Iran J Psychiatry 2025; 20: 1: 39-47

Original Article *https://doi.org/10.18502/ijps.v20i1.17400*

Role of Melatonin as an Adjunctive Treatment for Depression and Cognitive Impairment in Hemodialysis Patients: A Randomized, Double-Blind Clinical Trial

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Abstract

Objective: Chronic kidney disease (CKD) is a pervasive health issue associated with various complications, including cognitive impairment and depression among patients undergoing hemodialysis. This study aimed to assess the impact of melatonin on depression and cognitive function in hemodialysis patients.
Method: A randomized, double-blinded, placebo-controlled clinical trial was conducted in 50 hemodialysis patients, with half of the patients receiving 3 mg daily melatonin and the other half receiving a placebo for two months. Depression and cognitive function were evaluated using the Beck Depression Inventory (BDI) and Mini-Mental State Examination (MMSE) questionnaire, respectively. Quantitative variables were analyzed using a t-test. The Chi-square test also evaluated qualitative variables. Quantitative data were analyzed by covariance analysis before and after the intervention.
Results: Hypertension was the most prevalent underlying condition among study participants, affecting 40% of the intervention group. The intervention group exhibited baseline depressive symptoms (mean BDI score: 16.12 ± 7.12), which significantly improved post-intervention (13.6 ± 6.6). Notably, both the intervention and control groups demonstrated significant reductions in depressive symptoms, as assessed by paired t-tests (P = 0.033 and P = 0.02, respectively). Cognitive function, as measured by the MMSE, improved in both groups (1.28 ± 0.81 for melatonin, 1.52 ± 0.1 for placebo), with significant within-group differences (P = 0.048 and P = 0.002, respectively). ANCOVA analysis revealed no significant between-group differences in BDI scores (F(1,47) = 0.196, P = 0.66, partial eta-squared = 0.004). and in MMSE scores (F(1,47) = 0.003, P = 0.954, partial eta-squared = 0.00) post-intervention.
Conclusion: While this study did not demonstrate significant effects of melatonin on depression and cognitive impairment in hemodialysis patients, positive changes were observed, warranting further research to optimize treatment regimens and explore the potential therapeutic benefits of melatonin in this patient population.

Key words: *Chronic Kidney Disease; Cognitive Dysfunction; Depression; Hemodialysis; Melatonin; Randomized Controlled Trial*

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Article Information:
Received Date: 2024/08/08, Revised Date: 2024/11/10, Accepted Date: 2024/11/13

Chronic kidney disease (CKD) is a global health concern affecting approximately 13.4% of the population (1). Characterized by persistent kidney damage and a glomerular filtration rate (GFR) below 60 mL/min/1.73 m² for at least three months, CKD often necessitates renal replacement therapies such as hemodialysis (HD) (2). HD functions as an artificial kidney, removing metabolic waste products and regulating fluid and electrolyte balance (3). Depression is a prevalent comorbidity among hemodialysis patients, with estimates ranging from 20% to 30%, and up to 42% exhibiting depressive symptoms (4, 5).

Cognitive impairment, ranging from mild to severe, is a prevalent and debilitating complication among hemodialysis patients, significantly impacting mortality rates (6, 7). Dementia, a severe form of cognitive decline, further exacerbates functional limitations and quality of life (8). Depression, another common mental health challenge in this population, often remains undetected and untreated, contributing to a decline in overall well-being, treatment adherence, and increased healthcare utilization (9). Sleep disturbances compound these issues, exacerbating cognitive and mood impairments (10). Furthermore, hemodialysis patients exhibit significantly higher rates of medication non-adherence compared to the general population, particularly in those with cognitive impairment (58.2% vs. 25%, respectively) (11). Despite the high prevalence of depression and cognitive impairment in hemodialysis patients, effective treatment options remain limited and often underutilized.

Melatonin, a hormone synthesized within the pineal gland, was initially isolated in 1958 (12). Its involvement in regulating mood and cognitive function is evidenced by its altered production in conditions such as major depression and cognitive decline (13, 14). In mammals, melatonin plays a critical role in maintaining circadian rhythms through its hypothalamic synthesis from tryptophan and serotonin precursors (15). Beyond its chronobiotic function, melatonin exhibits antioxidant, anti-inflammatory, and antigenotoxic properties mediated by mechanisms such as nitric oxide inhibition, cytokine reduction, myeloperoxidase suppression, and nuclear factor-kappa B (NF-κB) inhibition (16, 17). Given its influence on sleep-wake cycles, brain energy restoration, and sleep quality and duration, melatonin is believed to positively impact physical and mental health (18-21). It can have beneficial effects on blood glucose, preventing antipsychotic drug-induced weight gain, and improve symptoms of sleep disturbance. This study aims to address the gap in current literature by investigating the potential benefits of melatonin as an adjunctive treatment for depression and cognitive function in hemodialysis patients, thereby contributing to improved management strategies for this vulnerable population.

Materials and Methods

Study Design

This investigation was a double-blind, placebo-controlled randomized clinical trial comparing the efficacy of a 3g daily melatonin regimen to a placebo control group in hemodialysis patients. The study was conducted at Taleghani Hospital in Urmia, Iran, from October 2017 till May 2018. A total of 50 adult hemodialysis patients referred to Taleghani Hospital in Urmia were included in this study. Inclusion criteria were patients with hemodialysis patients aged over 14 years old, who had undergone regular hemodialysis three times weekly for a minimum of three months. Exclusion criteria included patients with diabetes mellitus, neuropsychiatric disorders, using hypnotic or antidepressant medications, malignant diseases, and those taking melatonin supplements, antioxidant, and/or anti-inflammatory supplements within three months prior to enrollment in the study.

Participants were randomly assigned to either the melatonin or placebo group using a balanced simple randomization method. The randomization process was conducted as follows: 25 cards labeled "A" and 25 cards labeled "B" were mixed together and placed in a box, with each card enclosed in an envelope. Eligible participants randomly selected envelopes, determining their assignment to either the intervention group or the control group. This process continued until all cards in the box had been distributed. Baseline depression and cognitive function assessments were conducted prior to the intervention. Participants received either 3 mg melatonin or a placebo identical in appearance for eight weeks. To optimize treatment adherence, participants were instructed to consume the supplement at 10 pm daily. Follow-up assessments of depression and cognitive function were conducted at the end of the two-month intervention period. Participants were advised to maintain their usual physical activity levels and avoid anti-inflammatory, antioxidant medications, or supplements throughout the study. Medication compliance was monitored through container return.

Intervention

Both the melatonin and placebo capsules were manufactured by Razak Pharmaceutical Company (Tehran, Iran) to maintain identical appearance and packaging. All participants were instructed to administer the assigned intervention one hour prior to bedtime for a duration of eight weeks.

Depression and Cognitive Function Measures

To assess participants' depressive symptoms and cognitive function, the Beck Depression Inventory (BDI) (22) and Mini-Mental State Examination (MMSE) (23) were administered. Both questionnaires have been utilized in several studies, both in Persian and internationally, demonstrating established reliability and validity (24, 25). An MMSE score of 24-30 indicates normal cognitive function, while scores below 23

suggest potential cognitive impairment warranting psychiatric evaluation. The BDI yields scores ranging from 1 to 40, with higher scores reflecting greater depressive severity. A score of 0-16 suggests mild depression, 17-20 indicates a need for psychological or psychiatric consultation, 21-30 signifies moderate depression, and 31-40 represents severe depression.

Demographic data, including gender, age, weight, marital status, education level, comorbidities, primary dialysis cause, hemodialysis session duration, hospitalization history, and clinical parameters such as urea reduction ratio (URR), Kt/V, serum creatinine, blood urea nitrogen (BUN), calcium, iron, total iron binding capacity (TIBC), and body mass index (BMI) were collected for each participant.

Sample Size

Sample size was determined using a standard randomized clinical trial formula with a Type I error rate of 0.05 and a Type II error rate of 0.20 (power of 80%). Based on a previous trial (26), a standard deviation of 2.20 and a mean difference (d) in HOMA-IR of 1.75 were employed as effect size estimates for the primary outcome. The calculated sample size required for this study was 25 participants in each group.

Statistical Analysis

Statistical analysis was performed by the SPSS software version 16. Quantitative variables with normal distributions were analyzed using a t-test. The Chi-square test also evaluated qualitative variables. Quantitative data were analyzed by covariance analysis before and after the intervention. A P-value < 0.05 was considered statistically significant.

Ethical Consideration

The Ethical Committee of Urmia University of Medical Sciences approved this study (IR.UMSU.REC.1396.247). It was also registered at the Iranian Center for Clinical Trials with the IRCT20110226005914N3 code. This intervention was done in accordance with the Declaration of Helsinki and informed consent was taken from all participants.

Results

From an initial pool of 350 dialysis patients, 30 individuals were randomly allocated to the melatonin intervention group, while 25 were assigned to the placebo control group. Although 55 patients commenced the eight-week study, only 50 completed the trial, with five withdrawals occurring within the melatonin group (Figure 1).

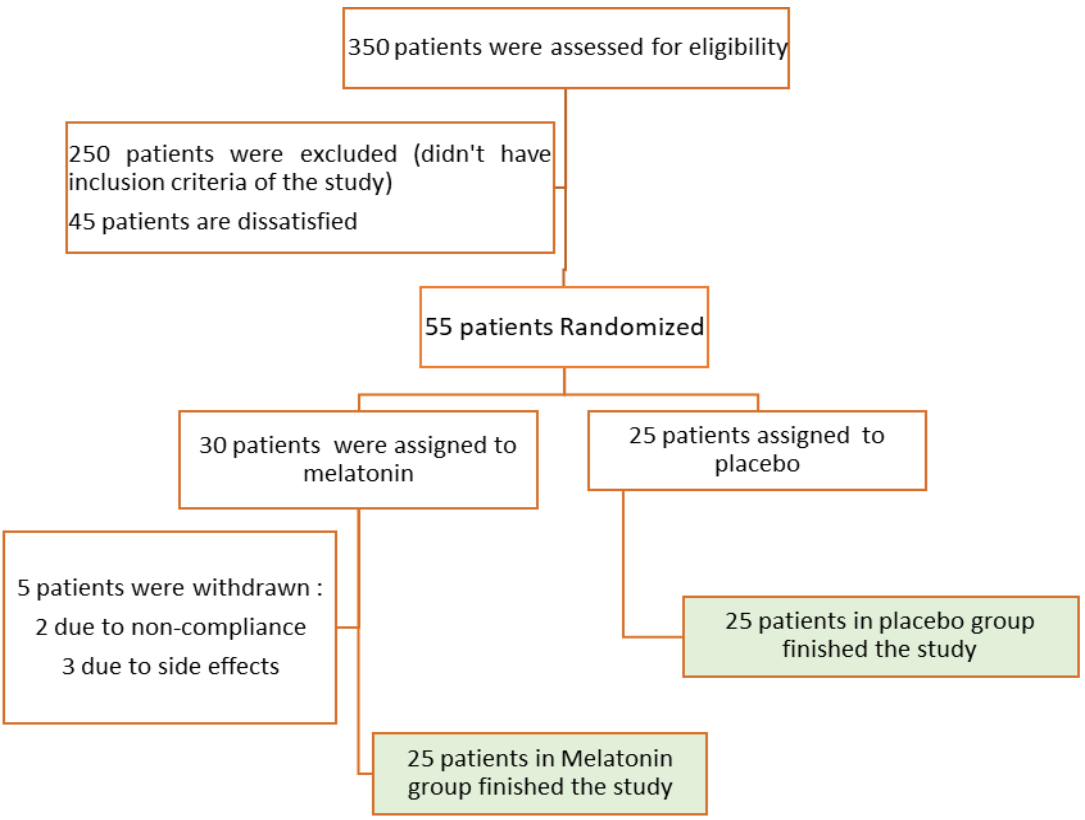

Figure 1. The Consort Flow Diagram of The Study Assessing The Impact of Melatonin or Placebo On Depression and Cognitive Function in Hemodialysis Patients.

Baseline demographic characteristics exhibited no significant differences between the intervention and control groups (Table 1). The mean age was 50.2 ± 11.7 years in the melatonin group and 51.2 ± 10.2 years in the control group. Gender distribution was predominantly male, with 52% of the melatonin group and 64% of the control group being male.

Table 1. Baseline Characteristics of the Patients among Melatonin and Placebo Group, N(%) or Mean ± SD

Characteristic	Melatonin(N = 25)	Placebo (N = 25)	Chi-square test
Sex			x^2 = 0.74
male	13(52)	16 (64)	d.f = 1
Female	12(48)	9 (36)	£p-value = 0.4
Marital status		20 (80)	x^2 = 1.79
Married	23(92)		d.f = 1
Single	2(8)	5 (20)	£p-value = 0.2
Education			
Illiterate	14(58)	14 (56)	x^2 = 0.206
Subdiploma	8(32)	7 (28)	d.f = 2
Diploma	3(12)	4 (16)	£p-value = 0.9
Comorbidity			
Hypertension	10(40)	8 (32)	x^2 = 6.36
Cardiovascular disease	4(16)	2 (8)	d.f = 3
Others	7(28)	4 (16)	£p-value = 0.1
No comorbidity	4(16)	11 (44)	
Reason of CKD			
Hypertension	13(52)	16 (64)	x^2 = 1.52
Others	9(36)	5 (20)	d.f = 2
Unknown	3(12)	4 (16)	£p-value = 0.5
BMI (kg/m^2)	25.96 ± 4.76	25.74 ± 5.24	0.87 ʲ
Age (years)	50.2 ± 11.7	51.2 ± 10.2	0.74 ʲ
Weight (kg)	72.5 ± 12.8	74.2 ± 13.1	0.63 ʲ
Each hemodialysis session duration (min)	218.8 ± 90.7	213 ± 41.3	0.78 ʲ
Bedridden(years)	4.31 ± 4.6	4.5 ± 4.7	0.89 ʲ
URR	63.9 ± 11.5	67.01 ± 11	0.35 ʲ
Kt/V	1.3 ± 0.48	1.3 ± 0.42	0.96 ʲ
BUN (mg/ml)	104.7 ± 29.8	120.4 ± 41.1	0.13 ʲ
Cr (mg/dl)	7.95 ± 2.2	8.6 ± 3.1	0.42 ʲ
Ca (mg/dl)	8.4 ± 0.95	8.7 ± 1	0.35 ʲ
TIBC (mcg/dl)	262.85 ± 122.9	271.6 ± 75.2	0.77 ʲ
Fe (mcg/dl)	110.2 ± 76.9	83.1 ± 35.8	0.13 ʲ

£Chi-square test, ʲ T-test, BMI: Body Mass Index, URR: urea reduction rate, Cr: serum creatinine, BUN: Blood urea nitrogen, Ca: Calcium, Fe: Ferrous, TIBC: Total Iron Binding Capacity

Hypertension emerged as the most prevalent underlying condition for CKD in both the intervention and control groups. While 44% of the control group reported no identifiable underlying condition, hypertension affected 40% of the intervention group. The mean dialysis duration for participants was 4.5 ± 4.6 years. Dialysis quality, as assessed by relevant metrics, was considered optimal in both groups (3.1 ± 0.88 and 1.3 ± 0.42, respectively).

BDI scores indicated mild depressive symptoms in both groups. The intervention group demonstrated a mean BDI score of 16.12 ± 7.12 prior to melatonin administration, which decreased to 13.6 ± 6.6 following the two-month intervention, suggesting a reduction in depressive symptoms. Conversely, the control group

exhibited a mean BDI score of 24.2 ± 1.37 after the two-month period, indicating persistent depressive symptoms (Table 2).

Table 2. Mean Score of Beck and MMSE[1] Questionnaire Before and After the Melatonin or Placebo Administration, Mean ± Standard Deviation

	Melatonin (N = 25)	Placebo (N = 25)
Beck		
Before	16.12 ± 7.12	17.08 ± 9.77
After	13.6 ± 6.4	14.84 ± 8.4
MMSE		
Before	23.4 ± 3.94	22.68 ± 3.12
After	24.68 ± 3.13	24.2 ± 3.22

[1] Mini-Mental State Examination

Table 3. Covariance Analysis of Beck and MMSE[1] Questionnaires between Melatonin and Placebo Group (between-Subjects)

Source	Type III Sum of Squares	D.f	Mean Square	F	Sig.	Partial Eta Squared
Dependent Variable: Beck After Administration						
Beck Before administration	1748.094	1	1748.094	87.102	< 0.001	0.650
Group	3.940	1	3.940	0.196	0.660	0.004
Error	943.266	47	20.069			
Dependent Variable: MMSE After Administration						
MMSE Before administration	227.095	1	227.095	41.315	< 0.001	0.468
Group	0.019	1	0.019	0.003	0.954	0.000
Error	258.345	47	5.497			

[1] Mini-Mental State Examination

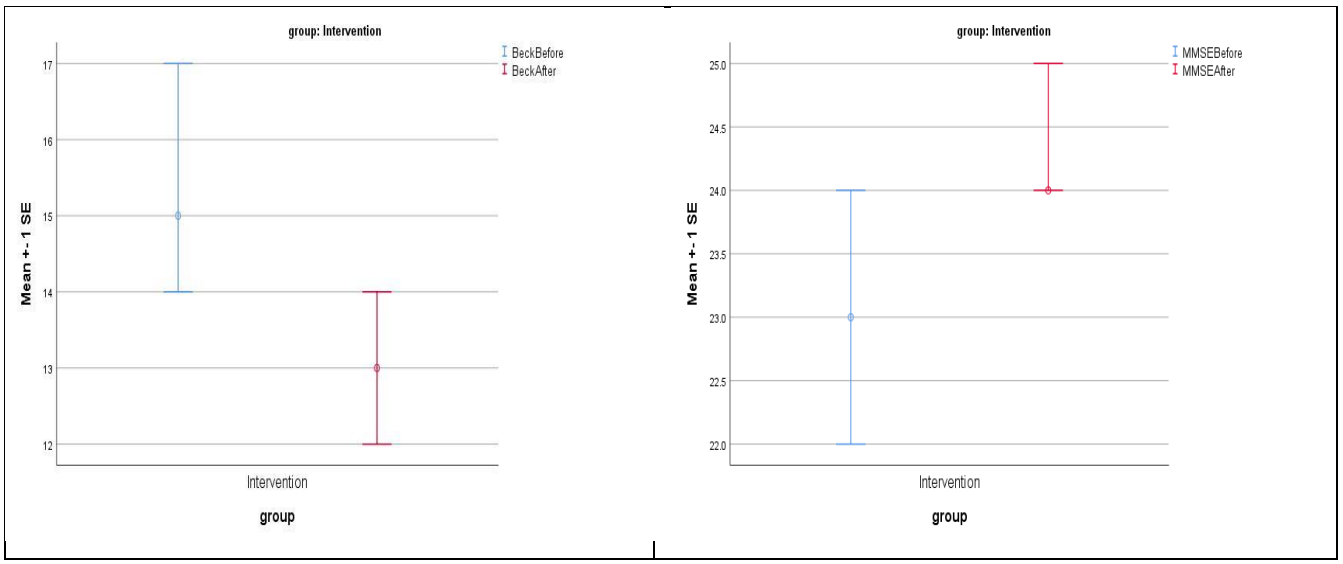

Figure 2. ANCOVA Profile Plot to Evaluate the Melatonin and Placebo Effect While Accounting for Baseline Differences. It illustrates the adjusted means of the dependent variable across different treatment groups, controlling for baseline covariates. Error bars represent the standard error of the mean. The analysis was conducted using ANCOVA (right figure for MMSE and left figure for Beck questionnaire).

ANCOVA analysis revealed no significant between-group differences in BDI scores following the intervention (F(1,47) = 0.196, P = 0.66, partial eta-squared = 0.004). However, paired t-tests demonstrated significant within-group improvements in BDI scores for both the melatonin and placebo groups (P = 0.033 and P = 0.02, respectively) (Table 3, Figure 2).

Regarding cognitive function, as measured by the MMSE, average scores increased by 1.28 ± 0.81 in the melatonin group and 1.52 ± 0.1 in the placebo group. ANCOVA indicated no significant between-group differences in MMSE scores post-intervention (F(1,47) = 0.003, P = 0.954, partial eta-squared = 0.00). Nevertheless, paired t-tests revealed significant improvements in MMSE scores within both groups (P = 0.048 for melatonin, P = 0.002 for placebo) (Table 3, Figure 2).

Safety

The vast majority of individuals exhibit tolerance to melatonin without manifesting any significant adverse reactions. Merely three participants reported complaints during the study, including nausea (one participant), abdominal cramps (one participant), and somnolence (one participant).

Discussion

CKD is associated with significant psychological burdens, including high rates of depression, which can adversely impact overall health and quality of life (27). Melatonin, a hormone with diverse physiological roles encompassing reproduction, immune modulation, antioxidant defense, and inflammation regulation, has been the subject of prior investigations (28). Previous research has established a correlation between depressive symptoms and impaired cognitive function, including processing speed, attention, and executive function, among maintenance hemodialysis patients (29). The present study evaluated the impact of melatonin supplementation on depressive symptoms and cognitive function in individuals undergoing maintenance hemodialysis. Our findings demonstrate that melatonin supplementation not only can alleviate depressive symptoms but also can enhance cognitive function, although these findings were not significant, suggesting its dual therapeutic potential in this particularly vulnerable population. The baseline BDI scores in the intervention group were markedly high, which is indicative of the mental health challenges faced by these patients.

The present study revealed a depression prevalence of 14% among participants, with a mean age of 51.52 ± 11.8 years and a male preponderance. A comparative study reported a higher depression rate (31.5%) in a slightly older hemodialysis population (55.7 ± 17.5 years), also demonstrating a male predominance. The mean age of our participants (52 years) may have influenced the treatment response, as optimal therapeutic windows for melatonin in ameliorating cognitive impairment and depression often occur earlier in life (30).

Notably, patients in the comparative study had a longer mean dialysis duration (seven years) compared to the current study (4.5 years) (31). A consistent body of literature suggests a positive correlation between age and depressive symptoms in end-stage renal disease (ESRD) patients receiving hemodialysis (32). A study conducted in Jordan further supports this association, demonstrating a higher severity of depressive symptoms in elderly ESRD patients compared to younger counterparts (33). Dialysis duration is postulated to be a critical factor influencing oxidative stress and subsequent depressive symptoms. Consistently, a study conducted in India assessing the psychiatric problems among patients with ESRD showed that patients who started HD treatment within the past six months before the study had higher rates of psychiatric illness than long-term HD patients (34).

A study by Esposito *et al*. (35) demonstrated that a ten-day regimen of 3 mg melatonin reduced sleep latency and increased the duration of sleep stage 2 without influencing insomnia or anxiety symptoms. While our study extended melatonin administration to two months, resulting in improved depressive symptoms and cognitive function as measured by the MMSE, similar improvements were observed in the placebo group. In fact, while both the melatonin and placebo groups exhibited improvements in depressive symptoms, the intervention group showed slightly more pronounced reductions in BDI scores, aligning with previous research suggesting that melatonin can effectively modulate mood disorders through its influence on circadian rhythms and sleep quality (36). In a related context, a randomized controlled trial demonstrated the beneficial effects of melatonin on mental health parameters in diabetic hemodialysis patients, further substantiating our findings (37). The cognitive improvements observed in both groups—especially within the melatonin group—support the hypothesis that enhanced sleep quality can lead to better cognitive performance, as noted in the literature on sleep disorders and cognitive decline (38). These findings suggest that the timing and frequency of melatonin administration may be critical determinants of its antidepressant efficacy. Masters *et al.* (39) posited that melatonin's antidepressant effects are optimized when administered several hours after darkness onset, coinciding with the natural melatonin secretion profile. Moreover, their animal model research indicated that divided melatonin dosing potentiates antidepressant effects through synergistic mechanisms, unlike single-dose administration.

The present study's utilization of a once-daily melatonin regimen may have contributed to the absence of significant between-group differences. Alternative dosing strategies, such as divided administration or the use of long-acting formulations, warrant exploration.

Furthermore, the oral delivery of melatonin is associated with lower bioavailability compared to intravenous administration (40).

Hypertension, identified as both an underlying condition (36%) and the primary cause of hemodialysis (58%) in our cohort, aligns with established literature linking hypertension to cognitive impairment (40). This may partially explain the relatively high prevalence of cognitive impairment (MMSE score < 24) observed in our study (62%). Additionally, certain studies have demonstrated the potential for melatonin to reduce blood pressure (41).

The relatively short duration of our two-month intervention may have limited the potential for observing significant treatment effects. Additionally, the low melatonin dosage (3mg) employed in the current study could have influenced the outcomes. Previous research has demonstrated the efficacy of higher melatonin doses (5-6 mg) in improving sleep patterns and exerting anti-inflammatory effects (41, 42). Furthermore, preclinical studies have reported antidepressant effects of melatonin at higher dosages (10mg/kg) in animal models (43).

Moreover, the potential neuroprotective effects of melatonin, attributed to its antioxidant and anti-inflammatory properties, may play a significant role in mitigating cognitive decline in CKD patients (44). Research indicates that oxidative stress and neuroinflammation are particularly pronounced in this population, suggesting that melatonin's mechanisms of action could be instrumental in addressing these underlying pathologies (45). The current study adds to the literature by providing empirical evidence that melatonin supplementation may yield significant improvements in both depressive symptoms and cognitive function, thus enhancing the overall therapeutic landscape for patients undergoing hemodialysis.

In the study by Ostadmohammadi *et al*., a higher dose of melatonin (10 mg daily) was used over a longer duration (three weeks) in patients with diabetes undergoing hemodialysis, compared to the 3 mg daily dosage in our study (37). Their findings demonstrated a significant improvement in the BDI scores compared to placebo. Additionally, melatonin in their study was able to significantly reduce fasting blood glucose levels and insulin levels. Furthermore, it is important to note that their study exclusively examined diabetic patients undergoing hemodialysis, whereas only 3.8% of the patients in our study were diabetic. This raises the possibility that melatonin may be more effective in a diabetic patient population.

In another study melatonin can control blood sugar concentrations in an insignificant manner (46). As Xu (47) states in his study, melatonin production is higher in the winter. Our study was also conducted in the winter, with some levels of melatonin. Therefore, this may be due to a lack of significant statistical differences in the intervention group. In this study, patients with a wide range of creatinine (3.4-1.3 mg/dl) were entered, of whom 50% had creatinine above 8 mg/dL. Based on some evidence, patients with creatinine levels greater than 8 mg / dL have lower endogenous melatonin concentrations than those with normal creatinine levels (0.2-0.6 mg/dl); this lower melatonin concentration is associated with a few problems experienced by hemodialysis patients (48).

Limitation

Despite these promising outcomes, we must acknowledge certain limitations inherent to our study. The relatively small sample size may restrict the generalizability of our findings, necessitating further research with larger cohorts to confirm these results and explore the long-term effects of melatonin on mental health and cognitive function in hemodialysis patients. Additionally, the low dose and short duration of the intervention may not fully capture the sustained effects of melatonin over time. Future studies should also investigate the optimal dosing strategies and potential interactions with other commonly prescribed medications in this population, as medication non-adherence is notably high among hemodialysis patients. Furthermore, investigating specific subgroups of hemodialysis patients, such as those with diabetes, may yield more straightforward results.

Conclusion

To conclude, our findings contribute to the growing body of evidence supporting the use of melatonin as a potentially effective adjunctive treatment for depression and cognitive impairment in hemodialysis patients. The current study findings indicate that a two-month melatonin regimen (3 mg/night) did not significantly ameliorate depressive symptoms or cognitive impairment in hemodialysis patients. Nevertheless, our findings contribute to the growing body of evidence supporting the use of melatonin in improving the depression and cognitive function measures and warrant further exploration. To optimize melatonin's therapeutic potential in this patient population, future research should focus on refining dosage, treatment duration, and patient selection criteria, considering factors such as age, comorbidities, and dialysis adequacy.

Acknowledgment

The authors would like to express their gratitude to the Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for their assistance with English writing and editing.

Conflict of Interest

None.

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