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Original Scientific Paper

THE DIFFERENCES IN BIOCHEMICAL REACTANTS IN THE ACUTE PHASE/STAGE AND SLEEP QUALITY CONSIDERING THE TYPE OF VASCULAR ACCESSS IN PATIENTS ON HEMODIALYSIS

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SUMMARY – In patients on hemodialysis (HD), there is a high prevalence of disturbed sleep quality caused by unknown causes. The study aimed to compare differences in the levels of biochemical reactants in the acute phase, creatinine, sociodemographic factors, alexithymia, and sleep quality in a group of HD patients considering the vascular approach, as well as to determine differences between HD patients with normal and low sleep quality and to determine predictive factors for sleep quality.

The research included 79 HD patients of both sexes, aged from 33 to 87, treated at UHC Osijek, General hospital Vinkovci, and Outpatient clinic Županja. Laboratory tests have been made on the HD, and clinical and sociodemographic information was collected.

The authors used the Croatian version of the Pittsburgh sleep quality questionnaire for Toronto alexithymia scale 26 and the Epworth scale for daily sleepiness. HD patients who are dialysed through central venous catheter have significantly lower levels of albumins (p=0.02 Mann-Whitney U test), creatinine (p=0.007 Mann-Whitney U test), and they remain on dialysis for a shorter period of time compared to the patients with arteriovenous fistule (p=0.002 Mann-Whitney U test). Patients who are longer on HD have a 1.395 times higher chance for lower sleep quality (OR = 1.395 95% CI 1.02 do 1.74). The only predictive factor for lower sleep quality in HD patients is the duration of HD treatment.

Key words: *alexithymia, hemodialysis, sleep quality, circulatory approach*

Introduction

In the Chronic Kidney Disease (CKD) patients stage 5 (GFR under 15 ml/min), with oliguria or anuria, metabolic acidosis, and hyperkalemia, there is an indication for Renal Replacement Therapy (RRT) using dialysis or preparation for a kidney transplantation [1]. Hemodialysis is a process that includes the diffusion of particles through a semipermeable dialysis membrane using diffusion or diffusion/convection and ultrafiltration of excess body fluids [2]. Hemodialysis treatment requires a lot of time with various somatic complications, which can be frustrating for the patients [3].

Hemodialysis access usually include arterio-venous fistula (AVF) or central venous catheter (CVC).

If it is possible, in HD patients, the preference is given to the AVF construction, considering that this approach of hemodialysis has fewer side-effects as muscle cramps and pruritus, and the possibility for infections is reduced through CVC, which can be a po-

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tential source of blood infections [4]. HD patients dialysed through CVC catheter are usually in a worse somatic state than HD patients with AVF because it is often impossible to construct an adequate AVF due to generalised atherosclerosis and/or heart failure [5].

Alexithymia is a personality trait, a term, and a state that describes difficulties in identifying emotions experienced by one's self or others and ways of thinking, which are led mainly by external factors instead of internal emotional states [6]. Patients who are on hemodialysis show significantly higher levels of alexithymia compared to the general population, which can be explained in several ways [7]. HD patients often have several comorbidities, they have dietary restrictions, and their treatment duration plays a role in their sense of well-being. They also suffer from mental disorders and sleep disturbances, all of which are associated with higher levels of alexithymia in the general population [8,9].

Patients dialysed with a CVC usually have more comorbidities, a higher risk of systemic inflammation, and display more mental illness risk factors such as low body weight and old(er) age, which makes them similar to the alexithymic individuals in the general population [10].

Based on this, the hypothesis is that the HD patients with CVC will have poorer laboratory indicators of somatic health than the HD patients with AVF; that is, they will have higher levels of inflammation markers like C-reactive protein and lower levels of negative reactants in the acute phase such as haemoglobin, albumin and creatinine.

Because these patients frequently have muscle pains and cramps, night-time pruritus, and generally poorer quality of life, it is to be expected that they will also have a higher level of alexithymia, low sleep quality, and will suffer from daily sleepiness much more than the patients with AVF, which is an issue that has not been researched so far [4,10]. Somatic issues such as locomotor pain, muscle cramps, and pruritus are, in fact, indicators of somatic health that are connected with high levels of alexithymia and sleep disturbances even in the general population [9].

In addition to the aim stated above, the purpose of this research is to determine the age differences, duration of renal replacement therapy and interdialytic yield of body mass between the two groups of patients (each group with a different circulatory approach).

Independently of the earlier aim, another aim of this research is related to the quality of sleep of HD patients, determined by the PSQ questionnaire: we aim to determine the differences in the stated clinical, biochemical, and sociodemographic variables, as well as in the levels of alexithymia, and to determine which factors are predictive of lower sleep quality in both groups of HD patients.

Patients and methods

Research has been done as a cross-sectional study in the period from February 2019 to February 2020. 79 hemodialysis patients (45 male and 34 female patients) at the Department for Nephrology in KBC Osijek, Hemodialysis Unit of Health Center Županja, and Nephrology Department in General Hospital Vinkovci were included in the study.

HD patients were sampled by simple random selection while strictly observing the study's inclusion and exclusion criteria. HD patients are included in the study by strict observation of the exclusion and inclusion criteria.

HD patients older than 18 years of age, who have been on the hemodialysis treatment or hemodiafiltration for at least three months, twice a week with every single hemodialysis duration not under three hours are included in the study. HD patients without heavier somatic or psychiatric diseases, like heart or liver failure, malignant disorder, major operations, or taking antipsychotics or antidepressants, are included in the study. Excluded from the study were HD patients for whom we have subsequently determined some kind of somatic or psychiatric comorbidity or those who have not filled out the questionnaires used in the study.

Just before the HD procedure, the patients are required to give a laboratory sample for the analysis of the biochemical parameters like blood count, albumins, creatinine, and from their medical files, we have collected data on the specificity of the hemodialysis process in every HD patient, such as the vascular approach and interdialytic mass yield. Interdialysis mass yield is defined according to the formula: body mass of patients on dialyses - body mass at the end of the last hemodialysis / number of days between dialyses / dry body mass HD [11].

HD patients filled out the sociodemographic questionnaire with information about the vintage of the

hemodialysis treatment, age of the patients, and scale for the measurement of alexithymia: Toronto alexithymia scale 26 (TAS 26), Pitsburg scale for sleep quality, Epworth scale for daily sleepiness.

TAS 26 is a self-rated scale consisting of 26 particles grouped in 4 subscales that measure difficulties in identifying feelings, difficulties in describing one's own feelings, reduced ability of fantasy, and exterior oriented thinking. It is validated in the Croatian language [12]. If an HD patient scores 62 points and less on the scale, they are not alexithymic; score values from 63 to 73 represent moderate levels of alexithymia, while scores over 74 represent high levels of alexithymia.

To determine sleep quality, HD patients filled out the Pitsburg scale (Pitsburg Sleep Quality Index (PSQ)) with 19 particles, grouped in 7 components for the elaboration of subjective sleep quality, time to fall asleep, duration of sleep, effective sleep, use of medications, daily functioning and disturbances during the sleep in the last month [13]. Patients with PSQ score 5 and higher are HD patients with low quality of sleep or "poor sleepers". To measure daily sleepiness, the authors used the Epworth scale for daily sleepiness (EES), a self-rating questionnaire with 8 offered particles. Every one of those measuring the respondents' daily sleepiness in described hypothetical situations. It is validated for usage in the Croatian language [14].

The authors have obtained approval of the Ethics Committees of UHC Osijek, General hospital Vinkovci, and Outpatient clinic Županja for conducting the research.

Statistical methods

The normal distribution of numerical data in the study has been tested with the Shapiro-Wilk test. Numerical data are presented with the arithmetic mean and standard deviation in the distribution, which follow a normal distribution, and in other cases with median and borders of the interquartile span. The differences in the numerical data between the CVC and AVF group of HD patients in the case of a normal distribution are tested with Student's t-test, and in the case of nonparametric distribution with Man-Whitney U test.

For the assessment of differences in biochemical, clinical, and sociodemographic variables relative to the sleep quality, HD patients are divided according to the score on the PSQ scale into groups of poor and good sleepers, independently of the type of vascular approach used in the HD treatment. The differences in biochemical, clinical, and sociodemographic variables among HD patients with regular and low sleep quality are tested in the case of a normal distribution with Student's t-test and in the case of nonparametric distribution with Man- Whitney U test, whereas the differences between categorical variables have been tested with a $\chi 2$ test.

Logistic regression is used for the analysis of many factors on the probability of sleep disorders in the sample of HD patients. SPSS (16.0, SPSS Inc., Chicago, IL, SAD) has been used for statistical analysis.

Table 1. Distribution of respondents characteristics according to CVC and AVF group

	Median (25%-75%)		P*
	CVC patients	AVF patients	
age (years)	67 (62 - 72)	66 (52 - 75)	0.31
vintage of HD (years)	1.1 (0.3 – 2.6)	3 (1.3 - 5.1)	**0.002**
CRP	5.3 (2.1 - 16.7)	3.7 (1.8 - 8.3)	0.10
Albumin	36.4 (32.9 - 38.1)	37.7 (35.7 - 39.5)	**0.02**
Hemoglobin	105.5 (94.8 - 111.8)	108 (103 - 116)	0.09
Interdialysis yield 1	0.8600 (0.01-1.46)	0.8600 (0.00-1.86)	0.733
Interdialysis yield 2	0.9250 (0.00-2.80)	0.900 (0.00-2.35)	0.558
Interdialysis yield 3	0.9500 (0.00-2.00)	0.9500 (0.00- 2.25)	0.650
Sleep quality (PSQ)	7 (4-11)	5.5 (4-9)	0.093
Daily slepiness (ESS)	6 (3.25-11)	7 (4-11.75)	0.650

*Man Whitney U test

Results

The study included 79 HD patients, 37 of which were in the group of CVC HD patients, and 42 in the AVF group of HD patients.

AVF HD patients have been significantly longer dialysed than the HD patients in the CVC group (p=0.002 Man Whitney U test). HD patients with arteriovenous fistule had significantly higher albumin levels than the HD patients in the CVC group (p=0.02 Man-Whitney U test).

In the group of HD patients with AVF, there is a negative correlation between levels of CRP and albumins (Spearman correlation, ρ=-0.594 p <0.001), while in the CVC group, there is no such connection (Spearman correlation, ρ= -0.12 p=0.950). There is no significant difference between patients with CVC and AVF in the levels of daily sleepiness (p=0.650 Man-Whitney U test) and the quality of sleep (p=0.093 Man-Whitney U test).

HD patients in the CVC group have a significantly lower creatinine level before hemodialysis than the HD patients in the AVF group (p=0.005 Student's t-test). Still, there is no difference in alexithymia levels between the two groups (p=0.933 Student's t-test).

In further analysis, HD patients from both groups are divided based on their score on the Pitsburg sleep quality scale into HD patients with or without disturbances in sleep quality for the purpose of assessing the differences in the observed variables. TThere are 32 HD patients with sleep disturbances and 47 HD patients without sleep disturbances in the sample.

There were no statistical differences between observed groups of respondents.

HD patients in groups of good and bad sleepers are not different compared to the levels of alexithymia (p=0,546 Student's t-test).

CVC and AVF group of HD patients exhibit no difference based on the quality of sleep (p=0.15 χ^2 test).

Logistic regression is used to rate the contribution of many factors on the probability of poor sleep (dependable variable). For the independent variables, age, sex, vintage of HD, CRP, albumins, hemoglobin, and interdialytic weight, and the type of vascular approach (CVC or AVF) were considered. For the conduction of the prediction model of poor sleep quality, multivariant logistic regression has been used.

For selecting the predictors, *Stepwise* logistic regression has been used, the criterion of statistical significance higher than 0.10 has been used, and research criterion 0.2 was the chosen border level. Only one predictor has a statistically significant contribution to the model, and that was the vintage of hemodialysis (Hosmer – Lemeshow test, P = 0.56). The model is in total statistically significant (χ^2 = 9.18, P = 0.002), and

Table 2. Distribution of the respondents' characteristics according to CVC and AVF group

	Arithmetic mean (st. deviation)		P*
	CVC group	AVF group	
creatinin before hemodialyses	654 (212)	800 (237)	0.005
alexithymia	67.22 (21.23)	66.87 (15.93)	0.933

*Student-'s t-test

Table 3. Distribution of respondents according to results on PSQ questionnaire

	Median (25%-75%)		P*
	Good sleep	Poor sleep	
age (years)	61.5 (52.8 - 68.5)	69 (63.5 - 75)	0.10
lenght HD	1.7 (0.7 - 3)	2.5 (0.8 - 6.5)	0.24
CRP	5.4 (1.3 - 10.2)	4.67 (2.3 - 10.6)	0.52
Albumins	37.9 (34.7 - 39.8)	37.05 (35.2 - 38.4)	0.31
Hemoglobin	108 (101.8 - 114.3)	107 (102.3 - 112)	0.63
Interdialysis weight 1	0.86 (0.3 - 1.1)	0.8 (0.6 - 1.2)	0.82
Interdialysis weight 2	0.95 (0 - 1.3)	0.9 (0.4 - 1.6)	0.38
Interdialysis weight 3	1.05 (0.4 - 1.3)	0.95 (0.6 - 1.5)	0.64
Daily sleepiness (ESS)	6 (3-10)	6.5 (3.25-11)	0.766

*Man Whitney U test

Table 4. Distribution of respondents according to CVC and AVF group

	Arithmetic mean (standard deviation)		P*
	good sleep	Poor sleep	
alexithymia	65.16 (22.21)	67.76 (16.49)	0.546
creatinine before hemodialyses	763 (268)	750 (203)	0.815

*Student's t-test

tients, considering that this vascular approach is connected with a higher level of systemic inflammation. A significantly lower level of albumins and the tendency to lower hemoglobin levels in this group could be explained by the fact that these proteins are negative reactants of the acute phase, allowing the possibility of connecting their levels with systemic inflammation to which these HD patients are inclined.

HD patients with CVC score somewhat higher in the Sleep Quality questionnaire (Table 1), which is in line with current research, as this group of patients is

Table 5. The Respondents' Results based on the PSQ Questionnaire

	Number of subjects (patients) (%)			P*
	Sleeping Well	Sleeping Poorly	Total	
CVC group	8 (28.6)	23 (45.1)	31 (39.2)	0.15
AVF group	20 (71.4)	28 (54.9)	48 (60.8)	
Total	28 (100)	51 (100)	79 (100)	

*χ^2 test

in total explains between i 18% (based on Cox & Snell) and 24.7% (based on Negelkerke) variance of bad sleep, and correctly classifies i 53,3% cases. Respondents who have been on HD for a longer period of time have a 1.34 times higher chance of poor sleeping (OR = 1,34 95%CI 1,02 do 1,74).

Discussion

It is well-known that HD patients with CVC have a higher incidence of mortality, more comorbidities, and a higher risk of infections compared to HD patients with AVF [15].

Although research suggests that HD patients with CVC are on average older than patients with AVF, this is not the case in this study [(16)]. Between the two groups of HD patients, the only significant difference is the duration of the treatment with hemodialysis in the case of the patients with constructed AVF. In accordance with the study's hypothesis, the CVC group of HD patients has slightly higher levels of C-reactive protein compared to the AVF group of HD patients. The difference is on the border of statistical significance, and this hypothesis should be tested on a more significant sample of patients. However, this result still shows the vulnerability of the CVC group of HD patients, considering that this vascular approach is connected with a higher level of systemic inflammation. A significantly lower level of albumins and the tendency to lower hemoglobin levels in this group could be explained by the fact that these proteins are negative reactants of the acute phase, allowing the possibility of connecting their levels with systemic inflammation to which these HD patients are inclined.

HD patients with CVC score somewhat higher in the Sleep Quality questionnaire (Table 1), which is in line with current research, as this group of patients is more prone to muscle cramps and uremic pruritus that objectively prevent falling asleep and sleeping [(4).] The differences between the two groups, however, are not statistically significant, so the research should be conducted with more subjects (more HD patients) to ensure that there is no statistical error type two, that is, the failure to detect existing differences due to a small sample of respondents [(17).]

The connection between sleep quality and the type of vascular approach in HD patients has only been tested in a small number of studies. Although the results are contradictory, more studies have shown that patients with CVC have poorer (lower) sleep quality [(10).] It is possible that the poor sleep quality in CVC HD patients is connected to the levels of haemoglobin, albumin and somewhat higher levels of the systemic inflammatory markers such as CRP, which are on the margin of statistical significance in our results, and that they represent a possible pathophysiological mechanism of influence of somatic health on the quality of sleep. This opens up the possibilities for further research on the subject.

A novel piece of data, so far undescribed in literature, is the realization of the equal levels of HD patients' daily sleepiness, regardless of the vascular approach. Daily sleepiness is a factor that is connected to

the high incidence of other morbidities, it lowers the quality of life of people in the general population, making their daily functioning more complicated, and in the population of HD patients, it is even more expressed than in the general population [3]. The results of our study point to the fact that the choice of the vascular approach in HD patients is not related to the levels of their daily sleepiness.

Although, in studies done so far on the population of HD patients, alexithymia is connected with the vintage of hemodialysis, anemia and a higher number of comorbidities, the authors haven't found a difference in the level of alexithymia in HD patients based on the type of vascular approach [6, 17].

AVF group of HD patients has been dialysed significantly longer and, based on current research, higher levels of alexithymia should be expected considering that the duration of dietary restrictions and everyday frustration is longer [18].

Significantly higher levels of albumins and the tendency towards higher levels of hemoglobin and lower levels of CRP in the AVF group of HD patients point to a better somatic state in this group, which points out the need for the evaluation of the number and seriousness of their comorbidities as well as assessment of the levels of alexithymia between the two groups considering the fact that this represents a limitation of our study [19].

If we categorize HD patients into groups with good and poor sleep quality based on their PSQ questionnaire score, regardless of the vascular approach used in their treatment, it is clear that there is no statistical difference in age or duration of dialysis treatment, biochemical variables, and interdialysis yield, which is partially in line with the current research on the quality of sleep in HD patients [20,21].

HD patients with CVC have a higher score on the sleep quality scale, which is in accordance with previous results, considering the fact that this group of patients has a tendency toward muscular cramps and uremic pruritus, which represent objective disturbances for falling asleep and sleeping (4). The differences between the two groups are not statistically significant; therefore, research should be done on a larger sample of HD patients to avoid the possible statistical mistake type two, that is, the existence of differences that are not detectable due to a small sample [20].

If HD patients are divided according to the PSQ scale result, in groups with normal and with poor sleep quality, independently of the type of vascular approach, there are no statistical differences in age, vintage of dialysis treatment, biochemical variables, and interdialysis mass yield. The absence of a connection between sleep quality and biochemical variables like CRP, albumins, hemoglobin, and creatinine is partly in accordance with the previous conclusions about sleep quality in a population of HD patients [21,22]. Consistent results about the connection between lower sleep quality and biochemical parameters exist only if we take into consideration an overall scale, like malnutrition-inflammatory score (MIS), which assesses the general condition of HD patients in relation to inflammatory variables and nutrient intake [23]. A similar type of research should be done in the future when rating the inflammatory-nutritive status of HD patients.

Even though the studies done so far show a connection between lower sleep quality and volume status in HD patients, we could not confirm the connection described with high interdialyses fluid delivery in HD patients [24]. The reason for this is probably in the fact that interdialyses fluid delivery on hemodialysis doesn't necessarily represent the volume status of HD patients, which should be measured with sensitive methods like bioimpedance [25].

In studies done so far in HD patients with heavy hyperparathyroidism, alexithymia is a factor that is directly connected with lower sleep quality and normalisation of sleep quality after paraidectomy. It is a predictive factor for the reduction of the levels in alexithymia [26].

In studies performed in the general population, alexithymia and lower sleep quality are connected through depression because the connection of alexithymia and sleep quality disappears when the effects of depression are included in the analyses [27].

There have been no similar studies so far, so our results have scientific significance as the first analysis of the connection between sleep quality and alexithymia on HD patients' population without serious somatic and mental disorders.

Sleep quality is a concept dependant on age-sex characteristics, as women develop sleep disorders more often than men, and that aging increases the appearance of disturbances of sleep quality [28].

In the statistical model in which we have included age, sex, biochemical variables, and interdialytic mass yield, the only factor that predicts lower sleep quality is

the vintage of the hemodialysis treatment, and every additional year of the hemodialysis treatment contributes a 1.34 higher possibility that an HD patient will develop disturbance in sleep quality. Based on the results, it is possible to determine that hemodialysis treatment, regardless of the biochemical and sociodemographic variables and the type of vascular approach, sex, age, and biochemical variables, contributes to the lower sleep quality. Dietary measures, a tendency toward developing a depressive disorder, everyday frustrations connected with time consumption, lower socioeconomic status, and somatic difficulties are factors that can contribute to the described deterioration [23,29].

Additional studies are needed on larger samples in order to determine if the existence of long-term complications of hemodialysis, such as muscle cramps and hypotension or more comorbidities in older age of HD patients, is crucial for the development of poor sleep quality in HD patients. The necessity for additional studies arises from the fact that sleep disturbances are one of the factors which significantly contribute to lower quality of life and morbidity of HD patients [30].

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Sažetak

RAZLIKE U BIOKEMIJSKOM REAKTANTIMA AKUTNE FAZE I KVALITETI SPAVANJA OBZIROM NA TIP KRVOŽILNOG PRISTUPA U BOLESNIKA LIJEČENIH HEMODIJALIZOM

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U bolesnika liječenih hemodijalizom (HD) postoji visoka prevalencija poremećaja kvalitete spavanja s nedovoljno utvrđenim uzrocima. Cilj istraživanja je usporediti razlike u razinama pojedinih biokemijskih, sociodemografskih čimbenika, aleksitimije i kvalitete spavanja u skupinama HD bolesnika s obzirom na tip vaskularnog pristupa, odrediti i razlike između HD bolesnika sa urednom i sniženom kvalitetom spavanja i utvrditi prediktivne faktore snižene kvalitete sna.

U istraživanju je sudjelovalo 79 ispitanika oba spola liječenih hemodijalizom, dobnog raspona između 33 do 87 godina iz KBC Osijek, OŽB Vinkovci i DZ Županja. HD bolesnicima su uzeti uzorci krvi za laboratorijsku analizu te su zabilježeni klinički i sociodemografski podaci.

Bolesnici su anketirani pomoću hrvatske inačice Pitsburškog upitnika za mjerenje kvalitete spavanja, Toronto aleksitimija skale 26 i Epworthove ljestvice dnevne pospanosti. HD bolesnici koji se dijaliziraju preko centralnog venskog katetera imaju značajno niže vrijednosti albumina (p=0,02 Mann-Whitney U test), kreatinina (p=0,007 Mann-Whitney U test) i kraće se dijaliziraju u odnosu na bolesnike sa arteriovenskom fistulom (p=0,002 Mann-Whitney U test). Ispitanici koji su dulje vrijeme na HD imaju 1,395 puta veću šansu za sniženu kvalitetu spavanja (OR = 1,395 95%CI 1,02 do 1,74). Jedini prediktivni faktor snižene kvalitete spavanja u HD bolesnika je trajanje liječenja hemodijalizom.

Ključne riječi: *aleksitimija, hemodijaliza, kvaliteta spavanja, krvožilni pristup*