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Serum iron, hemoglobin, CRP and calcium in hemodialysis patients with and without restless legs syndrome

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ABSTRACT

Restless legs syndrome (RLS) is a movement disorder that is characterized by a strong desire to move the legs during rest and sleep and it leads in disturbance of quality of life for hemodialysis patients. Biochemical factors and inflammatory processes have an important role in the pathogenesis of this syndrome. The aim of this study is to compare the serum levels of calcium, iron, hemoglobin and CRP in hemodialysis patients with and without restless legs syndrome. This cross-sectional study carried out on 74 patients with chronic hemodialysis in Zabol University of Medical Sciences (including 62 patients with Restless Legs Syndrome and 12 Patients without Restless legs syndrome). The including criteria were: at least six months had hemodialysis three times weekly and their hemodialysis last between 3 - 4 hours. Data gathered by a questionnaire about restless legs syndrome. At the same time completing the questionnaire, the patients' biochemical parameters were measured. The data was analyzed by SPSS software version 21.0. The results showed that 83.7% of hemodialysis patients involved with RLS. The findings showed that there was not any significant relationship between hemoglobin, iron, CRP with RLS, while there was a significant relationship between the mean of calcium and RLS ($P=0.026$). Considering that the calcium levels was much lower in hemodialysis patients with RLS than non-involved patients, performing the screening tests to measure calcium to provide the necessary measures is necessary to improve the clinical symptoms of the RLS.

Key words: Biochemical parameters, restless legs syndrome (RLS), Hemodialysis.

INTRODUCTION

Restless legs syndrome (RLS) was identified for the first time in 1685 by English physician Thomas Willis and it was used by Karl Ekbom (1944) to describe a disorder with symptoms of sensory and motor disorders of limbs, mainly during rest. RLS is a neurological motor disorder, and these involved patients have a strong desire to move legs during sleep. It describes the non-proper feeling periods of inactivity which worsen in periods of inactivity and often led to insomnia (1). RLS as one of the most common non-detectable diseases has been proposed (2). International Association IRLSSG (International Restless Leg Syndrome) has suggested special criteria for the diagnosis of restless leg syndrome or studies. These criteria are: desire to move extremities frequently associated with unpleasant symptoms to relief temporary by moving, the start or exacerbation of signs with rest or immobility, start or worse in the evening or night (3). Avoid shaking legs are causing unpleasant feeling in patients (4). Patients describes these unpleasant feelings to move a worm on the skin, the flow of water into the legs, feeling insect into bone, electricity power in the legs bone. The location of these unpleasant sensations in the legs is between the knees to the ankle, which triggering of disease signs, disease increase other body parts of body like trunk and pelvic regions. ALS symptoms have a circadian oscillations so that the signs start in the evening or night and subside in the early morning. The signs exacerbated in evening and this is the main cause of sleep disorders in patients (2). Bogan reported the prevalence RLS is 70% in

hemodialysis patients (5). In the studies of Mollahossieni and Alidousti have reported that 61.5% and 57.3% of hemodialysis patients suffering from RLS (6, 7). The prevalence of RLS in is 5-15% in the general population and it is 20-30 % among hemodialysis patients (8)

Which is also associated with increased mortality in these patients (9). It is reported the prevalence of this syndrome in 83-86% in uremic patients (10, 11). RLS is a complex disease. It seems that it has related to, a combination of genetic and biochemical factors contribute to its development (12). RLS has unknown etiology but some factors might effective. It is idiopathic or secondary to or due to some factors such as diabetes mellitus, kidney failure, pregnancy, iron deficiency anemia and multiple sclerosis. Earley and Ruottinen believed that dopamine receptors have reduced in the basal ganglia of the brain of RLS patients (13,14). Iron deficiency is also associated with RLS symptoms and it improves by the administration of iron. Iron acts as a cofactor for tyrosine hydroxylase because this enzyme is limiting the dopamine metabolism. With an increase in iron levels in the cerebrospinal fluid (CSF), the amount of dopamine increase (15). It is a probability that the prevalence of RLS patients with chronic renal failure is due to iron deficiency anemia (16). The results of a study in Ireland showed that RLS is more common with iron deficiency anemia (17). While the in Shahidi study, there was statistically significant relationship between chemical parameters such as iron, serum ferritin and hematocrit with RLS (18). The inflammatory processes also play an important role in the development of signs and symptoms in hemodialysis patients. In these patients, the body's natural homeostatic mechanisms change to achieve new levels of homeostasis of metabolic interactions which is specific to hemodialysis patients and these changes are creating a series of factors, including the production of acute phase proteins and most important of them is C - reactive protein (CRP) (19). Hypercalcemia also may exacerbate symptoms of RLS in hemodialysis patients (15). This syndrome has several side effects such as insomnia, excessive sleepiness during daytime and depression (8). Sleep disorders are the primary reason for patients with RLS to seek medical care and refer to health and treatment centers (20). The forth cause for insomnia is RLS after mental disorders, drug abuse and sleep-related respiratory disorders (21). To relieve the symptoms of RLS signs, the patients often walk during the night and fall in sleep in early morning as a result of sleep deprivation and daytime sleepiness may disrupt their daily functioning (22). Winkelmann also reported that RLS patients 2.6, 3.5 and 4.7 times more likely than healthy people prone to involve depression, anxiety and panic respectively (23). The results of a study also showed the relationship between RLS and lower quality of life in hemodialysis patients (24). Although the etiology of RLS is unknown (8), but the investigating of factors associated with this syndrome can help to improve the quality of life in hemodialysis patients, therefore, identification of factors affecting the incidence of RLS is one of the primary actions. On the other hand, because of the devastating impact RLS on quality of life and sleep patterns of patients undergoing hemodialysis and small and contradictory studies about risk factors for RLS in these patients, It is necessary to carry a research about risk factors of RLS in hemodialysis. Then the researchers intended to conduct a study to compare the serum levels of calcium, iron, hemoglobin and CRP in hemodialysis patients with and without RLS.

MATERIALS AND METHODS

In this cross-sectional study, the prevalence of RLS and its relation to serum levels of iron, hemoglobin, CRP and calcium has investigated in hemodialysis patients who referred to hospitals affiliated to Zabol University of Medical Sciences in 2014. The sample size was 74 patients in two group's hemodialysis patients with RLS and without RLS. Inclusion criteria were: 1- Willingness to participate in research 2. At least 18 years of age 3. At least one year of hemodialysis experience 4. Have record in the department of hemodialysis in hospitals which located in research location 5. Including in the list of weekly dialysis and do it 2 or 3 times weekly and it lasts 3 to 4 hours. 6. The lack of mental and physical disabilities.

7. Having full consciousness, acceptable hearing ability and speech to answer questions. 7. No smoking, not take sedatives, not take hypnotics or sedatives. At the same time people whether male or female, illiterate or literate could include in this research. Data gathered through a checklist of demographic data, lab results and restless legs syndrome questionnaire. The questionnaire contained items about the severity of RLS which measured by a four-point Likert scale. Checklist of demographic consisted of characteristics of the participants in relation to gender, marital status, age, family size, income, education level, physical activity, history of kidney disease, duration of hemodialysis and history of the underlying disease. The scientific validity of the research determined using content validity. The questionnaire reliability calculated through test-retest reliability (95%). In next, for obtaining data, interviews and questionnaires were used. Before the start of dialysis, 5 ml blood was taken from a peripheral vein of the upper limb and the samples have taken in less than an hour to laboratory. Then responses of tests were followed and attached the records of patients. The abnormal ranges informed to in-charge nurse. To analyze the data used SPSS version 21.0.

Data were analyzed through descriptive and inferential statistics. A significant level was considered of $P > 0.05$.

Findings

The results showed that the majority (62.1%) were male and the married were 73%.

The age mean of the participants was 45.1 ± 18.1 . Most of the participants 37.8% had guidance school education and then 32.4% had secondary education. The samples were from rural regions (62.2%). The participants had not exercise (67.6%). The most hemodialysis were performed on morning shifts (45.9%). Based on the findings, 83.7% % of hemodialysis patients were suffered of RLS (table 1). The findings also showed that calcium has a significant relationship with RLS (table2).

Table 1: Frequency of restless legs syndrome in hemodialysis patients

RLS	Number	Percentage
Non- involve	12	16.2
Mild involve	18	24.3
Moderate involve	30	40.5
Severe Involve	14	18.9

Table 2 : Comparison of scores of hemodialysis patients based on tests

Variables	Involve with RLS Mean \pm SD	Non- Involve with RLS Mean \pm SD	P-value
Hgb	9/91 \pm 1/5	2/28 \pm 1/36	0.679
Iron	539/0 \pm 322/1	686/5 \pm 231/3	0.295
Ca	4/82 \pm 1/24	9/63 \pm 1/32	0.026
CRP	1/03 \pm 0/75	2/28 \pm 0/82	0.289

CONCLUSION

Based on the results of this study, the majority of hemodialysis patients 7/83.7 % were affected with RLS so that 24.3% of patients with mild involvement, 40.5% of patients with moderate-involvement and 18.9% of the patients suffered from severe disorders. Serum levels of iron in hemodialysis patients with RLS were less than patients without RLS. But There was not a statistically significant relationship between the average iron with RLS. Serum calcium was less in hemodialysis patients with RLS than hemodialysis patients without RLS. There was a statistically significant relationship between the mean calcium with RLS. In a study, hemmati et al. titled association between quality of life in hemodialysis patients with RLS, the results showed that 57.3% had RLS and 42.7% had no RLS. The age mean in affected group with RLS was 59.27 ± 16.86 and in the group without RLS was 55.20 ± 17.95 . The average age difference between the two groups had not statistically significant ($p=0.131$)(24).

In this study, the non-affected patients with RLS were 16.2%. It observed a relationship between physical activity and RLS ($P < 0.05$). Also, 66% of participant who had RLS, they had between 6-10 years history of hemodialysis. So that, there was a significant relationship between the duration of hemodialysis and RLS($p < 0.05$). Based on the results of Ansariani et al. study, there was a positive positive significant difference between duration of dialysis in dialysis patients with RLS(51 ± 6.7 month and 34 ± 2.5 , $P = 0.025$) (16). In consistent of this study, Al-Jahdali Study results also showed that about 80% of dialysis patients suffered RLS(25). In study conducted by Salimipour et al. 33.1% patients underwent hemodialysis, had RLS and this syndrome had no relationship with ferritin (12). In this study, the serum level of iron in non-affected patients non with $686/5 \pm 231/3$ and in patients with RLS was 539.0 ± 322.1 , which was not statistically significant($P=0.295$). In contrast of our findings, in a research conducted by Habibzade et al. titled the relationship between iron deficiency and RLS in hemodialysis patients, the results showed that 38.7% of these patients had complain of RLS which the serum iron mean was 78 ± 29.3 $78 \mu\text{g/dl}$. In this research, serum levels of iron in hemodialysis patients with RLS was significantly lower than hemodialysis patients without RLS, but the statistical tests did not show a significant difference in this case($P < 0.05$) (2). The results of Okeeffe in a study with aim of survey the secondary etiology of RLS in elderly demonstrated that RLS is more common in the patients with Iron deficiency anemia (26). Guerreiro has carried out a study to evaluate the correlation between biochemical findings and RLS in patients with Parkinson's disease. The results had not cleared any statistical relationship between during of hemodialysis, age, Urea, Ferritin, Creatinin, Hemoglobin with RLS(27) which these findings are consistent with our findings. In this study, the calcium mean had significant statistical difference in both groups with RLS or without RLS and the serum calcium in affected group with RLS was lower which this result is in consistent with Vigna study(28). While in Agarwal study, the hemodialysis patients

with RLS had upper level calcium and this raising in calcium serum through unclear mechanisms lead in triggering the signs of RLS (15). In another research by Garcia-Borreguero, the researcher reported that taking calcium supplement is useful in RLS(29). Ansariani et al. Also studied the association between RLS and ferritin, serum iron in in patients with chronic renal failure(CRF). The results showed that there was not a significant difference between hemoglobin levels (10.1 ± 0.31 g/dl , 9.7 ± 0.18 g/dl , $p= 0.36$), iron(74.3 ± 6.6 , 72.2 ± 6.3 , $P=0.75$) and ferritin(519.8 ± 138 , 684 ± 97.4 , $p=0.34$). in both group of patients with CRF with RLS or without RLS. It observed a relationship between RLS and severity of daytime sleepiness in patients. Thus, according to the results of this study, in CRF patients, There was not a relationship between RLS and serum ferritin, serum and anemia (16) which is consistent with the results. In a research has conducted by Korkmaz titled investigation of biochemical and clinical characteristics in two group of patients undergoing dialysis with RLS or without RLS , It concluded that folic acid and Vitamin B in group affected by RLS was lower significantly than healthy group. Also there was not statically significant between the two groups in terms of hemoglobin mean, iron, TIBC, ferritin, folic acid, vitamin B12 and calcium(30). In our study, However, in our study, the mean of calcium were significantly associated with restless legs syndrome. Mao et al. found a statistically significant difference between calcium mean in dialysis patients with and without RLS (31) which the results which the results of this study contradict with our study. The difference in results with the results of other researches may be due to differences in diagnostic procedures for RLS, racial and social differences as well as the sample size is small. Because the high incidence of RLS in hemodialysis, some efforts do to find factors associated with RLS in these patients. They may be beneficial to have beneficial results. Therefore, given that the studies produced conflicting results on blood biochemical factors and this syndrome have suggested, studies with larger sample size is recommended.

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