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ORIGINAL ARTICLE

# Melody of sleep by sun: Association between serum vitamin D levels and sleep quality in ESRD patients

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A B S T R A C T

**Background**: Hemodialysis (HD) is a commonly employed treatment modality for chronic kidney disease (CKD) patients. Along with its other effects on the body, hemodialysis is also closely related to the sleep-wake cycle. It has both sleep-improving and deteriorating results. Sleep regulation is tightly coupled to vitamin D; hence, its deficiency might impact the duration and quality of sleep. This study intends to evaluate the association between sleep quality and serum vitamin D levels in HD patients.

**Objective:** To assess the quality of sleep in patients with ESRD on routine HD and determine the association of vitamin D deficiency with sleep quality.

**Methodology:** This cross-sectional analytical study was conducted on the patients presenting to the dialyzing centre of the Department of Nephrology, Holy Family Hospital, Rawalpindi, Pakistan, for twice-weekly routine hemodialysis, from May 2022 to June 2022. The chi-square or Pearson test evaluated correlations between the variables. Odds ratios (OR) were obtained using linear regression with 95% CIs (confidence intervals).

**Results:** In this study, the quality of sleep in End Stage Renal Disease (ESRD) patients on twice-weekly hemodialysis (HD) was assessed using the PSQI score. PSQI scores were associated with serum vitamin D levels in these patients. A significantly strong positive correlation existed between serum levels of 25-OH D and sleep quality ($r = -0.468$, $p = 0.001$).

**Conclusion:** More than half of the patients undergoing routine hemodialysis could not sleep well at night. Among other related factors, vitamin D deficiency was an independent risk factor for poor sleep quality. Further studies are needed to determine the impact of vitamin D supplementation on improving sleep quality to strengthen the association between vitamin D levels and sleep disorders.

**Keywords:** *ESRD, Hemodialysis, PSQI score, Vitamin D*

## Introduction

Sleep is a form of self-healing, and it occupies 20-40% of the day of an average human being. However, patients suffering from CKD commonly face the problem of poor sleep quality.[1] The health-related quality of life (HRQOL) is an effective tool for assessing patients' comprehensive perception of mental, physical, and emotional health, and it is accepted as a health outcome. Poor sleep quality directly correlates with the decline in HRQOL, leading to poor quality of life.[2] As hemodialysis is the primary treatment modality in ESRD, studying the effects of hemodialysis on the quality of sleep has recently caught the attention of healthcare providers. About 50-80% of patients undergoing hemodialysis experience sleep quality deterioration.[3]

Hemodialysis is closely related to the sleep-wake cycle of the patient. It not only confers the benefits of sleep-inducing effects by limiting mobility, accelerating interleukin-1 production, increasing body temperature, and altering the brain's osmotic imbalance, leading to reduced consciousness.[4] On the other hand, it also comes with many disadvantages, such as sleep apnea syndrome, restless leg syndrome, sleep disturbances, and excessive anxiety during the day, thus reducing sleep quality and duration. After a while, these sleep disturbances may lead to 'day-night reversal', that is, insomnia at night and sleepiness during the day, depressed mood, headache, and reduced daytime functionality.[4]

Poor sleep represents an independent predictor of mortality in HD patients.[5] Furthermore, and it can cause the development of cardiovascular diseases and sleep apnea, which can serve as a primary cause of death in patients with renal disease. A sleep span of fewer than 5 hours is associated with a rapid decline in renal function compared to sleeping 7–8 hours in healthy people.[6] Sleep deprivation also harms the body's immune responses.[7] Therefore, early diagnosis and timely action are necessary to improve these patients' sleep quality.

According to studies, 86.8% of CKD patients experience sub-optimal Vitamin D levels, as CKD is a risk factor for Vitamin D deficiency.[8] Multiple factors may contribute to vitamin D deficiency in patients with CKD, such as limited exposure to sunlight, impaired epidermal synthesis of vitamin D, impaired hepatic conversion of cholecalciferol to calcidiol, decreased intake of Vitamin D-rich foods, and inadequate absorption of vitamin D from the GI tract.[9] The sleep-wake cycle regulation is closely linked to vitamin D; hence, its deficiency harms sleep quality.

Vitamin D, directly and indirectly, affects circadian rhythm, as 25-OH D receptors (VDRs) have been found in the brain regions involved in sleep.[10] Recently, it has been suggested that vitamin D has an essential role in serotonin and melatonin regulation that, in turn, modulate the regulation of mood and sleep.[11, 12] Through this study, we aim to examine the possible association between serum vitamin D levels and sleep disturbance in HD patients. Multiple studies have shown that the prevalence of low sleep quality has become a common problem in ESRD patients.

Thus, patients' sleep quality needs to be evaluated periodically. So, the modifiable factors, including hypovitaminosis D can be duly addressed, and proper supplementation is undertaken to improve the quality of life of CKD patients.

## Methodology

This cross-sectional analytical study was conducted on 97 patients presenting to the dialyzing centre of the Department of Nephrology, Holy Family Hospital, Rawalpindi, Pakistan, for twice-weekly routine hemodialysis. The study was conducted from May 2022 to June 2022. Inclusion criteria were all ESRD patients aged 18-75 who have been on twice-weekly HD for at least the last three months and have given informed consent to participate in the study. The pediatric group of age less than 13 years and patients having any pre-defined independent risk factor that can adversely affect the quality of sleep, like anaemia (Hb < 10), diabetic nephropathy, or any active inflammatory state, was not included in the study. Similarly, patients with dementia, mental retardation, major depressive disorder, severe pulmonary diseases, acute heart failure, and a history of hospitalization within the last six months were also excluded from the study. After considering the inclusion and exclusion criteria, the study was conducted on 82 patients, out of which two patients lost follow-up due to changes in the dialysis centre and death, respectively. So, the final analysis was done on 80 patients.

Serum levels of 25 (OH) D were evaluated in patients before dialysis. Venous blood samples were withdrawn and sent to a well-known authentic laboratory affiliated with the department under strict protocols of care. The assay was performed via Chemiluminescent Microparticle Immunoassay (CMIA), and results were recorded as the standard unit of ng/ml. The patients were divided into three groups based on KDOQI guidelines: Sufficiency: >30 ng/ml, insufficiency: 16-30 ng/mL, mild deficiency: 5-15 ng/mL, and severe deficiency: <5 ng/mL.[13]

The Pittsburgh sleep quality index (PSQI) standard questionnaire was obtained from https://aurora.edu/documents/wellness/assessment.pdf. Previously, it has been used in and validated by multiple studies, and the specificity and sensitivity of this questionnaire have been well-defined.[14, 15] The

questionnaire was clearly explained to the patients and the data was collected through detailed interviews. The questionnaire consists of seven components. A global PSQI score between 0 to 21 was obtained by adding the score of individual components. The patients were divided into two groups based on their PSQI scores: a score of ≥ 5 suggests poor sleep quality and a score of < 5 is a marker of good sleep quality.[16]

Plan for Statistical Analysis: Data obtained were entered and analyzed via SPSS version 25. The patient's demographic and clinical characteristics were expressed as the mean ± SD (standard deviation). The prevalence of poor sleep quality and vitamin D deficiency in the sample population was calculated. Variables with normal distribution were analyzed by t-test. The chi-square or Pearson test evaluated correlations between the variables. Odds ratios (OR) were obtained using linear regression with 95% CIs (confidence intervals). p ≤ 0.05 was considered significant.

## Results

Our study assessed the sleep quality in 80 CKD patients on twice-weekly HD using the PSQI score obtained from a unit global questionnaire. PSQI scores were associated with serum vitamin D levels in these patients, as in Figure 1.

The mean age of participants was 42.9 ± 15.07 years; 48.3% (n=35) were women, and 51.7% (n= 45) patients were men. Various types of vascular access were used for HD procedures depending on the individual preferences and feasibility; 67.5% of patients had an arteriovenous fistula (AV fistula) (n = 54), 10.0 % had a permanent catheter (n = 8) and the rest of 22.5 % had double-lumen catheter (DLC) (n =18).

Furthermore, the initial indication for starting hemodialysis was assessed among patients. It was calculated that 71.25 % (n = 57) of patients had hypertensive nephropathy, 16.2 % (n = 13) of patients had AKI progressing to CKD; 8.75 % (n = 7) patients had chronic interstitial nephritis, and three patients (3.7 %) suffered from autosomal dominant polycystic kidney disease (ADPKD) that led to the initiation of hemodialysis.

The average PSQI score among the study population was 8.61 ± 5.66. 63.7 % (n = 51) of the population shows PSQI score ≥ 5, representing significant sleep disturbance. The people with poor sleep quality have a mean PSQI score of 12. The mean serum levels of 25 (OH) D (ng/ml), Ca, Mg, and P were 19.09 ± 15.59, 9.28 ± 0.98, 3.048 ± 0.82, and 3.963 ± 1,44, respectively. A significantly strong positive correlation existed between serum levels of 25-OH D and sleep quality (r = −0.468, p = 0.001). However, observations showed no significant correlation between age and patients' sleep disorders (p = 0.093) and no correlation between sleep quality and gender (p = 0.290). Similarly, no significant association was found between the quality of sleep and serum PTH (p = 0.417), serum Ca (p = 0.654), serum Mg (p = 0.095), and serum phosphate (p = 0.750), as in Table 1 and 2.

**Table 1: Demographic and clinical characteristics between patients with good and poor quality sleep**

| Characteristics | Patients with Good Sleep Quality | Patients with Poor Sleep Quality | *p-value* |
|---|---|---|---|
| Number (%age) | 29 (36.3%) | 51 (63.7%) | |
| Age (years) | 39.45 ± 11.48 | 45.00 ± 16.53 | 0.093 |
| Gender:<br>Men<br>Women | <br>16 (20 %)<br>13 (16.25 %) | <br>29 (36.25 %)<br>22 (27.5 %) | 0.290 |
| Vitamin D (ng/ml) | 29.21 ± 21.86 | 13.33 ± 4.80 | 0.001 |
| Serum Calcium | 9.48 ± 0.94 | 9.17 ± 0.99 | 0.654 |
| Serum Magnesium | 3.01 ± 0.47 | 3.06 ± 0.96 | 0.095 |
| Serum Phosphate | 3.84 ± 1.31 | 4.03 ± 1.52 | 0.750 |
| PTH | 555.66 ± 550 | 331.10 ± 506 | 0.417 |
| Duration of hemodialysis (years) | 11.25 | 12.67 | |
| **Mode of access for HD** | | | |
| AV fistula | 31 (38.75 %) | 23 (28.75 %) | 0.334 |
| Perma Cath | 03 (3.7 %) | 05 (6.2 %) | |
| DLC | 11 (13.7 %) | 07 (8.7 %) | |
| **Initial Indication for Hemodialysis** | | | |
| Hypertensive Nephropathy | 30 (37.5 %) | 27 (33.7 %) | 0.087 |
| AKI Progressing to CKD | 08 (10 %) | 05 (6.2 %) | |
| Chronic interstitial nephritis | 04 (5.0 %) | 03 (3.7 %) | |
| ADPKD | 03 (3.7 %) | 00 (0 %) | |

**Table 1: Correlation between the studied variables in patients with poor quality of sleep (PSQI Scores >5)**

| Variables | | Age | Vitamin D | Calcium | Magnesium | Phosphate | PQSI score | PTH |
|---|---|---|---|---|---|---|---|---|
| Age | *r* | 1 | -.090 | -.144 | -.040 | .078 | .170 | -.222 |
| | *p*-value | | .427 | .201 | .721 | .490 | .133 | .048 |
| Vitamin D | *r* | -.090 | 1 | .232 | .046 | -.049 | -.468 | .047 |
| | *p*-value | .427 | | .039 | .686 | .666 | .001 | .676 |
| Calcium | *r* | -.144 | .232 | 1 | .038 | -.054 | -.197 | -.133 |
| | *p*- value | .201 | .039 | | .741 | .634 | .080 | .239 |
| Magnesium | *r* | -.040 | .046 | .038 | 1 | .024 | -.137 | .045 |
| | *p*-value | .721 | .686 | .741 | | .835 | .227 | .692 |
| Phosphate | *r* | .078 | -.049 | -.054 | .024 | 1 | .041 | .270 |
| | *p*-value | .490 | .666 | .634 | .835 | | .720 | .016 |
| PQSI score | *r* | .170 | -.468 | -.197 | -.137 | .041 | 1 | -.318 |
| | *p*-value | .133 | .001 | .080 | .227 | .720 | | .004 |
| PTH | *r* | -.222 | .047 | -.133 | .045 | .270 | -.318 | 1 |
| | *p*-value | .048 | .676 | .239 | .692 | .016 | .004 | |

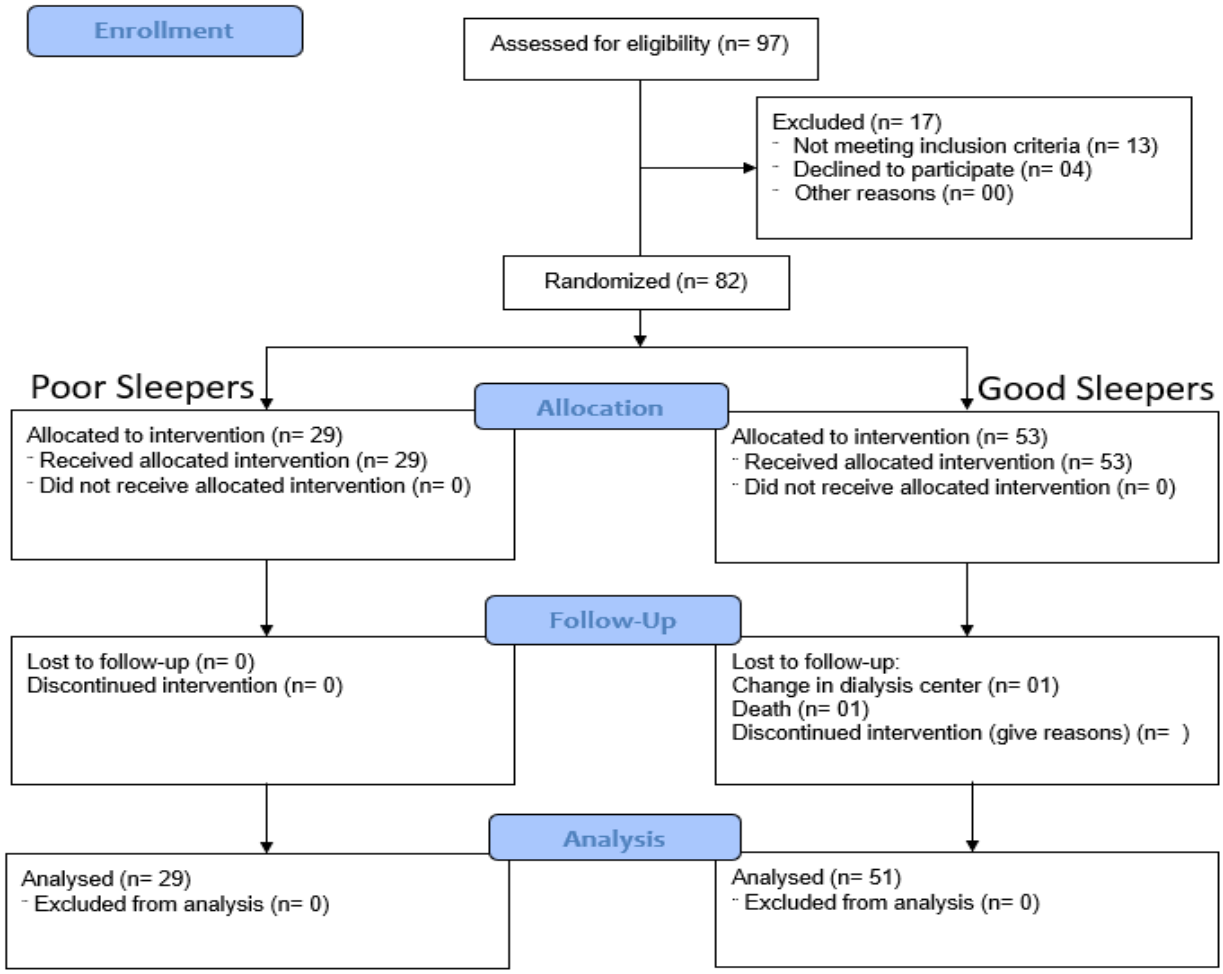


**Figure 1: The CONSORT 2010 flow diagram for hemodialysis patients**

## Discussion

Our study demonstrated that a significant percentage of patients suffering from CKD were experiencing poor sleep quality. Similar large-scale studies have been conducted in China and Korea, concluding that poor sleep might be an independent risk factor for CKD.[17-19] Poor sleep quality in CKD patients results from interlinked processes. The many factors involved make it challenging to designate a single causative agent as the sole cause of disturbed sleep patterns. These can be ESRD-specific factors like anaemia, obstructive sleep apnea, restless leg syndrome, and other comorbidities, metabolic acidosis, uremia, hypertension, diabetic nephropathy, and nephrogenic pulmonary oedema; psychological disorders including depression or anxiety; lifestyle factors (coffee/nicotine use, sleep hygiene) and treatment-related factors, which encompass dialysis shift timing, dialysis disequilibrium syndrome, side effects of medications as well as personal habits like daytime napping and disruptions in circadian rhythm.[20, 21] On the contrary to that, there are few other studies with limited sample sizes (n < 500) that have reported that individuals with poor sleep quality had better renal function as compared to others.[22]

These overlapping phenomena highlight the difficulty in assessing sleep disorders for clinical or research purposes and suggest that the issue should be dealt with comprehensively by applying a multi-layered approach. That's why the association between sleep quality and all these factors has been subjected to research repeatedly.

One of the modifiable factors brushed aside was hypovitaminosis D. In the past, few studies showed a negative correlation between serum vitamin D levels and sleep quality in CKD patients.[23] Furthermore, other studies suggested a strong association between vitamin D and quality of sleep in patients suffering from other diseases like systemic lupus erythematosus and elderly adults. [24, 25] Encouraged by past reports, we conducted this relatively smaller-scale study to find the association between 25-OH D levels and sleep quality in patients with CKD, which has yielded similar results.

Patients with CKD usually have vitamin D deficiency, considering that the cutoff limit for vitamin D in CKD is higher than in healthy adults, i.e., 30 ng/dl. Vitamin D plays diverse roles in the human body bone turnover, control of the inflammatory response, and cellular differentiation. Therefore its deficiency is closely related to disease progression and mortality. [26, 27]

It is also seen that in severe kidney hyperparathyroidism, PTH plays a pivotal role in causing sleep disorders, and parathyroidectomy could markedly alleviate these symptoms in about half of the patients undergoing HD.[28, 29] Even after adjusting confounding factors such as serum Ca, P, and PTH levels, the result remains the same, with a negative correlation between vitamin D levels and sleep quality.[23] Vitamin D supplementation has proven to be relatively safe and effective in patients undergoing HD [30, 31,] but it is also one of the most economical and accessible means of improving the overall patient quality of life index. Quite a few RCTs have previously shown that by increasing the serum level of vitamin D, the scores obtained from the PSQI questionnaire in these patients decreased, and as a result, the quality of sleep was improved. One such trial was conducted in 2008, which proved that daily oral supplementation of 25-OH D in doses as low as 10-30 mg/d entirely resolved vitamin D deficiency in HD patients while maintaining a high safety profile. However, this matter is still debatable as vitamin D supplementation might not show notable improvement in sleep quality, as observed in similar studies. [32]

Considering these contradictory results, we suggest a better interventional study involving multiple centres, as the present study showed some technical setbacks. As a cross-sectional study with a small sample size, not only could it establish a causal relationship between observed variables, it didn't rule out a possible bidirectional relationship either. The information was collected from a single dialyzing centre via self-reporting, and there might be recall bias, miscalculation, and lack of diversity.

The high incidence and underdiagnosis of nephrogenic pulmonary oedema, sleep apnea, restless leg syndrome, and insomnia in CKD patients necessitate well-designed experimental studies with large sample sizes and ethnic diversities. Upcoming research should target the complex interrelationships between sleep and kidney disease and, as a result, propose innovative treatments for sleep disorders that can take the multifaceted physiological and psychosocial challenges these patients go through. We

also suggest routine assessment of the sleep quality of patients to improve the overall quality of life, repeated measurements of vitamin D levels, and oral supplementation at regular intervals to take appropriate steps towards improving these effortlessly changeable yet commonly overlooked factors.

## Conclusion

This study concluded that more than half of the patients undergoing routine hemodialysis were unable to get sound sleep at night. Among other related factors, vitamin D deficiency was an independent risk factor for poor sleep quality. Further studies can be conducted to determine the impact of vitamin D supplementation on improving sleep quality to strengthen the association between vitamin D levels and sleep disorders.

## Recommendations

- Patients suffering from CKD commonly face the problem of poor sleep quality. Out of these, about 50-80% of hemodialysis patients experience deterioration in sleep quality.
- Poor sleep quality directly correlates with the decline in the Health-Related Quality of Life Index (HRQOL), leading to poor quality of life. It also represents an independent predictor of mortality in HD patients.
- Multiple factors contribute to vitamin D deficiency in patients with CKD, so much so that 86.8% of CKD patients experience sub-optimal Vitamin D levels.
- Vitamin D, directly and indirectly, affects circadian rhythm as 25-OH D receptors (VDRs) have been found in the brain regions involved in sleep. So, it has been found through multiple studies that vitamin D levels directly impact the patient's sleep quality.

## Funding

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