ORIGINAL ARTICLE

# Associations between symptoms of constipation and sleep quality in patients with nondialysis chronic kidney disease: a cross-sectional study

Jakub Ruszkowski[1,2], Zbigniew Heleniak[2], Ewa Król[2], Agnieszka Tarasewicz[2], Jacek M. Witkowski[1], Alicja Dębska-Ślizień[2]

1 Department of Pathophysiology, Faculty of Medicine, Medical University of Gdansk, Gdańsk, Poland
2 Department of Nephrology, Transplantology and Internal Medicine, Faculty of Medicine, Medical University of Gdansk, Gdańsk, Poland

**KEY WORDS**

chronic kidney disease, constipation, sleep disorders

**EDITORIAL**

by Tiwari and Parajuli, see p. 499

**ABSTRACT**

**INTRODUCTION** Sleep disturbances, similarly to constipation-related symptoms, are common problems in patients with chronic kidney disease (CKD) and are associated with worse health-related quality of life.

**OBJECTIVES** The aim of the study was to investigate sleep problems in conservatively treated patients with CKD and to assess association between sleep quality and constipation in that population.

**PATIENTS AND METHODS** In this cross-sectional study, 100 conservatively treated outpatients with CKD filled questionnaires addressing sleep quality (The Medical Outcomes Study 12-item Sleep Scale–Revised [MOS-Sleep-R]) and constipation-related symptoms (PAC-SYM, Rome III criteria).

**RESULTS** The T scores of none of the assessed sleep domains differed across the estimated glomerular filtration rate terciles (all $P > 0.05$). The scores from the PAC-SYM abdominal and stool subscales correlated with all assessed sleep quality domains. In both univariable and multivariable regression models adjusted for key clinical data, functional constipation, less than 7 bowel movements a week, abdominal discomfort, and pain as well as too small bowel movements were independently associated with increased prevalence ratio of decreased sleep quality.

**CONCLUSIONS** In patients with nondialysis CKD, sleep disorders might have common etiological factors with constipation-related symptoms.

**INTRODUCTION** Sleep is a complex physiological process that is crucial for maintaining well-being and overall health. Even though sleep disorders are prevalent, the underlying precise pathophysiological mechanisms are not always well understood.[1]

Chronic kidney disease (CKD) is a common condition (9.1%–13.4% of the global population)[2,3] that is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health.[4] That is, a decline in kidney function adversely affects multiple organs which leads to a decrease in both physical and mental health-related quality of life (HRQOL).[5]

As evidenced by recent meta-analyses, there is a high prevalence of several sleep disorders in patients with CKD.[6-8] Among patients with nondialysis CKD, pooled prevalence estimates (and 95% CIs) of sleep apnea, insomnia, excessive daytime sleepiness, and restless leg syndrome were 38% (21%–70%), 33.3% (22.2%–46.1%), 22% (18%–28%), and 9.9% (5.4%–17.5%), respectively.[6-8] The prevalence of sleep disorders is even higher among dialysis patients, and is partially normalized after kidney transplantation.[6,7,9] Since many studies failed to show an association between sleep quality and CKD progression, a greater focus has been placed on finding other factors associated with the increased prevalence of sleep disorders in patients with CKD.[10-14] Uncovering the manageable causes of sleep disorders in this population would be of great benefit.

Interestingly, there are factors associated both with CKD and sleep disorders, such as decreased melatonin level, increased body mass index, and functional constipation.[15-18] However,

Correspondence to:
Jakub Ruszkowski, MD, Department of Pathophysiology, Medical University of Gdańsk, ul. Dębinki 7, 80-211 Gdańsk, Poland, phone: +48 58 349 15 12, email: jakub.ruszkowski@gumed.edu.pl
Received: March 31, 2021.
Revision accepted: April 23, 2021.
Published online: April 27, 2021.
Pol Arch Intern Med. 2021; 131 (6): 512-519
doi:10.20452/pamw.15974

## WHAT'S NEW?

Sleep disorders are prevalent in patients with chronic kidney disease; however, the underlying precise pathophysiological mechanisms are poorly understood. In our study, we found that constipation and certain gastrointestinal symptoms commonly coexist with decreased sleep quality. Uncovering the manageable causes of sleep disorders in patients with chronic kidney disease would be of great benefit, and our study sheds light on new perspectives on these causes that should be verified in clinical trials.

the association between constipation-related symptoms and quality of sleep in patients with CKD has not been reported yet.

The aim of the study was to describe sleep problems in conservatively treated patients with CKD, and to explore the association between sleep problems and constipation-related symptoms in that population.

**PATIENTS AND METHODS** This study was conducted as part of a broad project that aimed to comprehensively assess the relationship between lower gastrointestinal symptoms and quality of life in conservatively treated CKD patients. The full methodology of the study was described previously.[19] The study protocol was approved by the Bioethical Committee for Scientific Research at the Medical University of Gdańsk, Poland (NKBBN/426–56/2018).

**Study population** Briefly, we screened 150 and recruited 111 outpatients visiting the Nephrological Outpatient Clinic (University Clinical Centre in Gdańsk) between June 2018 and December 2019. Participants were eligible for the study if they were adults (>18 years old) diagnosed with CKD. Exclusion criteria were as follows: current dialysis or a history of dialysis; a history of kidney transplantation; cognitive or visual deficits that rendered a patient unable to answer the questionnaire; serious illness in an acute treatment phase. All patients were informed about the nature and purpose of the study. As the research was based on voluntarily filled anonymous surveys, additional written informed consent was not required.

**Measures** Participants were asked to voluntarily complete a battery of questionnaires. Besides questionnaires reported in the previous study assessing HRQOL (the Polish 36-item Short Form Health Survey version 2.0, known as SF-36v2) and symptoms of constipation (the Patient Assessment of Constipation-Symptoms [PAC-SYM] questionnaire; simple questions containing Rome III criteria of functional constipation, question about the number of bowel movements [BMs] per week, and the Bristol Stool Form Scale [BSFS]), patients were asked to fill the Medical Outcomes Study Sleep Scale–Revised (MOS-Sleep-R). BSFS constipation was defined as type 1 ("separate hard lumps, like nuts [difficult to pass]") or type 2 ("sausage-shaped but lumpy") stool form.

The MOS-Sleep-R questionnaire includes 12 items that measure 6 dimensions of sleep with a 4-week recall period: sleep disturbance (4 items), daytime somnolence (3 items), sleep adequacy (2 items), snoring (1 item), awakening due to shortness of breath / headache (1 item), and sleep quantity (1 item). The sleep disturbance subscale addresses problems both with sleep initiation and maintenance. The somnolence subscale measures daytime sleepiness. Sleep adequacy represents morning restedness and getting the needed amount of sleep. Ten items are measured on a 5-point Likert scale ranging from "all of the time" to "none of the time." Two additional items address time to fall asleep (from "0–15 minutes" to "more than 60 minutes") and an average number of hours slept each night (7–8 hours are interpreted as "optimal" sleep quantity). Higher scores indicate better sleep outcomes. Scoring points are transformed into standardized T scores (mean [SD], 50 [10]) based on data from a 2009 United States internet-based general population survey.[20] The summary measure of sleep quality (called the Sleep Problems Index II) is derived from 9-item scores; due to the method of scoring, it is reported as "Sleep Quality" in this paper (the higher the score, the better quality of sleep).

The SF-36v2 questionnaire consists of 36 items that assess 8 dimensions of HRQOL: physical functioning; role limitations due to problems with physical health; bodily pain; vitality; social functioning; role limitations due to emotional problems; mental health; and general health perception. Higher scores indicate better HRQOL. Since the general health scale in the Polish version of the SF-36v2 is neither reliable nor valid,[19] we did not use the results of this domain in this study. To use both the MOS-Sleep-R and the SF-36v2, a noncommercial license agreement was made between JR and OptumInsight Life Sciences, Inc (license no., QM044526; Johnston, United States). Both questionnaires were scored using the desktop scoring software PRO CoRE Version 1.4 provided by Optum.

Data on gender, age, body weight, height, body mass index, estimated glomerular filtration rate (eGFR) based on CKD-EPI formula, etiology of CKD, comorbidities, and taken medications were collected by a physician, as reported previously.[19]

**Statistical analysis** Normal distribution of data was tested using the Shapiro–Wilk test. Continuous variables with nonnormal distribution were presented as medians and interquartile ranges (IQRs) and differences in their values between groups were presented as the Hodges–Lehmann estimate. Categorical variables were presented as a percentage share of the obtained data. Patient groups were compared using the Mann–Whitney test, the Kruskal–Wallis test (with a pairwise post hoc Dunn tests), and Pearson $\chi^2$ test. Statistical

testing was done with JASP 0.13.1 and Python libraries: Pandas,[21] Pingouin,[22] Statsmodels.[23] *P* values of less than 0.05 were considered significant. To adjust for multiple comparisons, all *P* values of post hoc tests were corrected using the Bonferroni–Holm adjustment method.

Due to a high disproportion in the number of patients across stages of CKD, patients were divided into 3 groups according to eGFR terciles: with low eGFR (≤32 ml/min/1.73 $m^2$), medium eGFR (33–43 ml/min/1.73 $m^2$), and high eGFR (≥44 ml/min/1.73 $m^2$).

To calculate the scores from the PAC-SYM subscales (abdominal, rectal, stool), scores for items within a given subscale were summed and divided by the number of items for that subscale.[24]

In the sleep quality analysis, we used only multi-item scales, that is, sleep disturbance, daytime somnolence, sleep adequacy, and summary Sleep Quality. Firstly, correlations of their T scores and the scores from the PAC-SYM subscales were tested using both Kendall (τ-B) and Spearman (ρ) rank correlation coefficients. To assess whether constipation-related symptoms were independently associated with deteriorated overall sleep quality among patients with CKD, we used modified log-Poisson regression models with robust variance (computed with the statsmodels adaptation of the R code published by Gallis and Turner)[25] to estimate the prevalence ratio (PR) of a decreased Sleep Quality score (defined as a T score <40) in patients with CKD.

Each of the gastrointestinal symptoms / disorders that was associated with a higher prevalence of decreased Sleep Quality in univariable analysis (Supplementary material, *Description S1* and *Table S2*) was further analyzed in multivariable analysis to verify the independence of the observed association. To select an optimal set of covariates for multivariable analyses, we performed 2-step variable selection from a wide range of variables that—based on the background knowledge—could be associated with decreased sleep quality (anthropometric and demographic data, diseases, drugs). Firstly, using univariable analyses, we selected all variables that might have been associated with disturbed sleep quality based on the collected data (Vovk–Sellke maximum *P* ratio >1.0; *P* <0.37); they were shown in Supplementary material, *Table S3*. At the next stage, from all selected variables in the previous step, we chose the most informative sets of variables for each domain: to balance goodness-of-fit and model complexity, optimal sets of variables were chosen using Akaike information criterion (Supplementary material, *Description S2*). Finally, multivariable regression models estimating the PR of decreased sleep quality according to each of the selected constipation symptoms, with adjustment for key demographic and clinical data, were performed.

## RESULTS

### Demographics and comorbidities

Out of 111 patients surveyed in our previous study for gastrointestinal symptoms and HRQOL,[19] 100 patients completed MOS-Sleep-R. Their demographic and clinical characteristics are presented in TABLE 1, and pharmacotherapy is shown in Supplementary material, *Table S1*.

Patients with high eGFR were significantly younger than patients with medium eGFR (adjusted *P* <0.001) and had significantly less severe PAC-SYM stool symptoms than patients with low eGFR levels (adjusted *P* = 0.002). There were less men among patients with medium eGFR than among those with low eGFR (adjusted *P* = 0.03). Patients divided by eGFR terciles seemed to differ with regard to the prevalence of diabetes, functional constipation, and rectal symptoms; however, post hoc tests ceased to be significant after corrections for multiple comparisons (data not shown). Moreover, there were no significant differences between women and men, except for higher frequency of hypothyroidism in women (women, 27.3% vs men, 8.9%; *P* = 0.02).

### Sleep quality and its correlation with health-related quality of life

The T scores of the assessed sleep domains did not differ across the eGFR terciles (all *P* >0.05; TABLE 2). Similarly, except for the higher frequency of snoring among men than women (T score median, 44.8 vs 52.4, respectively; *P* = 0.02), no other differences were found between genders. Not surprisingly, Sleep Quality score correlated with all HRQOL domains, with the highest coefficients in vitality and mental health (Supplementary material, *Figure S1*).

### Is sleep quality related to symptoms of constipation in patients with chronic kidney disease?

Since in our previous paper we showed several associations between constipation-related symptoms and decreased HRQOL in patients with nondialysis CKD,[19] we performed analyzes to further explore correlations between constipation-related symptoms and subjective sleep quality assessments (TABLE 3). Interestingly, the scores of abdominal and stool scales correlated with all assessed sleep quality domains; the former correlations were stronger and more robust (coefficients have not changed after removal of asymptomatic patients from the analysis, data not shown). Also, less than 7 BMs per week and symptoms of functional constipation were associated with worse sleep quality (TABLE 4). On the contrary, BSFS constipation was not associated with altered sleep quality (all *P* >0.05; TABLE 4). These results were confirmed in a reanalysis using only data of patients not using any laxative drugs (n = 97; data not shown).

### Independent factors associated with deteriorated sleep quality among patients with chronic kidney disease

Following analyses from the section above, we explored PAC-SYM items that could be responsible for the observed associations with decreased sleep quality. Based on univariable analyses, we found that abdominal discomfort and pain (PAC-SYM abdominal subscale), too small

**TABLE 1** Demographic and clinical parameters of the total study population and according to estimated glomerular filtration rate tercile

| Parameter | | All | High eGFR tercile | Medium eGFR tercile | Low eGFR tercile | *P* value |
|---|---|---|---|---|---|---|
| Participants, n | | 100 | 33 | 33 | 34 | – |
| Male sex, n (%) | | 56 (56) | 20 (60.6) | 12 (36.4) | 24 (70.6) | 0.02 |
| Age, y, median (IQR) | | 68 (55.8–74) | 64 (42–70) | 71 (68–76) | 66.5 (57–75.3) | 0.002 |
| BMI, kg/m$^2$, median (IQR) | | 28.65 (25.8–30.8) | 29.1 (25.5–30.8) | 28.6 (26.3–30.5) | 28.6 (25.3–31.5) | 0.86 |
| eGFR, ml/min/1.73 m$^2$, median (IQR) | | 38 (30–47) | 57 (47–67) | 38 (35–42) | 26.5 (17.3–30) | <0.001 |
| Comorbidities, n (%) | | | | | | |
| Hypertension | | 88 (88) | 28 (84.8) | 31 (93.9) | 29 (85.3) | 0.44 |
| Diabetes | | 32 (32) | 5 (15.2) | 12 (36.4) | 15 (44.1) | 0.03 |
| Heart failure | | 19 (19) | 3 (9.1) | 8 (24.2) | 8 (23.5) | 0.21 |
| Hypothyroidism | | 17 (17) | 6 (18.2) | 6 (18.2) | 5 (14.7) | 0.91 |
| Depression | | 4 (4) | 0 | 2 (6.1) | 2 (5.9) | 0.36 |
| Gastrointestinal symptoms | | | | | | |
| PAC-SYM abdominal subscale | ≥1 symptom reported, n (%) | 59 (59.6) | 21 (65.6) | 15 (45.5) | 23 (67.6) | 0.13 |
| | T score, median (IQR)[a] | 0.8 (0.5–1.25) | 0.5 (0.3–1) | 0.8 (0.6–1.3) | 0.8 (0.5–1.5) | 0.39 |
| | No data, n | 1 | 1 | 0 | 0 | – |
| PAC-SYM rectal subscale | ≥1 symptom reported, n (%) | 30 (30.3) | 8 (25) | 6 (18.2) | 16 (47.1) | 0.03 |
| | Score, median (IQR)[a] | 0.3 (0.3–1) | 0.3 (0.3–0.4) | 0.3 (0.3–1.1) | 0.7 (0.3–1.3) | 0.28 |
| | No data, n | 1 | 1 | 0 | 0 | – |
| PAC-SYM stool subscale | ≥1 symptom reported, n (%) | 69 (69.7) | 20 (62.5) | 21 (63.6) | 28 (82.4) | 0.14 |
| | Score, median (IQR)[a] | 0.6 (0.2–1) | 0.3 (0.2–0.5) | 0.6 (0.4–0.8) | 0.8 (0.4–1.2) | 0.007 |
| | No data, n | 1 | 1 | 0 | 0 | – |
| <7 BMs/week | Data available, n (%) | 34 (35.4) | 8 (24.2) | 13 (40.6) | 13 (41.9) | 0.25 |
| | No data, n | 4 | 0 | 1 | 3 | – |
| BSFS | Constipation, n (%) | 24 (26.7) | 6 (20) | 9 (30) | 9 (30) | 0.6 |
| | No data, n | 10 | 3 | 3 | 4 | – |
| Functional constipation, n (%) | | 19 (19) | 3 (9.1) | 5 (15.2) | 11 (32.4) | 0.04 |

**a** Only nonzero values were accounted. *P* values were calculated with the Kruskal–Wallis test and the Pearson $\chi^2$ test.

Abbreviations: BMI, body mass index; BMs, bowel movements; BSFS, the Bristol Stool Form Scale; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PAC-SYM, the Patient Assessment of Constipation-Symptoms questionnaire

BMs (PAC-SYM stool subscale), and painful BMs (PAC-SYM rectal subscale) were associated with an increased PR of decreased Sleep Quality (Supplementary material, *Table S2*). Unfortunately, the limited number of participants in the study makes it impossible to clearly determine whether these gastrointestinal symptoms are more often associated with impaired sleep quality in people with impaired versus normal kidney function. It seems, however, that one of these symptoms, abdominal discomfort, can be associated with a higher prevalence of a decreased Sleep Quality score among patients with lower eGFR than those with higher eGFR (Supplementary material, *Figure S2*).

In line with univariable analyzes, functional constipation, defecating less than 7 times a week, as well as presence / severity of abdominal discomfort and pain, as well as too small BMs, remained significantly associated with an increased PR of decreased Sleep Quality, even after adjustment for age, depression, and drugs (TABLE 5 and Supplementary material, *Tables S4–S7*). On the contrary, the association of painful BMs with an increased PR of decreased Sleep Quality ceased to be significant after inclusion of drugs into the model (TABLE 5 and Supplementary material, *Table S8*).

**DISCUSSION** In the current study using validated questionnaires, we confirmed the associations between sleep problems and constipation-related symptoms in patients with nondialysis CKD. To the best of our knowledge, this is the first study on these associations in patients with CKD. Moreover, according to the objectives of the study, we explored the associations and found a set of symptoms (abdominal discomfort and pain, too small BMs) that are independently associated with the increased PR of lower sleep quality in patients with CKD.

The link between functional gastrointestinal disorders and deteriorated sleep quality has been well documented in non-CKD adult patients. In a population-based study, Wu et al[18] found that excessive daytime sleepiness was significantly associated with an increased odds ratio of diarrhea-predominant irritable bowel syndrome (IBS), alternating IBS, and functional constipation in an

**TABLE 2** The results of the Medical Outcomes Study Sleep Scale–Revised across estimated glomerular filtration rate terciles

| Variable | | All | High eGFR tercile | Medium eGFR tercile | Low eGFR tercile | *P* value |
|---|---|---|---|---|---|---|
| Sleep quality | | | | | | |
| T score, median (IQR) | | 51.88 (43.11–57.5) | 53.29 (47.67–57.5) | 51.88 (40.66–57.5) | 47.67 (40.66–55.74) | 0.16[a] |
| T score <40, n (%) | | 18 (18) | 2 (6.1) | 8 (24.2) | 8 (23.5) | 0.09[b] |
| Multi-item scales | | | | | | |
| Disturbance, T score, median (IQR) | | 50.96 (42.22–57.2) | 52.21 (49.71–57.2) | 49.71 (42.22–57.2) | 47.21 (37.22–57.2) | 0.22[a] |
| Somnolence, T score, median (IQR) | | 48.23 (40.52–55.94) | 48.23 (44.37–55.94) | 48.23 (40.52–52.09) | 44.37 (37.62–52.09) | 0.2[a] |
| Adequacy, T score, median (IQR) | | 57.58 (47.9–62.43) | 57.58 (47.9–62.43) | 57.58 (47.9–62.43) | 52.74 (44.26–61.22) | 0.45[a] |
| Single-item scales | | | | | | |
| Shortness of breath | T score, median (IQR) | 55.25 (43.47–55.25) | 55.25 (43.47–55.25) | 55.25 (43.47–55.25) | 55.25 (43.47–55.25) | 0.76[a] |
| | "None of the time," n (%) | 58 (58) | 20 (60.6) | 17 (51.5) | 21 (61.8) | 0.65[b] |
| Snoring | T score, median (IQR) | 44.84 (44.84–52.44) | 44.84 (42.94–52.44) | 52.44 (44.84–52.44) | 44.84 (44.84–52.44) | 0.54[a] |
| | "None of the time," n (%) | 20 (20.4) | 6 (18.8) | 7 (21.2) | 7 (21.2) | 0.96[b] |
| | No data, n | 2 | 1 | 0 | 1 | – |
| Sleep quantity | Optimal, n (%) | 49 (49) | 19 (57.6) | 17 (51.5) | 13 (38.2) | 0.27[b] |
| | Duration, h, median (IQR) | 8 (6–8) | 8 (7–8) | 8 (6–8) | 7 (6–8) | 0.26[a] |

**a** Kruskal–Wallis test

**b** $\chi^2$ test

Abbreviations: see **TABLE 1**

**TABLE 3** Correlations between the T scores of the Medical Outcomes Study Sleep Scale–Revised (MOS-Sleep-R) and the scale scores of the Patient Assessment of Constipation-Symptoms (PAC-SYM)

| MOS-Sleep-R | Correlation coefficient | PAC-SYM score | | |
|---|---|---|---|---|
| | | Abdominal symptoms | Rectal symptoms | Stool symptoms |
| Sleep Quality | Spearman ρ | –0.57 (–0.69 to –0.42) | –0.23 (–0.41 to –0.03) | –0.5 (–0.64 to –0.34) |
| | *P* value | <0.001 | 0.02 | <0.001 |
| | Kendall τ B | –0.45 (–0.57 to –0.34) | –0.19 (–0.3 to –0.07) | –0.38 (–0.49 to –0.26) |
| | *P* value | <0.001 | 0.02 | <0.001 |
| Sleep disturbance | Spearman ρ | –0.47 (–0.61 to –0.3) | –0.21 (–0.39 to –0.01) | –0.46 (–0.6 to –0.29) |
| | *P* value | <0.001 | 0.04 | <0.001 |
| | Kendall τ B | –0.38 (–0.5 to –0.25) | –0.17 (–0.29 to –0.06) | –0.36 (–0.48 to –0.23) |
| | *P* value | <0.001 | 0.04 | <0.001 |
| Sleep adequacy | Spearman ρ | –0.43 (–0.58 to –0.25) | –0.17 (–0.36 to 0.03) | –0.28 (–0.45 to –0.09) |
| | *P* value | <0.001 | 0.09 | 0.005 |
| | Kendall τ B | –0.35 (–0.47 to –0.23) | –0.14 (–0.24 to –0.04) | –0.22 (–0.36 to –0.09) |
| | *P* value | <0.001 | 0.1 | 0.004 |
| Somnolence | Spearman ρ | –0.39 (–0.54 to –0.21) | –0.08 (–0.28 to 0.12) | –0.39 (–0.55 to –0.21) |
| | *P* value | <0.001 | 0.41 | <0.001 |
| | Kendall τ B | –0.3 (–0.42 to –0.18) | –0.07 (–0.19 to 0.05) | –0.31 (–0.44 to –0.18) |
| | *P* value | <0.001 | 0.39 | <0.001 |

adult Chinese population (age, 18–80 years). Interestingly, among French adult patients (mean [SD] age, 48.2 [16.7] years) with functional gastrointestinal disorders, functional constipation and bloating have been associated with insomnia, while functional diarrhea and nonspecific bowel disorders with drowsiness.[17] In our study, insomnia and excessive daytime sleepiness were measured with the MOS-Sleep-R sleep disturbance and somnolence scales, respectively. We found more disturbed sleep in patients with functional constipation and defecating less than 7 times a week, but higher sleepiness only in patients defecating less than 7 times a week. Moreover, the severity of both insomnia and daytime sleepiness correlated with the severity of PAC-SYM abdominal and stool symptoms.

Such strict associations between sleep and gastrointestinal symptoms in patients with CKD emphasize the importance of common risk factors, for example, obesity, depression, melatonin deficiency, or side effects of drugs. Indeed, obesity is an important modifiable risk factor for CKD (via a plethora of mechanisms such as induction

**TABLE 4** Differences in the T scores of the Medical Outcomes Study Sleep Scale–Revised between patients with and without constipation

| MOS-Sleep-R | Functional constipation | | Less than 7 BMs/week | | BSFS constipation | |
|---|---|---|---|---|---|---|
| | *P* value[a] | Difference[b] (95% CI) | *P* value[a] | Difference[b] (95% CI) | *P* value[a] | Difference[b] (95% CI) |
| Sleep Quality | 0.004 | –7.02 (–11.23 to –2.8) | <0.001 | –7.02 (–11.23 to –2.81) | 0.33 | –1.88 (–5.62 to 2.8) |
| Sleep disturbance | 0.01 | –5.0 (–9.99 to –2.49) | 0.003 | –5 (–9.99 to –2.5) | 0.41 | –2.49 (–7.49 to 2.5) |
| Sleep adequacy | 0.19 | –4.84 (–9.68 to 0) | <0.001 | –4.9 (–9.69 to –4.84) | 0.33 | –0.01 (–4.85 to 0) |
| Somnolence | 0.09 | –3.86 (–11.56 to 0) | 0.009 | –7.7 (–7.72 to –3.85) | 0.86 | 0.01 (–3.86 to 3.86) |

a Groups were compared with the Mann–Whitney test

b Difference between patients with versus without a specific condition presented as the Hodges–Lehmann estimate with 95% CI

Abbreviations: see TABLE 1

**TABLE 5** Log-Poisson regression models of a decreased Sleep Quality score prevalence ratio according to constipation-related symptom unadjusted and adjusted for key clinical data

| Constipation-related symptom | | Univariable analyses, unadjusted | | Adjusted model 1[a] | | Adjusted model 2[b] | |
|---|---|---|---|---|---|---|---|
| | | PR (95% CI) | *P* value | PR (95% CI) | *P* value | PR (95% CI) | *P* value |
| Frequency of defecation | 7 times/week | Reference | – | Reference | – | Reference | – |
| | <7 times/week | 7.24 (1.74–30.12) | 0.007 | 6.46 (1.55–26.83) | 0.01 | 4.64 (1.13–18.97) | 0.03 |
| | >7 times/week | 2.93 (0.53–16.19) | 0.22 | 2.55 (0.47–13.91) | 0.28 | 2.3 (0.43–12.41) | 0.33 |
| Functional constipation | | 2.71 (1.21–6.07) | 0.02 | 2.52 (1.15–5.54) | 0.02 | 2.96 (1.36–6.43) | 0.006 |
| Abdominal discomfort | Lack | Reference | – | Reference | – | Reference | – |
| | Mild | 4.31 (1.29–14.37) | 0.02 | 3.62 (1.07–12.29) | 0.04 | 3.6 (1.19–10.83) | 0.02 |
| | Moderate/severe | 7.34 (2.54–21.19) | <0.001 | 6.83 (2.34–19.95) | < 0.001 | 7.42 (2.5–21.99) | <0.001 |
| Abdominal pain | Lack | Reference | – | Reference | – | Reference | – |
| | Mild | 4.24 (1.56–11.52) | 0.004 | 3.52 (1.34–9.3) | 0.01 | 2.91 (1.19–7.15) | 0.02 |
| | Moderate/severe | 7.2 (2.87–18.03) | <0.001 | 7.98 (3.21–19.85) | <0.001 | 11.03 (4.82–25.26) | <0.001 |
| Too small BMs | Lack | Reference | – | Reference | – | Reference | – |
| | Mild | 3.34 (1.14–9.82) | 0.03 | 3.12 (1.09–8.96) | 0.03 | 2.97 (1.11–7.94) | 0.03 |
| | Moderate/severe | 7.6 (3.37–17.16) | <0.001 | 6.22 (2.51–15.43) | <0.001 | 5.24 (2.17–12.63) | <0.001 |
| Painful BMs | Lack | Reference | – | Reference | – | Reference | – |
| | Mild | 3.86 (1.69–8.86) | 0.001 | 2.91 (1.13–7.48) | 0.03 | 2.09 (0.84–5.18) | 0.11 |
| | Moderate/severe | 3.86 (1.26–11.89) | 0.02 | 3.87 (1.11–13.48) | 0.03 | 3.28 (0.89–12.02) | 0.07 |

a Adjusted for age ≥65 and depression

b Adjusted for age ≥65, depression, calcium channel blockers, and diuretics

Abbreviations: PR, prevalence ratio; others, see TABLE 1

of glomerular hyperfiltration, low-grade inflammation, and kidney lipotoxicity),[26,27] obstructive sleep apnea (via both mechanical airway narrowing/collapse and disturbances of airway neuromuscular control),[28] and constipation (via multiple hormones, including excessive endocannabinoid activity and decrease in ghrelin secretion[29]).[16] Also, depression is not only associated with sleep disorders in both nondialysis and dialysis CKD patients[13,30] but is also closely associated with a higher prevalence of constipation in both patients with CKD and the general population.[30,31] Interestingly, while CKD impairs endogenous melatonin synthesis,[15] beneficial effects of melatonin were suggested in the treatment of both specific sleep disorders and IBS with predominant constipation.[32] Moreover, side effects of drugs can underlie the observed coexistence of sleep and gastrointestinal symptoms in patients with CKD. Benzodiazepines, even though they should be avoided in the long-term therapy of insomnia, are frequently used and can cause constipation.[33,34] In our study, calcium channel blockers and diuretics were associated with an increased prevalence of deteriorated sleep quality. It is in agreement with recent studies that have shown that both drug groups are associated with nocturia[35-37] and decreased gastrointestinal motility.[19,38-40] Recent reviews comprehensively analyzed possible pathogenic mechanisms of CKD-related constipation.[41,42]

In this pilot study, we estimated that the prevalence of deteriorated sleep quality in nondialysis CKD patients is higher among those with certain gastrointestinal symptoms (decreased frequency of defecation, functional constipation, abdominal discomfort or pain, too small BMs) even after adjustment for age, depression, and taking drugs.

To elucidate the cause-effect relationship in this complex network of associations, interventional studies (eg, obesity or depression treatment, laxative drugs, melatonin supplementation) recruiting nondialysis CKD patients are needed.

**Limitations** Limitations of this study include single-center, cross-sectional design, no a priori sample size calculation, and a relatively low number of participants. As a result, we have adjusted the estimated PR of deteriorated sleep quality for some, but not all, possible covariates because inclusion of additional covariates without increasing the number of study participants could result in unreliable, over-fitted models. Even though the MOS-Sleep-R is a validated questionnaire, it cannot be used to diagnose sleep disorders, thus we did not provide associations between gastrointestinal symptoms and specific sleep disorders in patients with CKD.

**Conclusions** In patients with nondialysis CKD, sleep disorders coexist with constipation-related symptoms. Further studies are needed to fully understand the nature of the observed associations.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

## ARTICLE INFORMATION

**ACKNOWLEDGMENTS** This work was supported by the Medical University of Gdańsk (ST 02–0004/07/122; to ADŚ; MN 01–0421/08/262; to JR; and ST-58; to JMW).

**CONTRIBUTION STATEMENT** JR conceived the concept of the study. JR, ZH, JMW, and ADŚ contributed to the design of the research. JR, ZH, EK, and AT were involved in data collection. JR analyzed the data. ADŚ and JMW coordinated the funding for the project. All authors edited and approved the final version of the manuscript.

**CONFLICT OF INTEREST** None declared.



**HOW TO CITE** Ruszkowski J, Heleniak Z, Król E, et al. Associations between symptoms of constipation and sleep quality in patients with nondialysis chronic kidney disease: a cross-sectional study. Pol Arch Intern Med. 2021; 131: 512-519. doi:10.20452/pamw.15974

## REFERENCES

1 Pavlova MK, Latreille V. Sleep disorders. Am J Med. 2019; 132: 292-299.

2 Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. PLoS One. 2016; 11: e0158765.

3 Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020; 395: 709-733.

4 KDIGO. Chapter 1: definition and classification of CKD. Kidney Int Suppl. 2013; 3: 19-62.

5 Soni RK, Weisbord SD, Unruh ML. Health-related quality of life outcomes in chronic kidney disease. Curr Opin Nephrol Hypertens. 2010; 19: 153-159.

6 Lin Z, Zhao C, Luo Q, et al. Prevalence of restless legs syndrome in chronic kidney disease: a systematic review and meta-analysis of observational studies. Ren Fail. 2016; 38: 1335-1346.

7 Tan LH, Chiang HY, Tsai CW, Kuo CC. Prevalence of insomnia and poor sleep in patients with chronic kidney disease: a systematic review. Kidney Int Rep. 2019; 4: S117.

8 Huang Z, Tang X, Zhang T, et al. Prevalence of sleep apnoea in non-dialysis chronic kidney disease patients: a systematic review and meta-analysis. Nephrology (Carlton). 2019; 24: 1041-1049.

9 Parajuli S, Tiwari R, Clark DF, et al. Sleep disorders: serious threats among kidney transplant recipients. Transplant Rev (Orlando). 2019; 33: 9-16.

10 Sabbatini M, Pisani A, Crispo A, et al. Sleep quality in patients with chronic renal failure: a 3-year longitudinal study. Sleep Med. 2008; 9: 240-246.

11 De Santo RM, Bilancio G, Santoro D, et al. A longitudinal study of sleep disorders in early-stage chronic kidney disease. J Ren Nutr. 2010; 20: S59-S63.

12 Agarwal R, Light RP. Sleep and activity in chronic kidney disease: a longitudinal study. Clin J Am Soc Nephrol. 2011; 6: 1258-1265.

13 Tu CY, Chou YH, Lin YH, Huang WL. Sleep and emotional disturbance in patients with non-dialysis chronic kidney disease. J Formos Med Assoc. 2019; 118: 986-994.

14 Han Y, Song X, Liu Y, et al. The effects of depression and age on sleep disturbances in patients with non-dialysis stage 3-5 chronic kidney disease: a single-center study. Int Urol Nephrol. 2020; 52: 739-748.

15 Koch BCP, Van Der Putten K, Van Someren EJW, et al. Impairment of endogenous melatonin rhythm is related to the degree of chronic kidney disease (CREAM study). Nephrol Dial Transplant. 2010; 25: 513-519.

16 Full KM, Jackson CL, Rebholz CM, et al. Obstructive sleep apnea, other sleep characteristics, and risk of CKD in the Atherosclerosis Risk in Communities sleep heart health study. J Am Soc Nephrol. 2020; 31: 1859-1869.

17 Bouchoucha M, Mary F, Bon C, et al. Sleep quality and functional gastrointestinal disorders. A psychological issue. J Dig Dis. 2018; 19: 84-92.

18 Wu S, Chen S, Zhao Y, et al. Association between excessive daytime sleepiness and functional gastrointestinal disorders: a population-based study in China. J Neurogastroenterol Motil. 2017; 23: 298-305.

19 Ruszkowski J, Heleniak Z, Król E, et al. Constipation and the quality of life in conservatively treated chronic kidney disease patients: a cross-sectional study. Int J Med Sci. 2020; 17: 2954-2963.

20 Yarlas AS, White MK, Smith K, Bjorner JB. The development and validation of a revised version of the Medical Outcomes Study Sleep Scale (MOS-SLEEP-R). Value Heal. 2012; 15: A11.

21 McKinney W. Data structures for statistical computing in Python. In: van der Walt S, Millman J, eds. Proceedings of the 9th Python in Science Conference. Austin: SciPy; 2010: 51-56.

22 Vallat R. Pingouin: statistics in Python. J Open Source Softw. 2018; 3: 1026.

23 Seabold S, Perktold J. Statsmodels: econometric and statistical modeling with Python. In: van der Walt S, Millman J, eds. Proceedings of the 9th Python in Science Conference. Austin: SciPy; 2010: 92-96.

24 Khoury V, Staniek V, Dubois D. PAC-SYM Patient-assessment of constipation symptoms: information booklet. 1st ed. Lyon, France: Mapi Research Trust; 2007.

25 Gallis JA, Turner EL. Relative measures of association for binary outcomes: challenges and recommendations for the global health researcher. Ann Glob Heal. 2019; 85: 137.

26 Rashidbeygi E, Safabakhsh M, Delshad Aghdam S, et al. Metabolic syndrome and its components are related to a higher risk for albuminuria and proteinuria: evidence from a meta-analysis on 10,603,067 subjects from 57 studies. Diabetes Metab Syndr. 2019; 13: 830-843.

27 Escasany E, Izquierdo-Lahuerta A, Medina-Gomez G. Underlying mechanisms of renal lipotoxicity in obesity. Nephron. 2019; 143: 28-32.

28 Schwartz AR, Patil SP, Laffan AM, et al. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. Proc Am Thorac Soc. 2008; 5: 185-192.

29 Miron I, Dumitrascu DL. Gastrointestinal motility disorders in obesity. Acta Endocrinol (Copenh). 2019; 15: 497-504.

30 Kao YY, Lee WC, Wang RH, Chen JB. Correlation of sociodemographic profiles with psychological problems among hospitalized patients receiving unplanned hemodialysis. Ren Fail. 2020; 42: 255-262.

31 Ballou S, Katon J, Singh P, et al. Chronic diarrhea and constipation are more common in depressed individuals. Clin Gastroenterol Hepatol. 2019; 17: 2696-2703.

32 Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol. 2018; 175: 3190-3199.

33 Lee JY, Farrell B, Holbrook AM. Deprescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines. Pol Arch Intern Med. 2019; 129: 839-845.

34 Shinfuku M, Kishimoto T, Uchida H, et al. Effectiveness and safety of long-term benzodiazepine use in anxiety disorders. Int Clin Psychopharmacol. 2019; 34: 211-221.

35 Cruz R, Garcia-Rosa M, Faria C. Nocturia: prevalence and associated factors in community-dwelling subjects – a population-based study. Rev Assoc Med Bras. 2020; 66: 830-837.

**36** Santiapillai J, Tadtayev S, Miles A, et al. Dihydropyridine calcium channel blockers and obstructive sleep apnea: two underrecognized causes of nocturia? Neurourol Urodyn. 2020; 39: 1612-1614.

**37** Hall SA, Chiu GR, Kaufman DW, et al. Commonly used antihypertensives and lower urinary tract symptoms: results from the Boston Area Community Health (BACH) Survey. BJU Int. 2012; 109: 1676-1684.

**38** Bassotti G, Calcara C, Annese V, et al. Nifedipine and verapamil inhibit the sigmoid colon myoelectric response to eating in healthy volunteers. Dis Colon Rectum. 1998; 41: 377-380.

**39** Devasahayam J, Pillai U, Uppaluri C. Acute severe intestinal obstruction secondary to amlodipine toxicity. QJM. 2012; 105: 467-469.

**40** Fosnes GS, Lydersen S, Farup PG. Constipation and diarrhoea - common adverse drug reactions? A cross sectional study in the general population. BMC Clin Pharmacol. 2011; 11: 2.

**41** Sumida K, Yamagata K, Kovesdy CP. Constipation in CKD. Kidney Int Rep. 2020; 5: 121-134.

**42** Ikee R, Yano K, Tsuru T. Constipation in chronic kidney disease: it is time to reconsider. Ren Replace Ther. 2019; 5: 51.