Review article

Factors Associated With Sleep Disorders in Patients Undergoing Chronic Hemodialysis Treatment

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Abstract

Introduction: Patients undergoing chronic hemodialysis treatment (HD patients) experience sleep quality deterioration, which is associated with lower quality of life and represents an independent predictor of mortality in HD patients. Recently, the number of research papers aimed at assessing sleep quality in HD patients has been increased, due to the fact that it is such an important factor. Thus, this study aimed to identify the main factors related with low sleep quality in HD patients by reviewing scientific literature.

Materials and methods: A search based on key words was performed in the MEDLINE database and selected scientific papers were analyzed by using the matrix method. The initial search retrieved 472 scientific articles to which certain inclusion and exclusion criteria were applied, combined with a critical analysis, resulting in the selection of a total of 48 papers. Factors related with low sleep quality in HD patients were grouped in three sub-groups, while sociodemographic and clinical characteristics showed significant impact on low sleep quality in HD patients.

Results: It has also been proven that low sleep quality is correlated with biochemical variables such as inflammation factors, low albumin levels and other factors, whereas knowledge concerning factors involved in hemodialysis also contributes to the efforts of medical staff aimed at improving HD patients' quality of sleep.

Conclusion: Etiology of sleep quality deterioration in HD patients is manifold, and significantly affected by psychosocial, biochemical and clinical factors.

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Introduction

End-stage chronic kidney disease (CKD) is characterized by glomerular filtration rate below 15 ml/min, presence of oliguria and electrolyte imbalance. End-stage CKD requires hemodialysis treatment. The hemodialysis procedure can be extremely uncomfortable and painful for patients, who tend to suffer from muscle spasms and drop of arterial blood pressure. In addition, from a long-term perspective, patients with this disease have a lower quality of life due to high incidence of depressive disorder, sleep disorder, secondary alexithymia and other factors related to hemodialysis, comorbidities and general health status of the patient.

Disturbances of sleep quality and other sleep disorders constitute a factor that significantly reduces the quality of life of this group of patients and that is associated with the incidence of depressive disorder, at the same time being an independent predictor of mortality in patients undergoing hemodialysis (HD patients) (1, 2). Prevalence of sleep disorders in HD patients is 41%-83%, depending on the results of the conducted research. In addition, etiology of sleep disorders is manifold and complex (3). Sleep disorders are classified according to their most important features. We thus distinguish the following sleep disorders: insomnia, breathing-related sleep disorders, parasomnia, hypersomnia, disorders of the circadian wake/sleep rhythm and disorders related to movements of extremities (4). Breathing-related sleep disorders, which encompass both obstructive sleep apnea and disorders related to movements of extremities such as restless legs syndrome, are significantly more common in HD patients than in the general population; however, risk factors that contribute to the development of these disorders have not yet been fully elucidated (5, 6). Due to disturbances in endogenous melatonin production cycle and the intermittent character of hemodialysis, HD patients tend to suffer more from disturbances of the circadian wake/sleep rhythm (7). In their studies on sleep disorders in HD patients, majority of researchers decided to focus on sleep quality considering that it is a comprehensive and widely accepted concept and that implies both quantitative and qualitative aspects of sleeping (8). Sleep quality is a concept that encompasses duration of sleep, latency before falling asleep, sleep efficiency and the patient's subjective assessment of whether they feel refreshed after sleep. For this reason, the majority of authors use instruments for assessment of the quality of sleep in their studies (8).

The objective of this paper was to conduct a review of medical literature and determine the impact of socio-demographic, clinical, laboratory- and hemodialysis-related factors on deteriorated quality of sleep in chronic hemodialysis patients.

Methods

The searched scientific database was MEDLINE and the search was performed by using the key words „HD patients" and „sleep quality". Studies that did not contain these key words in their title or in the abstract were excluded from the search. Literature search included original scientific papers, qualitative research and case reports, whereas results of scientific reviews or letters to the editor were not the subject of analysis. Most of the articles were published over the course of last ten years, including some dating back even earlier than that, which were included due to the fact that they provided significant knowledge. This resulted in the analyzed period being the period from 1999 to 2019. Articles that focused on the pediatric population and therapeutic procedures for treatment of sleep disorders unrelated to hemodialysis (except new knowledge about melatonin), as well as articles that were not published in English, were excluded from the analysis, as were articles focused on analyzing the quality of sleep in transplantees and peritoneal dialysis patients.

Results

Database search based on the above-mentioned key words and the analyzed time period retrieved 472 scientific articles. After application of the mentioned elimination criteria and exclusion of scientific reviews, analysis was reduced to 93 articles. Based on a detailed examination of the titles and abstracts of the articles against the objectives of this scientific review, 48 articles were identified as suitable, 17 of which were free-access articles, whereas 31 articles required access authorization. Final analysis included 48 studies published in the period from 1999 to 2019, 35 of which were cross-sectional, 4 were prospective studies, 8 were randomized clinical trials and one was a qualitative study. Results of the studies listed provide insights into the recent discoveries regarding correlation between sleep quality in HD patients and laboratory variables, levels of depression and alexithymia, factors related with hemodialysis, as well as regarding the impact of specific sleep disorders, such as restless legs syndrome, on sleep quality in HD patients (Table 1)..

Table 1. Factors associated with low sleep quality in HD patients

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A) Psychosocial factors	Alexithymia	It implies difficulty distinguishing between feelings and bodily sensations; in HD patients, it predicts low sleep quality independently of depression.
	Depression	Depression reduces sleep quality; prevalence of depression among HD patients is four times higher compared to general population.
B) Sociodemographic factors	Female gender, old age, low physical activity, high body mass index	These factors are related to decreased sleep quality in HD patients independently of depression.
	Poor financial status, unemployment	Poor financial status and unemployment impair sleep quality.
C) Biochemical factors	CRP, IL-6, TNF-alfa, IL-1beta	Sleep disorders in HD patients are associated with high levels of proinflammatory and low levels of anti-inflammatory cytokines.
	Decreased appetite, low serum albumin and creatinine levels	Researchers assess nutritional parameters together with inflammation using the Malnutrition Inflammation Score, which is an independent predictor of low sleep quality in HD patients.
	Secondary hyperparathyroidism, hyperphosphatemia	High PTH, phosphate and calcium levels impair sleep quality in HD patients.
	Loss of circadian rhythm of melatonin secretion	HD patients have a disrupted melatonin rhythm; administration of exogenous melatonin improves sleep quality.
D) Factors related to hemodialysis procedure	Dialysis shift and relative hyperhydration	High relative hyperhydration causes sleep disorders in HD patients; patients treated in the nocturnal shift have better sleep quality.
	Presence of tunneled central venous catheter	These HD patients more often have muscular cramps and uremic pruritus, which causes low sleep quality.

Assessment of sleep disorders in HD patients was performed by using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), the Berlin Questionnaire and the STOP Bang Questionnaire for measuring obstructive sleep apnea, RLS and IRLSSG questionnaires for assessment of restless legs syndrome severity, Insomnia Severity Scale (ISS), CHEQ (Choice Health Experience Questionnaire), Holland Sleep Disorders Questionnaire, Hatoum's Sleep Questionnaire, and Athens Insomnia Scale (AIS).There were two studies that used polysomnography and two that used actigraphy. Three of the studies analyzed different sleep variables by using individual questions, which represents a limitation of those studies.

As far as assessment of depressive symptoms is concerned, researchers used the Beck Depression Inventory (BDI-I and II), the Center for Epidemiologic Studies Depression Scale (CES-D), the Hospital Anxiety and Depression Scale (HAS-D), the Taiwanese Depression Questionnaire (TDQ), and the Patient Health Questionnaire (PHQ-2).

For assessment of alexithymia, the Toronto Alexithymia Scale-20 (TAS-20) was used.

The final result of this integrative scientific literature review was the formation of three sub-topics in this context, one being recent discoveries in the correlation between depression, quality of life and quality of sleep and the other two being laboratory variables and hemodialysis-related variables..

Discussion

Correlation between depression, alexithymia, socio-demographic factors and sleep disorders in HD patients

Alexithymia is a construct, a stable personality trait that implies difficulty distinguishing between feelings and bodily sensations, difficulty describing feelings to other people, constricted imaginal processes and a cognitive style of thinking that is oriented towards external stimuli rather than feelings (9). Prevalence of alexithymia is higher in HD patients than in the general population, as high as 30%, this being a cause of their significantly reduced life quality (1). Alexithymia is a strong predictor of mortality in HD patients, regardless of age, sex or possible depressive disorders. Patients suffering from alexithymia had a 4.29 % higher mortality rate at later stages of the five-year monitoring period (1). The way alexithymia affects sleep disorders has not been sufficiently elucidated; there have only been a few studies dealing with this issue on samples of HD patients and it has long been unclear whether the impact of alexithymia on sleep quality deterioration was indirect or direct. Gennaro et al. conducted a large cross-sectional study on a population of students and reached a conclusion that alexithymia was a confounding factor and that if depression is included in the statistical models, its impact on the quality of sleep disappears (10). Researchers that analyzed the same issue on a sample of HD patients confirmed the impact of alexithymia on poorer quality of sleep, but on a sample of HD patients, this impact was not correlated with depression. In particular, De Santo et al. used a sample of 40 HD patients who underwent parathyroidectomy due to high PTH levels and who were found to suffer from high intensity depression, alexithymia and sleep disorders. Their study showed that the impact of alexithymia on sleep disorders was not related with levels of depression. However, the study was limited by a small number of subjects, which represents a weakness inherent in the study (11). Although research into the correlation of alexithymia and biochemical variables in HD patients is scarce, it has been confirmed that alexithymia, or rather its component in the form of external stimuli-oriented cognitive thinking, represents an independent predictor of low phosphorus levels in HD patients, which are in turn related with poor quality of sleep (12).

Depressive disorder is a mood disorder defined as a feeling of sadness, unhappiness, loss of will and motivation that lasts for more than two weeks. It is one of the most common mental disorders, whereas sleep disturbance is one of the most prominent symptoms of depressive disorder (13). Based on available discoveries,

prevalence of depression in HD patients is almost four times higher than in the general population and amounts to between 43% and 72% (14). Depression has a significant impact on sleep disturbances in patients receiving chronic hemodialysis treatment, it considerably reduces the quality of life and is an independent predictor of patients' mortality (1, 15, 16). Social support has a preventive effect when it comes to depressive disorder and improves the quality of life of HD patients (17). According to the study carried out by Pan et al. , the form of social support that includes analytical appraisal of virtues and positive personality traits of such patients reduces the impact of disturbed sleep quality on life quality and depression in HD patients (17). In their cross-sectional study, Maung et al. found that depressive HD patients tend to suffer more frequently from daytime sleepiness (measured using ESS), lower sleep quality, restless legs syndrome as well as from sleep-related difficulties the night after receiving hemodialysis treatment (15). Latest discoveries point to the importance of additional factors that modify this two-way interaction. According to the results of recent research, sleep disturbances are significantly more frequent in women than in men receiving chronic hemodialysis treatment (18- 20). Only one study found higher incidence of low quality of sleep in the male sex, but the study was conducted on a sample of Malaysian subjects, so it is possible that such result was caused by culturological and racial differences (19). Scientists have also considered the role of depression as a confounding factor in this relationship because it is more frequent in women; however, recent studies have identified female sex to be an independent risk factor when it comes to development of sleep disorders during hemodialysis treatment (14, 21). It is interesting to note that according to the PSQI, the age of HD patients also represents an independent risk factor for sleep disorder. However, Lin et al. found that this influence disappears if monthly pecuniary income of respondents is taken into account. It is possible, as the authors indicated, that the impact of age was dependent on financial status, as financial status drops significantly in the population of retirees, so this is something that should definitely be taken into consideration in future studies (21).

Financial status and unemployment were defined in two studies as the factors that contribute to poor sleep quality in HD patients (23, 24). Tomita et al. found that duration of hemodialysis treatment could also result in poor sleep quality measured by the PSQI questionnaire. Specifically, patients who have been undergoing dialysis for more than five years exhibit more difficulty in functioning during the day as a result of daytime sleepiness, which is an element measured by the PSQI questionnaire, whereas independent analysis shows the correlation between advanced age and sleep disorders, regardless of the levels of patients' depression (24).

Lower physical activity of HD patients has an independent negative effect on the quality of sleep. Namely, using a large sample of 1678 patients undergoing peritoneal dialysis and hemodialysis covered by CDS (Comprehensive Dialysis Study), Anand et al. found that lower physical activity is more frequent in depressive patients, but also that independent of depression, low physical activity functions as a factor that causes poor sleep quality (25). Apart from lower physical activity, studies have shown that BMI (Body Mass Index) is another factor that negatively affects the quality of sleep in HD patients (27, 28).

It is a well-known fact that depression has a seasonal character and that depressive symptoms in patients suffering from depressive disorder as well as depression-related insomnia or hypersomnia tend to become worse during certain seasons. According to the results of Afsar et al., seasonal remission of depression symptoms is not accompanied by an improved quality of sleep. Authors claim that remission of depression symptoms can be perceived only in non-smoking patients and in those with increased levels of serum albumin during the summer (28).

Many research studies have been conducted on the impact of laboratory variables on sleep disorders and depression in HD patients and

most of them concluded that laboratory variables have a stronger impact on depression than on sleep disorders, which is logical since depression is a disorder caused by biochemical imbalance of neurotransmitters, whereas sleeping can be affected by many different socio-economic factors (14). Afsar et al. established that aggravation of chronic kidney disease is accompanied by higher cortisol levels and that these increased cortisol levels in turn cause higher depression frequency. However, this factor does not cause sleep disorders (29). Depression in HD patients is connected with elevated levels of phosphorous, low levels of creatinine and hemoglobin, and low albumin levels, which serve as indicators of their nutritional status (21, 22, 30) .

When discussing disturbances of sleep quality and depression in patients, we must not disregard religious feelings and beliefs, which have been identified, in the context of general population, as factors that help patients to overcome stress even when other anti-stress mechanisms falter. Eslami et al. proved that a high level of spiritual well-being and religious feelings have an independent and positive effect on sleep quality in HD patients (30).

Effect of biochemical variables on sleep disorder in HD patients measured using PSQI

When talking about recent discoveries, one needs to mention the correlation between sleep disorders and inflammatory mediators, which has been confirmed by results of many studies. The factor that all of these studies focus on is the relatively nonspecific but highly sensitive C-reactive protein (CRP), the level of which many cross-sectional studies found to be significantly higher in HD patients suffering from sleep disorders (28, 32). The study conducted by Chiu et al. reveals that the level of pro-inflammatory cytokine IL-1beta, which is responsible for triggering inflammatory responses in the human body, is significantly increased in patients who are undergoing chronic hemodialysis treatment and who are suffering from sleep disorder, and that there is a correlation between the levels of other pro-inflammatory cytokines such as TNF-alpha or IL-6 and deteriorated sleep quality (32). It is possible that elevated pro-inflammatory mediators are the consequence rather than the cause of sleep disorder because, as specified by Chiu et al., sleep deprivation may cause a temporary increase in arterial blood pressure, which then triggers inflammatory response and the synthesis of CRP in the liver cells (32). Results obtained by the group of researchers led by Taraz confirm the pro-inflammatory theory, albeit with reference to lower levels of anti-inflammatory cytokine IL-10 in patients suffering from sleep disorder; however, the importance of this study is limited by the small number of respondents (33). It is possible that lower vitamin D level found in HD patients is the cause of higher levels of pro-inflammatory cytokines TNF, IL-6 and IL-1 as well as lower sleep quality; nevertheless, it is also possible that there is an independent mechanism by which vitamin D affects vitamin D receptors in areas of the brain regulating sleep (34). Conversely, CRP levels represent a more trustworthy proof of the importance of inflammation when it comes to sleep disturbances, because CRP levels are stable during the 24-hour period, whereas cytokine secretion reaches its maximum level according to its specific circadian rhythm (34). The study carried out by Razeghi and Ali included 108 HD patients and revealed that patients who had CRP levels above 3.8 ug/L were more prone to suffer from poor sleep quality according to the Pittsburgh Sleep Quality Index (PSQI), including insomnia, restless leg syndrome (RLS) and obstructive sleep apnea syndrome (35). However, it is necessary to emphasize that several studies did not reveal any kind of correlation between CRP and pro-inflammatory cytokine levels on the one side and poor sleep quality on the other (36).

Another factor that is closely related to inflammatory components and their indirect or direct impact on sleep quality is the nutritional status of patients suffering from end-stage chronic kidney disease. (37). The patient's nutritional status and loss of appetite are closely related to dietary restrictions for HD patients, mental condition, age as well as to the level of

inflammatory components. For this reason, some researchers assess these parameters together using Malnutrition Inflammation Score (MIS) (31). MIS and albumin level represent independent predictors of poor sleep quality in HD patients. Research focusing on albumin serum levels obtained the most reliable results, which almost always point to inverse correlation between albumin levels and sleep quality (28, 35, 39). Correlation between low albumin levels on the one side and shorter sleep duration and lower sleep efficiency one the other has also been proven by polysomnography (PSG), which is a gold standard in sleep disorder research (39). Dilek Ongan found that, according to their scale, patients with moderate appetite were exposed to 3.26-fold higher risk of poor sleep quality, whereas patients with bad appetite were exposed to 4.2-fold higher risk of developing sleep disorders (40). An additional confirmation that nutritional status is associated with sleep quality is strong correlation between creatinine levels and sleep quality in the examined groups of patients, considering that the serum creatinine level is a consequence of good appetite. In addition, Dilek Ongan revealed a positive effect that intake of vitamins B1, B6 and B9 has on sleep quality (40). Only a very small number of studies concluded that a patient's nutritional status has no impact on the issue in question (34, 37).

Previous studies found that metabolic acidosis and venous bicarbonate level are associated with higher frequency of obstructive sleep apnea episodes in samples of population not suffering from chronic kidney disease, whereas results of the study conducted on a sample of HD patients confirmed an independent impact of venous bicarbonate and PH levels on poor sleep quality measured by PSQI (38).

Restless legs syndrome (RLS), which is significantly more common in HD patients, is an independent predictor of sleep disturbances, whereas its occurrence is also correlated with higher levels of CRP and white blood cells (41). Patients with RLS have an uncontrollable urge to move their lower extremities due to an uncomfortable feeling in their legs. These symptoms occur during the night when patients are motionless. RLS is not caused by other pathological conditions such as diabetes. The uncomfortable feeling is experienced before the person has moved his or her legs (42). It has been found that homocysteine may potentially be the cause of RLS, considering that the levels of this amino acid are higher in RLS positive patients, provided that the portion of homocysteine bound to serum albumin is taken into account (43).

Loss of circadian rhythm of melatonin secretion is an abnormality detected in HD patients, which clearly has an impact on sleep quality; however, the impact-related mechanisms have not yet been thoroughly examined. Application of melatonin therapy in a randomized controlled clinical trial carried out by Nejad et al. proved that exogenous melatonin administration had a positive impact on sleep quality, sleep efficiency and contributed to lower disturbances during sleep in HD patients with previous sleep disorders (44). It is well-known that application of melatonin during twelve months causes resistance to treatment, lower sleep quality, impaired endogenous melatonin secretion and loss of circadian rhythm of secretion (45). It has also been observed that application of melatonin in a study conducted by Nejad et al. reduced the quantity of erythropoietin required to correct the hemoglobin value, which was also correlated in some studies with poorer quality of sleep in HD patients (46). As early as in 1999, Peterson found, by polysomnography, reduced periodic limb movements and sleep fragmentation as well as total sleep prolongation and improved daytime alertness in a sample of patients suffering from chronic kidney disease whose anemia was successfully corrected by application of short-acting erythropoietin (47). According to more recent studies, the impact of anemia on sleep quality is questionable. There are many studies that failed to prove the correlation between lower hemoglobin levels and sleep quality, which is most likely the result of the fact that this group of studies did not take into account application of erythropoietin as a confounding factor (18, 32). That such studies are nevertheless carried out is justified by the fact that some researchers have

identified anemia as an independent cause of nocturnal sleep fragmentation and daytime sleepiness in HD patients (33, 35).

Secondary hyperparathyroidism is a consequence of end-stage chronic kidney disease because the body uses higher levels of parathyroid hormone (PTH) in order to adapt to the initial hypocalcemia, which is the result of lower vitamin D synthesis and hyperphosphatemia (48). Hyperparathyroidism in end-stage chronic kidney disease is accompanied by high levels of calcium and phosphorous. It seems that PTH is the cause of sleep disorders, depression and alexithymia in patients only when the value of PTH is particularly high and cannot be treated by pharmacological therapy (11). De Santo et al. proved lower PTH levels and ameliorated depression, alexithymia and sleep disorders after parathyroidectomy, after having studied a sample of 40 HD patients (49). Studies that examined PTH levels using a sample of patients receiving pharmacological therapy obtained contradictory results when it comes to the effect of PTH levels on sleep quality. Namely, Nejad et al. identified significantly lower levels of intact PTH in the group of patients with sleep disorders, whereas Taraz et al. identified significantly higher levels (34, 51). Patients suffering from restless legs syndrome, which has already been identified as a predictor of sleep disturbances, also have higher levels of parathyroid hormone (43). PTH has a direct impact on brain tissue. In a study in which magnetic resonance imaging was used, Ma et al. found a decreased N-acetylaspartate to creatine ratio in the thalamus of HD patients, which is significantly associated with the level of parathyroid hormone and patients' PSQI score (51). N-acetylaspartate is the marker of axonal stability in brain tissue and its decreased ratio in comparison with the ratio found in patients not suffering from chronic kidney disease is a sign of axonal injury. Discoveries concerning the impact of ionized phosphorous are unique and the impact of calcium levels on sleep quality deterioration remains unclear. Hyperphosphatemia is a clear factor and predictor of low quality of sleep (20, 35, 37).

Impact of factors related to characteristics of hemodialysis treatment on deteriorated sleep quality

The fact that hemodialysis shift may impact sleep quality and circadian rhythm alteration was examined in several studies, with conflicting and contradictory results. In their study that included 220 respondents, Wang et al. successfully proved that better sleep quality is associated with morning-shift dialysis and with already familiar sleep disturbance factors such as depression and anxiety (52). The authors made a critical remark regarding the results of their study, stating that they did not take into account napping during dialysis as a possible confounder and that nocturnal sleep quality potentially depends on this variable. However, Firoz and Hosseini did not prove either that there is a correlation between hemodialysis shift and deteriorated sleep quality or that sleep quality is affected by change of the dialysis shift (23). Undergoing nocturnal hemodialysis has certain advantages in terms of sleep duration being better in HD patients undergoing hemodialysis in the night shift than in the case of hemodialysis in two daytime shifts. Furthermore, the intensified hemodialysis program, within which hemodialysis is performed six times per week, is associated with better sleep quality. This correlation does not, however, show statistical significance (36).

The quality of hemodialysis treatment is defined by the dose of hemodialysis required by patients with end-stage chronic kidney disease in order to ensure that their mortality and life quality parameters are the same as those of patients not suffering from chronic kidney disease (54). It is clinically defined as urea clearance passing through the dialyzer multiplied by the duration of an individual hemodialysis session, divided by urea distribution volume in the body (54). Urea distribution volume is total water volume in the body less ultrafiltration volume in an individual hemodialysis session. Recent studies have not succeeded to indicate a correlation between the quality of hemodialysis and deteriorated sleep quality (23, 56). In their study, Unruh et al. divided patients into daily and nocturnal hemodialysis shifts during a one-year period and at the end of

this period they found sleep quality to be higher in the nocturnal group, which group also had better hemodialysis quality. However, the results were not statistically significant (54, 57).

One study proved a lower level of disturbances of sleep quality in patients who have a hemodialysis arteriovenous fistula (AVF) in comparison with patients who undergo hemodialysis using tunneled central venous catheter (55). According to the results obtained by Hilda et al., patients who undergo hemodialysis via an arteriovenous fistula are less prone to suffer from muscular cramps and uremic pruritus, which conditions are associated with poor sleep quality (55). Uremic pruritus or itch occurs as a result of higher levels of phosphorus and uremic toxins, and it is also caused by lower hemodialysis quality (2, 56).

During hemodialysis treatment, the level of ultrafiltration or the volume of fluid that is removed from the patient's body represents a special challenge. Bioimpedance is the standard for estimation of dry body weight, which in turn determines the level of ultrafiltration. Studies in which the said method was used in order to study the impact of fluid overload and low ultrafiltration on the quality of sleep revealed predominantly consistent results. Relative hyperhydration in HD patients, which is defined as surplus bodily fluids above 7%, is independently associated with lower sleep quality and daytime sleepiness (57). Abreo et al. found that relative hyperhydration has an impact on lower sleep duration, more frequent night-time waking and more difficulty returning back to sleep (58).

Studies that are focused on different forms of renal replacement therapy usually compare treatment by standard hemodialysis with hemofiltration and hemodiafiltration. As opposed to hemodialysis, in addition to the physical process of diffusion of small molecules, hemofiltration also uses conduction laws for quick flow of dialysate solution, which enables removal of larger harmful molecules (54). Hemodiafiltration is a combination of these two methods. In their cross-sectional study, Hilda et al. found that hemodiafiltration has a positive impact on disturbances of sleep quality only in male patients (55). On the other hand, in their prospective study, Gu et al. found that at the end of a two-year period, treatment using a combination of hemodialysis and hemofiltration, which took up half of the hemodialysis treatment session (HD+HF), had a positive impact on PTH, calcium, phosphorus, CRP and melatonin levels, as well as on sleep quality (59). The study also indicated that HD+HF treatment of patients is associated with an increase in the overall survival in comparison with patients who are treated only by hemodialysis (59).

Conclusion

Previous research studies focusing on the topic of sleep quality in HD patients have consistently arrived at the conclusion that depression has an independent impact on sleep quality in HD patients and that alexithymia has an indirect and significant impact on sleep quality in HD patients. Depression is a factor that is often accompanied by alexithymia and that reduces the quality of life of HD patients and it is an independent predictor of mortality. Results obtained by studies examining the impact of biochemical variables on sleep quality are inconsistent, indicate higher level of correlation with the depressive disorder and fail to provide an answer regarding various confounding factors such as anemia medications, electrolyte imbalance and PTH levels. Future studies should include a prospective approach, they should use more objective methods such as polysomnography or actigraphy and take into account the impact of medications on the said biochemical variables. The results obtained by studies focused on dialysis and vascular access modalities lead to the conclusion that creation of an AV fistula in HD patients and usage of hemodiafiltration method are justified because of their impact on better sleep and life quality and their contribution to lower frequency of muscle cramps after a hemodialysis session. Given that sleep quality is a factor that is independently associated with life expectancy of HD patients, future studies should focus on

identification of factors that reduce sleep quality by using more objective methods, such as PSG, and conducting the study during a longer time period.

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