Effects of Melatonin on Salivary Levels of Cortisol and Sleep Quality of Hemodialysis Patients: A Randomized Clinical Trial

Elham Hasannia¹, Firoozeh Derakhshanpour¹*, Mohammad Ali Vakili²

Abstract

Objective: The aim of this study was to investigate the effects of exogenous melatonin on the quality of sleep in patients undergoing dialysis and to investigate its mechanism for the regulation of total circadian rhythm and salivary levels of cortisol in hemodialysis patients admitted to Pange Azar hospital in Gorgan in winter of 2017.

Method: This was a double-blind randomized clinical trial. Samples were transferred to the laboratory by maintaining the cold chain. Then, the patients were divided into two groups. In a double-blind trial, one group received three mg melatonin and another group received placebo for two weeks at 10 PM. At the end of two weeks, sampling was performed to investigate the salivary level of cortisol under the same conditions. The research instrument was Pittsburgh questionnaire. Data were analyzed before and after intervention using SPSS 16 software.

Results: Salivary levels of cortisol decreased significantly after the intervention in the melatonin group (melatonin: 1.40 ± 1.82 and placebo: 4.94 ± 4.43; P = 0.008). Salivary levels of cortisol in the morning after intervention were also lower in the melatonin group, but were not statistically significant (melatonin 3.99 ± 3.45 and placebo: 5.35 ± 4.9; P = 0.93). Also, the difference in salivary levels of cortisol at night and before and after intervention significantly decreased in melatonin group. PSQI difference (interventional dimension) and PSQI (before intervention) were significantly decreased in melatonin group (P = 0.0001). The rate of change in the subscales of sleep latency, sleep efficiency, and sleep disorders in the melatonin group than in the placebo group was significantly higher.

Conclusion: Melatonin can be used as a safe and cost-effective treatment to improve sleep quality and can also reduce salivary cortisol increased in hemodialysis patients at night.

Key words: Hemodialysis; Melatonin; Sleep

1. Golestan Psychiatry Research Center, Golestan University of Medical Science, Gorgan, Iran.
2. Health Management and Social Development Research Center, Department of Statics and Epidemiology, School of Health, Golestan University of Medical Sciences, Gorgan, Iran.

*Corresponding Author:
Address: Golestan Psychiatry Research Center, Golestan University of Medical Science, Gorgan, Iran, Postal Code: 4916937948.
Tel: 98-17 32344198, Fax: 98-17 32328363, Email: Derakhshan@goums.ac.ir

Article Information:
Received Date: 2020/04/15, Revised Date: 2020/10/29, Accepted Date: 2020/12/03
End-stage renal disease (ESRD) is a clinical condition in which the kidneys are unable to perform metabolic functions and maintain fluid and electrolyte balance in the body. Hemodialysis as the most commonly used method for treatment of this disease creates various problems in different aspects of patient’s life (1). A chronic kidney disease can cause circadian rhythm disorders such as sleep and wakefulness problems that have a major impact on quality of life and morbidity (2,3). About 80% of dialysis patients suffer from sleep disorders (4). In a study performed by Holley on 70 dialysis patients, 67% had difficulty in sleeping, other 80% complained about waking up during the night, and 72% had early wake-ups (5). In the Walker’s study, drowsiness with 66.7% had been reported to be the most common symptom throughout the day (6). These sleep disorders can cause headaches, depression, and the performance and life quality drop of the patient. The salivary cortisol level is primarily related to plasma cortisol in normal renal function. In patients with end-stage renal disease, plasma and salivary cortisol levels increased. Clearly, in these patients, the relationship between plasma cortisol and ACTH is healthy, but the normal circadian rhythm of cortisol is disturbed. Inflammatory markers such as c-reactive protein (CRP) increased in CKD which impairs cortisol circadian rhythm in these patients (7).

Melatonin hormone produce in the pineal gland and is secreted throughout the night and regulates the rhythm of circadian and sleeping (8). Also, its anti-inflammatory and antioxidant effects have been proven (9). Recent studies have shown that there is no physiological increase in melatonin at night in the serum of patients with chronic renal disorder (10, 11). They also showed the evidence of the benefits of exogenous melatonin prescription in improving sleep in patients undergoing dialysis (12).

In addition, low melatonin production was associated with higher prospects for improved sleep positively with melatonin therapy (13). It is not clear whether the two phenomena in hemodialysis patients are causally related together: decreased melatonin levels and early onset of cortisol production overnight. Intravenous administration of CRH in healthy men inhibits melatonin excretion compared with placebo administration, indicating that CRH has an inhibitory effect on melatonin secretion from the pineal in normal humans (14).

We hypothesized that melatonin therapy with increase the performance of the biological clock could improve disruption of cortisol circadian rhythm and followed sleep disorders in hemodialysis patients. To test this hypothesis, we conducted this trial to assess the impact of bedtime melatonin on salivary cortisol levels, sleep disturbance, and eventually circadian rhythmicity, which assessed objectively by diurnal patterns of salivary cortisol and subjectively by a sleep questionnaire in hemodialysis patients admitted to Pange Azar hospital in Gorgan in the winter of 2017.

Materials and Methods

Participants

This double-blind, randomized clinical trial study was recorded in Iran clinical trials center (IRCT20180117038418N1). Consent to participate in the study was obtained from all participants. The statistical population was composed of all patients with severe renal failure who referred to hemodialysis center of Pange Azar hospital in Gorgan for dialysis. Patients aged younger than 75 years, dialysis duration of more than three months, not using drugs affecting sleep continuously, not using corticosteroid, and scores higher than or equal to five in the Pittsburgh questionnaire were included. Exclusion criteria were patients with severe and serious illness that has impaired the process of sleep or has created severe inflammation (eg: malignancy, congestive heart failure, and active infection), pregnancy, iron deficiency anemia, uncontrolled diabetes (HbA1c > seven and a half), severe depression, and psychotic disorders.

In this study, 19 men and 21 women participated. Seven patients, including three women and four men, were excluded from the study. In the intervention group, five people were excluded from the study, four of whom (80%) were not cooperating and one person (20%) was admitted because of a diabetic foot ulcer. In the placebo group, two people, one due to hospitalization for respiratory infection complication and one due to drowsiness and unwillingness to continue taking the medications, were excluded from the study. Comparative results in patients excluded from the study didn’t show any significant difference in sleep score and cortisol at night and in the morning in the intervention and control groups. Finally, the information related to 33 patients was investigated.

Procedure

At the beginning of the study, the goals, the advantages of participating in the study, and the probable unwanted side effects of the drug were fully explained to the participants, and after obtaining informed consent, a special container was given to the patients to collect the saliva samples. The sample preparation method and its storage and transfer conditions were explained to the patients. Patients prepared saliva sample at 11 PM before dialysis and at seven AM of the next day before beginning dialysis. Samples were transferred by the researcher to the laboratory by maintaining the cold chain. Then, the patients were divided into two groups. To harmonize the drug and placebo groups, completely isolated capsules were filled in with some melatonin pills and some others with flour. In a double-blind way, one group received three mg melatonin and another received placebo for two weeks at 10 PM. Both the participants and the researcher were blinded to the
Effect of Melatonin on Cortisol in Hemodialysis Patients

intervention. At the end of the two weeks, sampling was performed again to investigate the salivary level of cortisol under the same previous conditions.

Questionnaire Features
The tool used in this research was Pittsburgh Questionnaire. PSQI or Pittsburgh Sleep Quality Index is a nine-question questionnaire containing 18 items that assess sleep quality and disturbance in seven areas of sleep latency, sleep mental quality, sleep efficiency, sleep duration, sleep disorders, taking hypnotic drugs, and daytime dysfunctions during a month ago (15); each item is scored from zero to three. This questionnaire has been widely used in Iranian studies. The overall PSQI score is calculated in the range of zero to 21 by scoring each of these seven areas. scores ≥five are considered abnormal. In this study, the questionnaire was completed by the patients themselves or with the help of a researcher during dialysis. At baseline and two weeks later this questionnaire was repeated. Initial PSQI scores ≥five were enrolled.

Statistics
A sample size of 40 was calculated (20 in each group) assuming to find a final difference of three and a half scores on the Pittsburgh Sleep Quality Index, with type I error of 0.05, and power of 80% (according to the study conducted by Edalat-Nejad and et al (16)). Considering an attrition rate of 20%, a final sample size of 40 was needed (20 in each group). Data were analyzed before and after melatonin intervention by SPSS software version 16. At first, the normality score of sleep and cortisol level were measured by Shapiro-Wilk's test. As the before and after scores of sleep and cortisol level have been significantly different, the analyses were performed in the main scale and subgroups based on comparing the differences between the two groups. Regarding the normality, to test the hypotheses of research, independent t test was used to find the difference between the mean of groups; Significance level of all tests was considered as 0.05.

Results
In this study, 15 (45.5%) cases were located in the melatonin group and 18 (54.5%) cases were located in the placebo group. In the group treated with melatonin, five (33.3%) cases were male and 10 (66.7%) female; and in the placebo group, 10 (55.6%) cases were male and eight (44.4%) female. The gender distribution of patients in the two groups has not been statistically significant (P = 0.202). The mean age of all patients in this study has been 57.12 ± 10.43 years, and the youngest age of patients was 24 years and the oldest 71 years. The mean age of patients in the melatonin group has been 54.80 ± 8.03 years and 59.05 ± 11.95 years in the placebo group. Due to the lack of assumptions, the age normality in the two groups and based on the nonparametric Mann-Whitney statistical test, the mean age in the two groups did not have a significant statistical difference (P = 0.108).

The salivary level of cortisol didn’t have a significant difference between the two groups the night before the intervention (melatonin: 10.31 ± 4.47 and placebo: 9.87 ± 4.51; P =0.762), while the salivary level of cortisol at the night after the intervention was significantly different in the two groups and was less in the melatonin group (melatonin: 1.40 ± 1.82 and placebo: 4.90 ± 4.43; P = 0.009). Also, the salivary level of cortisol in the morning before the intervention was not significantly different in the two groups (melatonin: 14.60 ± 5.67 and placebo: 12.29 ± 5.83; P = 0.260). In the melatonin group, the salivary level of cortisol in the morning after the intervention was lower than before the intervention and also in comparison with the placebo group, but this difference was statistically significant (melatonin: 3.99 ± 3.45 and placebo: 6.35 ± 4.21; P = 0.093) (Table 1). The changes ratio of the salivary level of cortisol at the night and morning before and after taking melatonin and placebo was evaluated in the two groups. In both groups the salivary level of cortisol decreased significantly at the night and morning before and after consuming melatonin and placebo (P < 0.05). The difference in the salivary level of cortisol at the night and morning before and after administering melatonin and placebo was investigated in the two groups. The salivary level of cortisol at night and morning in the melatonin group significantly decreased (P < 0.05). Then, the Pittsburgh sleep quality index before and after administering melatonin or placebo was investigated in the two groups. Based on the obtained results, the PSQI score (before intervention) in the placebo group was significantly higher than the melatonin group (melatonin: 11.33 ± 1.49 and placebo: 13.55 ± 2.61; P = 0.007). Also, the PSQI score (after intervention) in the melatonin group has been significantly lower (with very higher significance compared with before intervention) than the placebo group (melatonin: 5.06 ± 3. 21 and placebo: 11.22 ± 2.79; P = 0.0001). The difference of PSQI (after intervention) and PSQI (before intervention) was evaluated in the two groups, which significantly decreased in the melatonin group (P = 0.0001). The Pittsburgh sleep quality index changes before and after administering melatonin or placebo in both groups were investigated. In both groups, the Pittsburgh sleep quality index was (P = 0.0001). Also, the correlation between the Pittsburgh sleep quality index scores before and after administering melatonin in a melatonin-treated group and melatonin-treated group with salivary levels of cortisol at the night and morning before and after the intervention was investigated. Only in the melatonin group there was a significant positive correlation between the salivary level of cortisol at night after the intervention with the saliva level of cortisol in the morning after the intervention (r = 0.627; P = 0.005) and in other cases, this correlation was not observed.
The subscale scores of the Pittsburgh sleep quality index before and after administering melatonin and placebo were evaluated in the two groups, and the mean scores changes in each subscale were also evaluated. The mean scores obtained from the subscales of the Pittsburgh sleep quality index did not have a significant difference before the intervention between the two groups, while the scores of all subscales after intervention were significantly lower in the melatonin group than in the placebo group, indicating improvement in the sleep quality in all subscales in the users of melatonin. The ratio of reduction changes in the subscales scores of sleep latency, sleep efficiency, and sleep disorders was significantly higher in the melatonin group than in the placebo group, indicating a greater improvement in the use of melatonin in the areas related to sleep quality (Table 2).

### Table 1. Salivary Level of Cortisol before and after Melatonin or Placebo (Independent T Test)

| Variables                      | Melatonin Group | Placebo Group | P Value |
|--------------------------------|-----------------|---------------|---------|
| Cortisol Night (Before Intervention) | 10.30 ± 4.47    | 9.87 ± 4.51   | 0.762   |
| Cortisol Night (After Intervention) | 1.40 ± 1.82     | 4.90 ± 4.43   | 0.009   |
| Cortisol Morning (Before Intervention) | 14.60 ± 5.67    | 12.29 ± 5.83  | 0.260   |
| Cortisol Morning (After Intervention) | 3.99 ± 3.45     | 6.35 ± 4.21   | 0.093   |

### Table 2. Subscales’ Scores of Pittsburgh Sleep Quality Index before and after Administering Intervention

| Variables                                      | Melatonin Group | Placebo Group | P Value |
|------------------------------------------------|-----------------|---------------|---------|
| Sleep mental quality (before intervention)     | 1.66±0.48       | 2.16±0.85     | 0.054   |
| Sleep mental quality (after intervention)      | 0.53±0.63       | 1.33±0.84     | 0.005   |
| Sleep mental quality changes before and after intervention | -1.13±0.63      | -0.83±0.61    | 0.182   |
| Sleep latency (before intervention)            | 3.40±0.91       | 3.50±0.70     | 0.725   |
| Sleep latency (after intervention)             | 0.93±1.03       | 2.11±0.83     | 0.001   |
| Change in sleep latency before and after intervention | -1.46±1.06      | -0.38±0.69    | 0.001   |
| Duration of sleep (before intervention)        | 2.46±0.99       | 2.88±0.47     | 0.118   |
| Duration of sleep (after intervention)         | 1.33±1.17       | 2.38±0.91     | 0.007   |
| Changes in the duration of sleep before and after intervention | -1.13±1.06      | -0.50±0.85    | 0.067   |
| Sleep efficiency (before intervention)         | 2.40±0.91       | 2.33±1.02     | 0.847   |
| Sleep efficiency (after intervention)          | 1.06±0.96       | 2.16±0.98     | 0.003   |
| Sleep efficiency changes before and after intervention | -1.33±1.04      | -0.16±0.61    | 0.0001  |
| Sleep disorders (before intervention)          | 1.26±1.45       | 1.22±0.42     | 0.775   |
| Sleep disorders (after intervention)           | 0.80±0.41       | 1.16±0.38     | 0.013   |
| Changes in sleep disorders before and after intervention | -0.46±0.51      | -0.05±0.41    | 0.017   |
| Using hypnotic drugs (before intervention)     | 0.20±0.77       | 0.88±1.23     | 0.070   |
| Using hypnotic drug (after intervention)       | 0.06±0.25       | 0.66±0.90     | 0.019   |
| Changes in hypnotic drug use before and after intervention | -0.13±0.51      | -0.22±0.54    | 0.637   |
| Daily dysfunction (before intervention)        | 0.93±0.88       | 1.55±1.19     | 0.106   |
| Daily dysfunction (after intervention)         | 0.33±0.61       | 1.38±1.03     | 0.002   |
| Changes in daily dysfunction (before and after intervention) | -0.60±0.91      | -0.16±0.78    | 0.152   |
Discussion

This study aimed to assess the impacts of exogenous melatonin on the pattern of diurnal salivary level of cortisol and sleep quality in patients undergoing dialysis. Since melatonin is widely found in nature and in the human body, the pineal gland is known as intradermal hormone of sleep regulator (17). In various studies, the effectiveness of exogenous melatonin has been reported in sleep disorders, insomnia, regulation of blood pressure, metabolic syndrome, oxidative damage disorders and neurodegenerative diseases (18-21). In the present study, the salivary level of cortisol did not show significant differences between the nights before the intervention. While the salivary level of cortisol showed significant differences the night after the intervention, and also it was lower in the melatonin group. The salivary level of cortisol in the morning before the intervention in the two groups did not show any significant differences, and the salivary level of cortisol in the morning after the intervention was lower in the melatonin group, but it was not statistically significant. The salivary level of cortisol at night and morning in the melatonin group was decreased significantly. Also, in the present study, there was a significant positive relationship between the salivary level of cortisol at night after the intervention and the salivary level of cortisol in the morning after the intervention in the melatonin-treated group, and in other cases, this correlation was not observed.

To date, no study have examined the effect of melatonin on cortisol levels in dialysis patients. However, Zisapel et al conducted a placebo-controlled randomized crossover study. They studied 8 patients 55 years of age and older with insomnia who had low or delayed melatonin secretion. This study showed that administering two mg of long-acting melatonin in the evening can correct early onset cortisol production. Delayed nocturnal cortisol secretion may partly improve sleep quality in elderly patients with insomnia (22).

A recent study conducted by Edalat-Nejad et al in Arak university, suggested that treatment with melatonin can significantly improve the global PSQI scores, particularly sleep efficiency, subjective sleep quality, and sleep duration. But did not any change in sleep latency and daytime sleepiness. In this study melatonin can also increased the high-density lipoprotein (HDL) cholesterol in hemodialysis patients (16).

In a study, Hershel Raff et al compared serum and salivary levels of cortisol of 16 patients with ESRD who were dialyzed twice daily, with eight people from the control group. In this research, dialysis patients showed higher serum and salivary levels of cortisol at the end of night and also higher serum level of ACTH than the control group (23). This study has only measured the serum and the salivary level of cortisol but did not investigate sleep quality.

In another study on HD patients, Koch et al found that melatonin may cause an improvement in some of sleep parameters. They used three mg of melatonin for six weeks in 20 dialysis patients and then the quality of sleep was assessed with a sleep questionnaire and an actigraphy. This study showed that melatonin can significantly improve objective sleep-onset latency, sleep efficiency, and total sleep time (24). Koch et al found that patients with more severe renal dysfunction had lower mean serum melatonin concentration and vice versa. This relationship was not found about cortisol. Also, no relationship was observed between the serum levels of melatonin and cortisol in this study (25).

Another study by Wen-Pei Chang et al evaluated relationships rhythm of salivary cortisol and melatonin to sleep quality in patients with lung cancer who have recently been diagnosed. This study showed these patients compared to the control group had lower sleep quality and more depression. Also they had lower salivary melatonin levels and higher cortisol levels. According to this study, cortisol level and fatigue score predict sleep quality scores (26).

Brzezinski et al in a meta-analysis assessed data from 17 different studies that examined the effect of melatonin on sleep quality. The results of this meta-analysis, which involved a total of 284 participants, showed that melatonin can significantly improve sleep duration, sleep latency and sleep efficiency (27).

Another meta-analysis by Braam W used data from nine different studies) totally 183 participants) with intellectual disabilities. This study showed that treatment with melatonin increase total sleep time, decrease latency in falling asleep, and reduce the number of waking up every night in patients (28).

In contrast, in a meta-analysis conducted by Buscemi et al, exogenous melatonin didn’t have any significant effect on sleep quality and sleep output. This study included six randomized controlled trials, with 97 participants in all age groups. Based on this study, melatonin had no effect on sleep latency, removing fatigue after sleep, sleep quality, and total sleep time in people with insomnia, which is not consistent with the present study (29).

In our study the scores of all subscales of PSQI significantly decreased after melatonin therapy. The ratio of reduction changes in the subscales scores of sleep latency, sleep efficiency, and sleep disorders has significantly been higher in the melatonin group than in the placebo group.

Limitation

Since one of the main limitations of this study is the lack of poly somnography or acticography without which it is not possible to specify the exact cause of insomnia and sleep disorder, it is suggested that designing and conducting studies by combination of using this tool and cortisol investigation is performed. Also, in this study, the duration of the study was short. Therefore, long-term studies with further follow-ups to confirm the
advantages of exogenous melatonin in hemodialysis patients will be needed in the future.

**Conclusion**
This study showed that melatonin can reduce salivary cortisol increased in hemodialysis patients at night and may be partly effective in regulating the circadian rhythm of this hormone in these patients. Also, melatonin can be used as a safe and low-cost treatment to improve the sleep quality in hemodialysis patients.

**Acknowledgment**
This study was derived from a PhD thesis in psychiatry, which was approved at the ethics committee of Golestan University of Medical Sciences (code: IR.GOUMS.REC.1396.246). We thank all the patients who participated in this study. We would like to acknowledge Dr. Hamide Akbari and Dr. Hamidreza Joushaghi for their valuable consultations.

**Conflict of Interest**
None.

**References**

1. Poorgholami F, Jahromi MK. Effects of self-care education with telephone follow-up on self-efficacy level in hemodialysis patients. Biosciences Biotechnology Research Asia. 2016;13(1):375-81.
2. De Santo RM, Bartiromo M, Cesare MC, Di Iorio BR. Sleeping disorders in early chronic kidney disease. Semin Nephrol. 2006;26(1):64-7.
3. Morfin JA, Fluck RJ, Weinhandl ED, Kansal S, McCullough PA, Komenda P. Intensive Hemodialysis and Treatment Complications and Tolerability. Am J Kidney Dis. 2016;68(5S1):S43-S50.
4. Gul A, Aoun N, Trayner EM, Jr. Why do patients sleep on dialysis? Semin Dial. 2006;19(2):152-7.
5. Holley JL, Nesper S, Rault R. A comparison of reported sleep disorders in patients on chronic hemodialysis and continuous peritoneal dialysis. Am J Kidney Dis. 1992;19(2):156-61.
6. Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. Am J Kidney Dis. 1995;26(5):751-6.
7. Raff H, Trivedi H. Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease. Endocr Connect. 2013;2(1):23-31.
8. Aperis G, Prakash P, PalLOURAS C, Papakonstantinou N, Aliviane P. The role of melatonin in patients with chronic kidney disease undergoing haemodialysis. J Ren Care. 2012;38(2):86-92.
9. Srinivasan V, Spence DW, Pandi-Perumal SR, Trakht I, Cardinali DP. Therapeutic actions of melatonin in cancer: possible mechanisms. Integr Cancer Ther. 2008;7(3):189-203.
10. Russcher M, Koch B, Nagtegaal E, van der Putten K, ter Wee P, Gaillard C. The role of melatonin treatment in chronic kidney disease. Front Biosci (Landmark Ed). 2012;17:2644-56.
11. Hirotsu C, Tufik S, Bergamaschi CT, Tenorio NM, Araujo P, Andersen ML. Sleep pattern in an experimental model of chronic kidney disease. Am J Physiol Renal Physiol. 2010;299(6):F1379-88.
12. Russcher M, Koch BC, Nagtegaal J.E., van Ittersum FJ, Pasker-de Jong PC, Hagen EC, et al. Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (Melody study): a randomized controlled trial. Br J Clin Pharmacol. 2013;76(5):668-79.
13. Leger D, Laudon M, Zisapel N. 2003. Nocturnal 6-sulphatoxymelatonin excretion in insomnia patients and its relationship to their response to melatonin replacement therapy. Am J Med 116:91-95.
14. Kellner M, Yassouridis A, Manz B, Steiger A, Holsboer F, Wiedemann K. Corticotropin-releasing hormone inhibits melatonin secretion in healthy volunteers—a potential link to low-melatonin syndrome in depression? Neuroendocrinology. 1997;65(4):284-90.
15. Buyssse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
16. Edalat-Nejad M, Haqverdi F, Hosseini-Tabar B, Ahmadian M. Melatonin improves sleep quality in hemodialysis patients. Indian J Nephrol. 2013;23(4):264-9.
17. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol. 2004;25(3-4):177-95.
18. Garfinkel D, Zorin M, Wainstein J, Matas Z, Laudon M, Zisapel N. Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. Diabetes Metab Syndr Obes. 2011;4:307-13.
19. Cardinali DP, Cano P, Jimenez-Ortega V, Esquifino AI. Melatonin and the metabolic syndrome: physiopathologic and therapeutic implications. Neuroendocrinology. 2011;93(3):133-42.
20. Scheer FA, Van Montfrans GA, van Someren EJ, Mairuho G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertension. 2004;43(2):192-7.
21. Scheer FA, Van Montfrans GA, van Someren EJ, Mairuho G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertension. 2004;43(2):192-7.
22. Zisapel N, Tarrasch R, Laudon M. The relationship between melatonin and cortisol.
Effect of Melatonin on Cortisol in Hemodialysis Patients

23. Raff H, Trivedi H. Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease. Endocr Connect. 2013;2(1):23-31.

24. Koch BC, Nagtegaal JE, Hagen EC, van der Westerlaken MM, Boringa JB, Kerkhof GA, et al. The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study). Br J Clin Pharmacol. 2009;67(1):68-75.

25. Koch BC, Van der Putten K, Van Someren EJ, Wielders JP, Ter Wee PM, Nagtegaal JE, et al. Impairment of endogenous melatonin rhythm is related to the degree of chronic kidney disease (CREAM study). Nephrol Dial Transplant. 2010;25(2):513-9.

26. Chang WP, Lin CC. Relationships of salivary cortisol and melatonin rhythms to sleep quality, emotion, and fatigue levels in patients with newly diagnosed lung cancer. Eur J Oncol Nurs. 2017;29:79-84.

27. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhadanova I, Ben-Shushan A, et al. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev. 2005;9(1):41-50.

28. Braam W, Smits MG, Didden R, Korzilius H, Van Geijsswijk IM, Curfs LM. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. Dev Med Child Neurol. 2009;51(5):340-9.

29. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ. 2006;332(7538):385-93.