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**Original Article**

# The Association between Biochemical Parameters and Sleep Related Disorders in Hemodialysis Patients

Jing-Yi Chen[1,2], Yen-Chung Lin[1,2], Hsi-Hsien Chen[1,2], Chih-Chin Kao[1,2], Fan-Chi Chang[1,2], Tzen-Wen Chen[1,2], Mai-Szu Wu[1,2]

[1]Devision of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan
[2]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

**BACKGROUND:** Sleep disorders in long-term hemodialysis patients with comorbidities are common. They affect the quality of life and physical well-being of patients. However, little attention has been paid to this phenomenon.
**METHODS:** Thirty-nine long-term hemodialysis patients with > 3 months of care at Taipei Medical University Hospital were prospectively enrolled. Participants' biochemical data and sleep disorder scores were collected for analysis using questionnaire. Laboratory data were evaluated and scored by association, and further analyzed by both univariate and multivariate binary logistic regression analyses.
**RESULTS:** The age range of the study population was 55.2 ± 11.1 years. In the correlation study, insomnia, determined by a higher Pittsburgh Sleep Quality Index (PSQI) score, was directly correlated with the severity of restless legs syndrome. After adjusting for age and sex in the multivariate analysis, a low serum creatinine level did not correlate with insomnia ($P$ = 0.05); low serum sodium, potassium, and chloride levels strongly correlated with the severity of restless legs syndrome ($P$ = 0.04, 0.02, and 0.003, respectively). Furthermore, elevated uric acid and fasting blood glucose levels were associated with depressed mood according to the Beck Depression Inventory ($P$ = 0.012 and 0.024 respectively). However, only blood glucose level was associated with depressed mood according to the Center for Epidemiologic Studies Depression Scale (CESD) ($P$ = 0.03).
**CONCLUSION:** Biochemical differences exist between patients with sleep disorders and those without. In addition to impaired renal function and related electrolyte imbalance, metabolic problems such as hyperlipidemia and hyperuricemia may also affect the diagnosis of sleep disorders in hemodialysis patients. However, further research is warranted to confirm these results.

***Keywords: depressive disorder, hemodialysis, insomnia, restless legs syndrome, sleep disorders***

## Introduction

Maintenance renal replacement therapy (RRT) plays an important role in prolonging life in patients with end stage renal disease (ESRD) (1), even though the quality of life perceived by ESRD patients remains less optimistic than that of the general population (2, 3). Sleep disorders are a common phenomenon in ESRD patients, and have an impact on their quality of life and mortality rates (4).

An increasing number of studies have elucidated that uremia-related common sleep disorders (e.g., insomnia), depressed mood, excessive daytime sleepiness, obstructive sleep apnea and restless legs

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Corresponding author: Yen-Chung Lin, Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, No. 252, Wuxing St., Xinyi Dist., Taipei City 11031, Taiwan. Tel: 886-2-27372181, Fax: 886-2-27363051,
E-mail: yclin0229@tmu.edu.tw

syndrome are associated with frequent hospital visits, disruptions in work and social activities, arteriovenous fistula, graft puncture, fluctuations in hemodynamic status, and other complications. In addition, biochemical data such as inflammation markers, hemoglobin, phosphate, and triglyceride levels may be correlated with the effectiveness of dialysis treatment, and they are associated with sleep disorders (5-8).

We conducted a prospective cohort study in order to evaluate the biochemical findings of chronic hemodialysis patients in a single medical center, and search for possible associations with sleep disorders.

## Materials and Methods

This was a prospective cohort study. Patients receiving regular hemodialysis treatment in our hospital for a minimum of 3 months were considered eligible candidates. During the surveillance period, patients with relatively unstable physical conditions (e.g., acute medical concerns, an inpatient status, or incompetent to understand or mark the questionnaire themselves) were excluded. Participants were told to keep taking their hypnotics as prescribed. Finally, a total of 39 patients were included in the statistical analysis. All participants signed informed consent documents, and the study was regulated by the Institutional Review Board (ID number: 201503052). Regularly checked biochemical parameters were collected for 3 months from May, 2015 to July, 2015. A series of questionnaires including Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Beck Depression Inventory (BDI), Center for Epidemiologic Studies Depression (CESD) and International Restless Legs Syndrome Study Group (IRLSSG) criteria were used to evaluate the symptoms of insomnia, daily sleepiness and depression, and the severity of restless legs syndrome, respectively. All collected data were analyzed by SPSS software, version 19.

## Results

### Participants' Attributes with the Average Laboratory Values Distribution and Scales

Thirty-nine patients including 17 males and 22 females enrolled in this study. The age range was 55.2 ± 11.1years (mean ± standard deviation). The underlying systemic and chronic diseases included hypertension in six patients, diabetes mellitus in four patients, heart diseases in four patients, hypothyroidism in one patient, and autoimmune diseases (i.e., vasculitis and systemic lupus erythematosus) in two patients.

The participants' age, average laboratory values, and different score values are listed in Table 1.

### The Relationship between the Laboratory Values and the Different Scores

In evaluating the different scores, it was noted that patients with a high PSQI score have more severe restless legs syndrome (Spearman's correlation = 0.423, $P = 0.008$). Furthermore, patients with a high BDI score also have a high score in CESD (Spearman's correlation = 0.538, $P = 0.001$). We evaluated the relationship between the laboratory values and the different scores, and they are listed in Table 2.

Serum creatinine, mean corpuscular volume (MCV), and ferritin levels affected the patient's PSQI scores with a statistically significant $P$ value ($P$ = 0.034, 0.013 and 0.035, respectively). Restless legs syndrome scores were statistically significant when correlated with electrolyte imbalance: sodium and potassium ($P = 0.022$ and $P = 0.029$, respectively). The ESS scores were statistically significant with serum GOT and GPT values ($P = 0.010$ and $P = 0.027$, respectively). The BDI scores were influenced by serum hemoglobin levels ($P = 0.042$). The CESD Scale showed an association with fasting blood glucose and globulin levels ($P = 0.041$ and $P = 0.010$, respectively).

### The Relationship between the Laboratory Values and the Insomnia Status

The PSQI is a self-reporting questionnaire that is widely used to assess one's sleep quality over the past month. A high score of five or more is considered poor sleep status. According to the scores of PSQI, the 36 patients were divided into two groups: PSQI ≥ 5 (with insomnia) and PSQI < 5 (without insomnia) with a sensitivity of 89.6% and a specificity of 86.5%. After adjusting for age, sex, lipid profile and liver function; low creatinine values were statistically significant between the group with insomnia and the group without insomnia ($P = 0.043$, $t = 0.398$).

### The Relationship between the Laboratory Values and Restless Legs Syndrome

The National Institute of Health/International

**Table 1.** The average values of laboratory data and scores

| | |
|---|---|
| PSQI score | 9.66 ± 4.15 |
| BDI score | 9.69 ± 8.14 |
| ESS score | 7.15 ± 3.60 |
| RLS fitting criteria items | 2.13 ± 1.44 |
| CESD score | 15.88 ± 8.72 |
| Age | 55.24 ± 11.17 |
| Fasting sugar [mg/dL] | 109.94 ± 51.94 |
| Albumin [g/dL] | 3.79 ± 0.31 |
| Globulin [g/dL] | 3.38 ± 0.48 |
| Cretinine [mg/dL] | 11.18 ± 2.59 |
| Uric acid [mg/dL] | 7.08 ± 1.28 |
| Cholesterol [mg/dL] | 178.62 ± 38.92 |
| Triglyceride [mg/dL] | 126.90 ± 74.71 |
| Alkaline phosphatase [U/L] | 102.27 ± 88.04 |
| Glutamate oxaloacetate transaminase [U/L] | 17.36 ± 11.007 |
| Glutamic-pyruvate transaminase [U/L] | 13.76 ± 7.51 |
| Chloride (Cl) [mEq/L] | 94.03 ± 2.86 |
| Sodium (Na) [mEq/L] | 137.11 ± 3.21 |
| Potassium (K) [mEq/L] | 5.11 ± 0.70 |
| Calcium (Ca) [mg/dL] | 9.13 ± 0.86 |
| Phosphate (P) [mg/dL] | 5.93 ± 1.53 |
| White blood cell (WBC) [10^3/uL] | 7.19 ± 2.05 |
| Red blood cell (RBC) [10^6/uL] | 3.81 ± 0.55 |
| Hemoglobin (Hgb) [g/dL] | 11.25 ± 1.55 |
| Hematocrit (Hct) [%] | 33.88 ± 4.63 |
| Mean corpuscular volume (MCV) [fL] | 89.59 ± 7.94 |
| Platelet (PLT) [10^3 /uL] | 191.19 ± 57.27 |
| Iron (Fe) [ug/dL] | 61.79 ± 25.86 |
| Total Iron Binding Capacity (TIBC) [ug/dL] | 226.53 ± 43.53 |
| Ferritin [ng/mL] | 487.21 ± 330.51 |
| Intact parathyroid hormone | 429.62 ± 323.00 |

RLS Study Group (IRLSSG) mandated four criteria that must be met in order for the diagnosis of restless legs syndrome. An imbalance of sodium, potassium and chloride also meets the diagnostic criteria of RLS ($P$ = 0.042, 0.013 and 0.027, respectively).

## The Relationship between the Laboratory Values and Daytime Sleepiness Status

The ESS, introduced in 1991 by Dr. Murray Johns of Epworth Hospital in Melbourne, Australia, is a scale intended to evaluate the severity and frequency of daytime sleepiness. The scale consists of eight questions with the highest possible score of 24. A score of less than eight is considered no daytime sleepiness. As the score increases so does the severity of the condition. Although liver function seemed to have an impact on daytime sleepiness, there were no statistically significant results under further regression evaluation.

**Table 2.** Spearman's rho and significant between laboratory level and different scores

| | | PSQI | BDI | ESS | RLS | CESD |
|---|---|---|---|---|---|---|
| Glucose | Spearman's rho | .216 | .302 | .067 | .200 | .374 |
| | *P* values | .227 | .083 | .705 | .256 | .041 |
| Albumin | Spearman's rho | -.056 | .151 | -.045 | .113 | .131 |
| | *P* values | .744 | .372 | .791 | .504 | .474 |
| Globulin | Spearman's rho | -.059 | -.053 | -.131 | -.025 | .451 |
| | *P* values | .734 | .756 | .439 | .883 | .010 |
| Creatinine | Spearman's rho | -.375 | .021 | .186 | .179 | -.034 |
| | *P* values | .034 | .909 | .299 | .319 | .863 |
| Uric acid | Spearman's rho | .134 | -.009 | .321 | .252 | -.006 |
| | *P* values | .459 | .958 | .064 | .150 | .976 |
| Glutamate oxaloacetate transaminase | Spearman's rho | .027 | .067 | -.426 | -.280 | -.064 |
| | *P* values | .877 | .697 | .010 | .099 | .730 |
| Glutamic-pyruvate transaminase | Spearman's rho | .227 | .045 | -.364 | -.092 | -.169 |
| | *P* values | .184 | .792 | .027 | .587 | .356 |
| Chloride | Spearman's rho | -.010 | -.171 | -.050 | .049 | -.343 |
| | *P* values | .958 | .333 | .781 | .783 | .063 |
| Sodium | Spearman's rho | -.220 | -.136 | -.210 | -.380 | -.338 |
| | *P* values | .204 | .428 | .219 | .022 | .063 |
| Potassium | Spearman's rho | -.159 | -.182 | -.298 | -.364 | .093 |
| | *P* values | .363 | .289 | .078 | .029 | .617 |
| Calcium | Spearman's rho | -.224 | -.218 | .258 | -.078 | -.343 |
| | *P* values | .209 | .215 | .141 | .661 | .064 |
| Phosphate | Spearman's rho | -.057 | .151 | -.175 | -.104 | .027 |
| | *P* values | .743 | .379 | .307 | .544 | .886 |
| Hemoglobin | Spearman's rho | -.083 | -.350 | .030 | -.125 | -.351 |
| | *P* values | .645 | .042 | .867 | .483 | .057 |
| Hemotocrit | Spearman's rho | -.034 | -.333 | .085 | -.103 | -.348 |
| | *P* values | .850 | .054 | .633 | .561 | .060 |
| Mean corpuscular volume | Spearman's rho | -.448 | -.176 | -.055 | -.088 | -.230 |
| | *P* values | .013 | .344 | .767 | .637 | .248 |
| Platelet | Spearman's rho | -.160 | .253 | -.137 | .168 | .334 |
| | *P* values | .351 | .131 | .420 | .320 | .062 |
| Total iron binding capacity | Spearman's rho | .084 | .041 | -.080 | -.320 | .065 |
| | *P* values | .641 | .817 | .653 | .065 | .732 |
| Ferritin | Spearman's rho | -.374 | -.130 | -.088 | -.301 | .009 |
| | *P* values | .035 | .469 | .626 | .089 | .962 |
| Intact parathyroid hormone | Spearman's rho | -.335 | -.070 | .206 | .087 | -.024 |
| | *P* values | .061 | .698 | .250 | .631 | .903 |

### The Relationship between the Laboratory Values and Depression Status

The BDI is a self-reporting inventory consisted of 21 multiple-choice questions. It is a widely used psychometric test for measuring the severity of depression. According to the score design, a score of more than 13 indicates a depression status. A score between 14 and 19 is considered mild depression. A score between 20 and 28 is considered moderate depression. A score more than 28 is considered severe depression. Higher fasting glucose and uric acid levels were significantly correlated with depressed mood ($P = 0.024$ and $P = 0.012$, respectively) under multivariate regression after adjusting for age and sex (Table 3).

The CESD Scale is a 20-item questionnaire with a total possible score of 60. This is another frequently used tool for depression diagnosis and psychological status evaluation. Referral to a mental health practitioner for further evaluation is recommended with a score of more than 16. A high glucose level was associated with a CESD score of more than 16 ($P = 0.030$, $t = 1.023$). Referral to a psychological department was provided for those participants with a score of 16 and higher for mental health evaluation and treatment.

We thereafter summarized the relationship between clinical laboratories and sleep disorder as shown in Fig. 1.

## Discussion

In this study, we found that biochemical differences were noted between the two groups (sleep disorders, and non-sleep related disorders). Some of the laboratory data indicated that there is a relationship between insomnia and electrolyte imbalance; however, hyperlipidemia, anemia, and metabolic problems (e.g., elevated fasting blood glucose and uric acid levels) are considered to have an even stronger correlation with insomnia.

ESRD patients receiving regular hemodialysis treatments are chronically ill and dependent on the dialysis machines (9). The diagnosis of a sleep disorder proves to be clinically significant, because it substantially disturbs the quality of life in these groups. Manifestations such as daytime sleepiness, mood problems, and higher mortality rates can all be attributed to the presence of sleep disorders (10-12). Many studies have been done to investigate the possible factors such as medical and non-medical issues that affect a patient's sleep disorder status. The common goal of these studies is to improve the quality of life in these groups.

Various biochemical parameters were considered to be strongly associated with sleep disorders or depression status in patients undergoing hemodialysis treatment.

A study of the global PSQI score showed that poor sleep quality is positively correlated with serum triglyceride, high-sensitivity C-reactive protein (hsCRP) and IL-1β levels; and negatively correlated with hemoglobin and phosphate levels (13). An increasing number of studies have been investigating the roles of cytokines in the regulation of sleep and wakefulness; among them, interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the most studied. Yang *et al.* have elucidated that a high plasma interleukin-18 level, a new member of the IL-1 cytokine superfamily, is associated with poor quality of sleep in peritoneal dialysis patients (14). Chen *et al.* have reported that cognitive-behavioral therapy is effective not only for correcting disorganized sleep patterns but also for reducing inflammation and oxidative stress in hemodialysis patients (15).

Sleep quality was independently related to venous pH and bicarbonate levels (16). It was also shown that hyperglycemia and hyperuricemia are associated with depression disorder among patients receiving hemodialysis treatment. This indicates that metabolic problems should be considered as possible causes affecting the quality of life and emotional disorder status within this patient population.

Our study revealed that several biochemical parameters are correlated with the quality of life in patients undergoing hemodialysis treatment in various aspects. Clinical physicians have the responsibility to closely monitor and properly correct the abnormal biochemical values of their patients.

Blood creatinine is generated from muscle metabolism and may reflect one's muscle mass status. A high creatinine level was associated with less insomnia ($P = 0.043$, $t = 0.398$) than a low creatinine level. A reasonable explanation is that muscle mass may indicate muscle strength, physical status, or self-care ability.

Restless Legs Syndrome (RLS) is a neurological movement disorder which also occurs in the general

**Table 3.** Data affecting the insomnia and depressed mood in ESRD patient

| | | | |
|---|---|---|---|
| PSQI ≥ 5 (N = 31) vs. PSQI < 5 (N = 5)<br>Sex ($P$ = 0.253, $t$ = 0.342), Age ($P$ = 0.294, $t$ = 1.041) | | | |
| Uni-variate regression | | Milti-variate regression | |
| Creatinine | $P$ = 0.043, $t$ = 0.398 | Creatinine | $P$ = 0.984. $t$ = 0.000 |
| | | Cholesterol | $P$ = 0.984, $t$ = 95.904 |
| Cholesterol | $P$ = 0.066, $t$ = 1.045 | Creatinine | $P$ = 0.265, $t$ = 0.008 |
| | | Triglyceride | $P$ = 0.215, $t$ = 1.067 |
| Triglyceride | $P$ = 0.227, $t$ = 1.010 | Creatinine | $P$ = 0.053, $t$ = 0.419 |
| | | GPT | $P$ = 0.325, $t$ = 1.226 |
| GPT | $P$ = 0.172, $t$ = 1.212 | | |
| Fit 4 criteria of RLS (N = 10) vs. Fit 0~3 criteria of RLS (N = 26)<br>Sex ($P$ = 0.390, $t$ = 1.855), Age ($P$ = 0.245, $t$ = 0.963) | | | |
| Uni-variate regression | | Milti-variate regression | |
| Sodium | $P$ = 0.028, $t$ = 0.724 | Sodium | $P$ = 0.042, $t$ = 0.675 |
| | | Potassium | $P$ = 0.022, $t$ = 0.065 |
| Potassium | $P$ = 0.017, $t$ = 0.071 | Potassium | $P$ = 0.013, $t$ = 0.036 |
| | | Chloride | $P$ = 0.027, $t$ = 0.631 |
| Chloride | $P$ = 0.057, $t$ = 0.726 | Sodium | $P$ = 0.212, $t$ = 0.769 |
| | | Chloride | $P$ = 0.702, $t$ = 0.913 |
| BDI ≤ 13 (N = 29) vs. BDI > 13 (N = 8)<br>Sex ($P$ = 0.682, $t$ = 0.722), Age ($P$ = 0.555, $t$ = 0.979) | | | |
| Uni-variate regression | | Milti-variate regression | |
| Fasting glucose | $P$ = 0.025, $t$ = 1.020 | Fasting glucose | $P$ = 0.024, $t$ = 1.025 |
| | | Uric acid | $P$ = 0.012, $t$ = 4.203 |
| Uric acid | $P$ = 0.013, $t$ = 3.421 | Fasting glucose | $P$ = 0.082, $t$ = 1.015 |
| | | White blood cell | $P$ = 0.095, $t$ = 1.459 |
| White blood cell | $P$ = 0.105, $t$ = 1.011 | Uric acid | $P$ = 0.056, $t$ = 2.736 |
| | | White blood cell | $P$ = 0.260, $t$ = 1.277 |
| CESD ≥ 16 (N = 14) vs. CESD < 16 (N = 18)<br>Sex ($P$ = 0.487, $t$ = 1.630), Age ($P$ = 0.756, $t$ = 1.010) | | | |
| Uni-variate regression | | Milti-variate regression | |
| Fasting glucose | $P$ = 0.037, $t$ = 1.020 | Fasting glucose | $P$ = 0.030, $t$ = 1.023 |
| | | Platelet | $P$ = 0.055, $t$ = 1.017 |
| Platelet | $P$ = 0.052, $t$ = 1.017 | Fasting glucose | $P$ = 0.105, $t$ = 7.032 |
| | | Globulin | $P$ = 0.191, $t$ = 1.013 |
| Globulin | $P$ = 0.056, $t$ = 5.976 | | |

population, affecting 5 ~ 15% of people, and may be under diagnosed. RLS is a major contributor to severe insomnia symptoms in hemodialysis patients. Many studies have concluded that the negative effects of Restless Legs Syndrome have a higher prevalence than any other sleep disturbances in patients receiving dialysis treatment. A cross-sectional study containing two hundred and thirty-two patients has also come to the conclusion that there is a significant positive correlation between the RLS severity and the PSQI score (r = 0.445, $P$ = 0.006). The RLS severity was positively correlated with the inflammatory parameters, such as white blood cell count and C-reactive protein levels (r = 0.427, $P$ = 0.008 and r = 0.418, $P$ = 0.010)

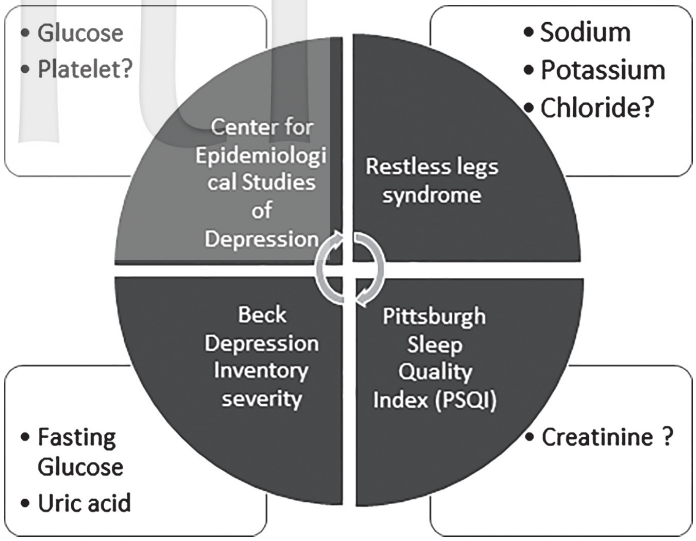


**Fig. 1.** We demonstrated the possible relationship between biochemistries and sleep related disorders.

(16). Within the study group, a coherent relationship between RLS and insomnia was also obtained. Furthermore, electrolyte imbalance, especially low sodium, potassium and chloride levels, was also significantly correlated with RLS. Patients with ESRD are susceptible to electrolyte imbalance because of their impaired renal function. They are unable to maintain electrolyte regulation and fluid balance. As a result, ESRD has an impact on the neurological movement related to the development of RLS. Iron deficiency and chronic kidney disease are the strongest predictors of RLS in older hospitalized patients. A ferritin level of less than 70 ng/mL is the best cut off value for identifying possible iron deficiency in RLS patients with inflammatory conditions (17). The study also indicated that high ferritin levels are related to high PSQI scores ($P = 0.035$).

Depressed mood was also frequently found in these patients with ESRD. Both the BDI and CESD scores were used to determine depression status. In evaluating the possible causes of depression, the laboratory data and high fasting blood glucose levels were strongly correlated with the depressed mood status and the need for a mental health referral. Inadequate blood sugar control was reflected in the poor physical status of these patients with acute and chronic medical problems, such as infection or metabolic problems; it could possibly contribute to the psychological status of depression.

High uric acid levels also significantly affected a patient's depression condition in the ESRD group ($P = 0.012$, $t = 4.203$). Uric acid, a product of the metabolic breakdown of purine nucleotides, is reflected in the body's energy source, signaling transmission and antioxidant activity. High uric acid levels reflect metabolic disorders, and may result in a series of medical or psychological problems. Recently, there has been an increase in the discussion regarding the role of uric acid in psychological disorders (13, 18).

Hemodialysis patients suffer a range of symptoms and disturbances, and these biochemical values may provide us the ability to link them to chronic hemodialysis treatment and the resulting biochemical imbalance, because they objectively reflect the physical status of a patient.

A limitation of this cohort study was its small sample size. This was a cross-sectional, single center study on sleep related disorders, and the biochemical abnormalities that may have contributed to their cause. Our strength was the use of the four different questionnaires in approaching and collecting data from these chronic hemodialysis patients.

In summary, the prevalence of hemodialysis treatment increases in Taiwan, and sleep disorders are getting more attention as an important factor linked to the quality of life. In a clinical setting, biochemical abnormalities may be associated with the deterioration of sleep quality in chronic hemodialysis patients.

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