual Renal Function More Impact in Restless Legs Syndrome than the Modality of the Dialysis Therapy?

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### Abstract

**Background.** Restless Legs Syndrome (RLS) is a common disorder in renal replacement therapy patients. It is accused to have an impact on sleep disorders and to affect the quality of life. The aim of the study is the assessment of the frequency and factors influencing RLS in Hemodialysis (HD) and Peritoneal dialysis patients (CAPD).

**Methods.** The study involved 88 patients in maintenance hemodialysis 31F/57M aging averagely 42,99±11,69 years, and 32 patients in maintenance PD 17F/15M aging 48,31±15,21 years. Median time since starting dialysis was 50,94±46,53 months in HD and 19±14,30 months in CAPD patients.

The patients completed a questionnaire during the dialysis sessions. We used the four clinical criteria suggested by the International Restless Legs Syndrome Study Group (IRLSSG) for the diagnosis of RLS. The result was considered positive only in case the patients gave a positive response to all the diagnostic criteria. Demographic, clinical and laboratory data were recorded.

**Results.** We found difference in frequency of RLS between HD and PD patients, 20 patients in HD (22.7%) and 4 pts in PD (12,5%) were positive for RLS. The analysis of the laboratory data of the level of residual renal function (RRF) in PD patients was significantly higher than in HD patients respectively 1,97±2,12 ml/min vs 0,22 ±0,56 p<0.001. When a comparison took place between the patients with RLS and those without RLS it was found out that there was no difference concerning the age, duration of dialysis, iron, ferritin, calcium, phosphorus, PTH and Hb. In addition, there was no significant correlation between RLS and age, gender, alcohol and coffee intake. Moreover, linear regression analysis showed that it existed a significant correlation with the history of diabetes, BUN, seric albumin, RRF and RLS (p<0,001; p=0,013; p+0,024; p=0,018) respectively. Patients suffering RLS were found to have a great risk of having insomnia and impaired well being.

**Conclusion.** The prevalence of RLS in PD patients was lower than in HD patients but this difference was not significant. Furthermore, RRF has a significant correlation with RLS. This evidence may give us the right to

conclude that the Residual Renal Function have more impact in RLS than the modality of dialysis treatment.

**Keywords:** dialysis, Restless legs syndrome, residual renal function, sleep disorders

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### Introduction

Restless legs syndrome (RLS) is a sensorymotor disorder [1] that is often associated with a sleep complaint. Although the exact prevalence is uncertain, limited studies indicated that 2-15% [2] of the population may experience RLS.

RLS can occur as an idiopathic form or as secondary one to other conditions such as pregnancy, iron deficiency and end-stage renal failure.

In 1995, the International Restless Legs Syndrome Study identified four basic criteria of RLS [3]:

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, for at least as long as the activity continues.
4. The urge to move or unpleasant sensations begin to worsen in the evening or late at night than during the day or occur only in the evening or night.

RLS sensations are often described by people as burning, creeping, tugging, or having the feeling of an insects crawling inside the legs[4]. In the more recent papers that have applied the IRLSSG diagnostic criteria, the prevalence of the disorder in the ESRD population was reported to be between the level 10% and 20%. However, the definitions of the disorder used in those reports were still quite variable [5]. In the general population, the prevalence of RLS increases with age, and women are more frequently affected than men [6]. Other potential correlations of RLS in both the general population and in patients with kidney disease are anemia and iron

deficiency [7,8]. Uremia may be one of the most important pathogenic factors in patients with ESRD [9;10]. Recently, it has been suggested that RLS is associated with increased mortality and impaired health-related quality of life (QoL) in patients on maintenance dialysis [11]. One of the factors that may mediate the potential effect of RLS on QoL is the impact of RLS on sleep [12].

## Methods

The methodology utilized consisted in the conduction of an observational cross-sectional study in the Dialysis Center of University Hospital Center "Mother Teresa". All stable patients on chronic dialysis were enrolled in this study; Hemodialysis (HD) and Peritoneal dialysis (CAPD). The confused patients and those patients who refused to participate and sign the written consent were excluded from this study. In order to study the incidence of the different sleep disorders, and of RLS in particular, a questionnaire was administered to all the patients in dialysis units who agreed to participate. The first part of the questionnaire included questions about demographic data, general medical history, history of renal disease, dialytic treatment, patients life style limited to cigarette smoking and daily intake of coffee and alcohol. The second part, which was self-administered, explored the patient's complaints about sleep, the presence of the minimal International Restless Legs Syndrome Study Group (IRLSSG) criteria for the diagnosis of RLS [13]. The result was considered positive only if the patient met all the diagnostic criteria. A questionnaire based on the Athens Insomnia Scale (AIS) questions was used to assess insomnia [14]. The first 3 questions covered night-time symptoms of insomnia (1-difficulty initiating

sleep; 2-difficulty maintaining sleep; 3- early morning awakening) and two other questions probe daytime consequences of disturbed sleep (4-well-being; 5- functioning capacity and daytime sleepiness). For each patient a special form was filled out by the attendant nephrologists, including some clinical and dialytic data, as well as predialysis values of Creatinin, BUN, Hb, iron, ferritin, Alb, Ca, Phosphor, PTH and residual renal function (RRF). The method of quantifying residual renal function is done by 24 h urine collection, calculating GFR as the mean of urea and creatinine clearance and normalized by 1.73 m<sup>2</sup> surfacing area.

*Statistical analyses.* All analyses were performed using SPSS 14.0. The continuous variables were expressed in mean value  $\pm$  SD. The discrete variables were expressed in absolute and percentage value. The differences between two continuous variables were analyzed using Student's t test. The multivariate linear regression analysis was used to analyze the association between restlessleg and other factors (age, gender, diabetes, coffee intake, alcohol intake, Hb, BUN, creatinin, seric albumin, PTH and RRF). A two-sided p-value of 0,005 differences was considered to be statistically significant.

## Results

The total number of patients recruited in the study were 88 pts in HD and 32 pts in PD. Mean age in HD was 42,99 $\pm$ 11,69 years, 64,8% were males and the prevalence of diabetes was 6 %. Mean age in PD was 48,31 $\pm$ 15,21 years, 46,7% were males and prevalence of diabetes was 18,7%. Median time since starting dialysis was 50,94 $\pm$ 46,53 months in HD and 19 $\pm$ 14,30 months in PD pts.

**Table 1.** Comparison of demographic, life style and biochemical data between the the patients on Hemodialysis and Peritoneal dialysis treatment

	Hemodialysis (88)	Peritoneal Dialyse (32)	Sig. (2-tailed)
Age	42,99 $\pm$ 11,69	48,31 $\pm$ 15,21	,045
Time on dialysis	50,94 $\pm$ 46,53	19,00 $\pm$ 14,30	,000
Nr of coffees per day	1,72 $\pm$ 1,63	1,03 $\pm$ 0,93	,026
Quantity of alcohol	0,14 $\pm$ 0,46	0,16 $\pm$ 0,37	NS
BUN	80,87 $\pm$ 18,37	62,72 $\pm$ 19,48	,000
Creatinemia	10,17 $\pm$ 2,36	8,39 $\pm$ 3,41	,002
Seric albumin	3,81 $\pm$ 0,39	3,45 $\pm$ 0,42	,000
RRF	0,22 $\pm$ 0,56	1,97 $\pm$ 2,12	,000
Hb	10,91 $\pm$ 1,30	10,68 $\pm$ 1,00	NS

The total number of patients who met all criteria for the diagnosis of RLS were 20 pts 22,7 % in HD group and 4 pts 12,5% in PD group but this difference was not significant. When patients in HD were compared to those in PD was seen that, there were significant difference between two groups regarding the age, BUN level, Creatinin, time on treatment, number of coffee intake, level of albumin and RRF (p=0,045; p<0,001; p=0,002; p<0,001; p=0,026; p<0,001; p<0,001) respectively (Table 1). After the evaluation of sleep complaints we observed that

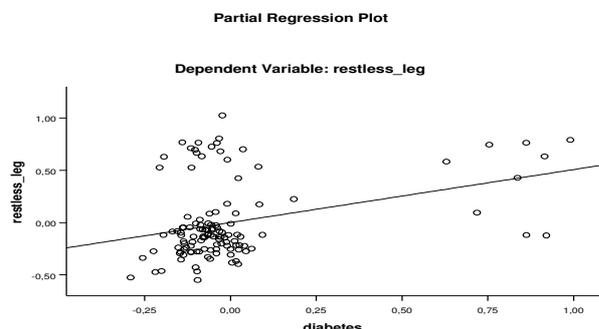
insomnia was a frequent symptom in both groups but there were no significant difference between the groups neither in the questions that cover night symptoms nor in the questions that probe daytime consequences of disturbed sleep.

The most frequent symptoms of insomnia in both groups was difficulty in maintaining sleep in 54,5% of the HD pts and in 46,9% of the PD pts. Using IRLSSG criteria the prevalence of RLS in dialysis patients in our study was 20%.

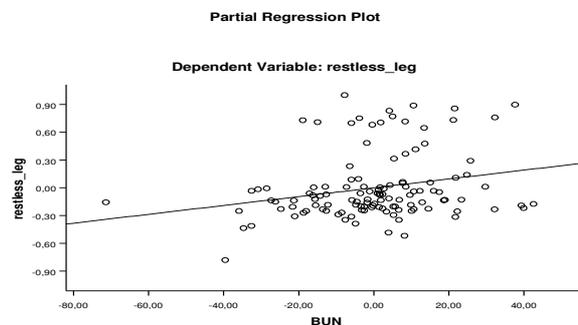
**Table 2.**The frequency of sleep disorders in groups with and without RLS

Characteristics	RLS		P value
	NO (n=96)	YES (n=24)	
Gender			
F	38 (39,6)	10 (41,7)	NS
M	58 (60,4)	14 (58,3)	
Diabetes			
Yes	5 (3,1)	6 (25,0)	0,002
No	93 (96,9)	18 (75,0)	
Employed			
Yes	21 (21,9)	6 (25,0)	NS
No	75 (78,1)	18 (75,0)	
Sleep question 1			
Yes	38 (39,6)	13 (54,2)	NS
No	58 (60,4)	11 (45,8)	
Sleep question 2			
Yes	50 (52,1)	13 (54,2)	NS
No	46 (47,9)	11 (45,8)	
Sleep question 3			
Yes	38 (39,6)	15 (62,5)	0,037
No	58 (60,4)	9 (37,5)	
Sleep question 4			
Yes	36 (37,5)	18 (75,0)	0,001
No	60 (62,5)	6 (25,0)	
Sleep question 5			
Yes	42 (43,8)	14 (58,3)	NS
No	54 (56,3)	10 (41,7)	
Groups			
Hemodialysis	68 (70,8)	20 (83,3)	NS
Peritoneal dialysis	28 (29,2)	4 (16,7)	

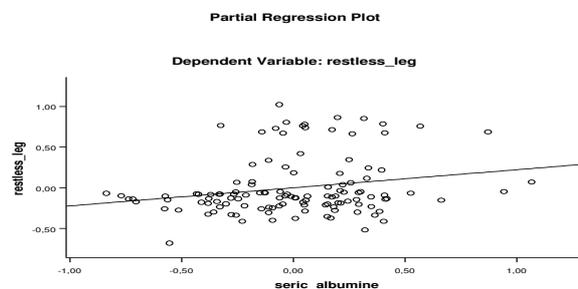
When patients with RLS were compared to those without RLS, it was found out that there was no difference concerning age, duration of dialysis, iron ferritin, calcium, phosphorus, PTH and Hb (Table 2). In addition, there was no significant correlation between RLS and age, gender, alcohol, coffee intake. A linear regression analysis showed that there was significant correlation with the history of diabetes, BUN, seric albumin, RRF and RLS ( $p < 0,001$ ;  $p = 0,013$ ;  $p = 0,024$ ;  $p = 0,018$ ) respectively as shown in Figure 1-4.



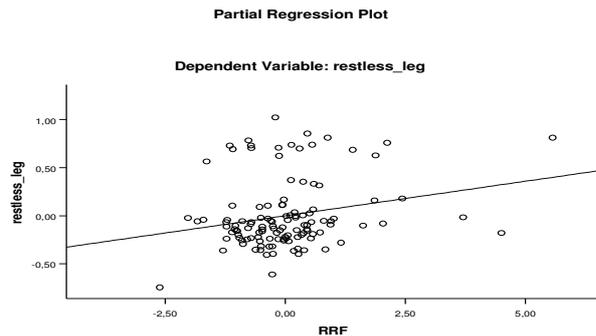
**Fig. 1.** Correlation between history of diabetes and Restless legs syndrome



**Fig. 2.** Correlation between BUN and Restless legs syndrome



**Fig. 3.** Correlation between seric albumin and restless legs syndrome



**Fig. 4.** Correlation between RRF and Restless legs syndrome

Furthermore, patients with RLS reported more frequently the presence of the specific sleep problems assessed by the individual AIS items (Table 3) but significant difference was seen in early awakening ( $P=0.037$ ) and in impaired well being ( $P<0.001$ )

## Discussion

Large epidemiological studies have identified several correlations of RLS in the general population: the prevalence of the condition was higher among the elderly and the females, but this was not seen in all studies and is not always true among patients undergoing dialysis treatment [10,15]. Some studies found an association between the presence of RLS and lower socio-economic status [16]. In our population, RLS was not associated with gender, age or employment. Laboratory and clinical factors were reportedly associated with RLS in dialysis patients in recent studies, however none of those were found consistently to be associated with the syndrome across the studies [8,17]. During this study it was also found a somewhat high serum albumin in patients with RLS compared with the group without RLS condition, but we think that this is not a really clinical factor; it might be connected with the high prevalence of RLS in HD group which had and more high serum albumin value compared with PD group ( $p<0,001$ ). Furthermore, inadequate dialysis, higher level of BUN was associated marginally with RLS in a linear regression model. These findings might suggest that in dialysis patients uremia is the most important, overwhelming risk factor for RLS and, therefore the association of any other factor with the condition is difficult to detect. In addition, it was found a significant correlation between RLS and RRF ( $p=0,018$ ). The prevalence of RLS in PD patients was lower than in HD (12,5% vs 22,7%) although the greater mean age of pts [3] in this modality ( $p=0,045$ ), but this difference was not significant. This evidence may give us the right to conclude that the Residual Renal Function have more impact in RLS syndrome than the modality of dialysis treatment.

RLS was associated with the presence of diabetes mellitus in our study ( $p<0,001$ ) but in this study there were not examined the patients for evidence of diabetic neuropathy, which may contribute to the severity of RLS. Anemia and iron deficiency have been linked to RLS;

however, more recent studies have failed to confirm those earlier findings [5,7,17]. In this study, RLS was not associated with serum hemoglobin level or the presence of iron deficiency (assessed by serum ferritin). The routine use of erythropoietin and relatively large doses of intravenous iron in this population may explain the lack of that expected association as suggested by others [18,23]. It is also possible that parameters used to assess peripheral iron stores might not reflect brain iron metabolism properly and it is brain and not peripheral iron that might be associated with RLS, as suggested by recent studies [19]. In this study was not found any significant correlation between RLS and daily regular use of either coffee or cigarette smoking [20,21]. Consequently, it was suggested a association between RLS and insomnia in patients on maintenance dialysis suggested already by a few other previous papers [12,22]. In this study it is reported that patients with RLS have more frequent and suffer more severe insomnia symptoms [22]. Importantly, daytime consequences of disturbed sleep, assessed by the AIS items, were also reported more frequently by RLS patients. These results are consistent with the notion that RLS interferes with sleep, resulting in impaired daytime well-being, increased daytime sleepiness and reduced mental and physical functioning capacity. However, several limitations of this report should also be noted. The cross-sectional design precludes any directional or causal conclusions. Furthermore, RLS is best diagnosed by an experienced clinician. On the other hand, the use of standard, validated questionnaires may still be necessary and useful in studies involving large numbers of patients. In this study it was found a significant correlation between RLS and diabetes but there was no information on peripheral neuropathy of these patients.

## Conclusion

By using the IRLSSG questionnaire to identify dialysis patients with RLS, the prevalence was 20% comparable to recent reports in similar populations. In addition, RLS was associated with other sleep disorders. The high prevalence of RLS and other sleep disorders among uremics requires careful investigation and better treatment. The significant correlation between RRF and RLS may give us the right to conclude that the Residual Renal Function have more impact in RLS than the modality of dialysis treatment.

*Conflict of interest statement.* None declared.

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