Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: Nigar Sekercioglu, Bryan Curtis, Sean Murphy & Brendan Barrett (2015) Sleep apnea in patients with chronic kidney disease: a single center experience, Renal Failure, 37:1, 83-87, DOI: 10.3109/0886022X.2014.962408

To link to this article: https://doi.org/10.3109/0886022X.2014.962408

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2015; 37(1): 83–87
 DOI: 10.3109/0886022X.2014.962408

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CLINICAL STUDY

Sleep apnea in patients with chronic kidney disease: a single center experience

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Abstract

Purpose: The primary objective of this cross-sectional study was to test factors associated with sleep apnea in patients with chronic kidney disease (CKD). The prevalence of sleep apnea was also assessed. *Methods*: We recruited patients with CKD Stage 3–5 who lived in the St. John's area from September 2012 to December 2012. The Berlin Questionnaire and Short Form 36 Quality of Life Health Survey Questions (SF-36) were administered to all participants. *Results*: We recruited 303 patients (41% female). A total of 157 (51.8%) patients had a high risk for sleep apnea. Higher body mass index and young age were correlated with sleep apnea. Physical component score of SF-36 (PCS) tested as a continuous variable indicated a significant association with the risk for sleep apnea (OR: 0.97, 95% CI: 0.94–0.99, $p = 0.03$). The association implies 3% change per one point increase in PCS. We categorized mental component score of SF-36 (MCS) into four quartiles, as the linearity assumption was violated. There was a 61% risk increase for poor sleep in those with an MCS score less than the 75th percentile, when compared to those above the 75th percentile (OR: 0.39, 95% CI: 0.21–0.71, $p = 0.002$). *Conclusions*: Sleep apnea is common in kidney patients. People who have low PCS and MCS scores are more prone to sleep apnea or vice versa. Our results also indicate that high BMI and young age are associated with sleep apnea.

Keywords

Berlin questionnaire, chronic kidney disease, quality of life, sleep apnea

History

Received 20 June 2014
Revised 10 August 2014
Accepted 28 August 2014
Published online 26 September 2014

Introduction

Chronic kidney disease (CKD) is a global public health problem that is expected to affect a great number of people in coming years.[1–3] Although the incidence and prevalence of CKD exhibit large variations between countries, ~8–16% of people are thought to be affected by CKD worldwide.[4] The condition can be irreversible and related to shorter life expectancy.[2] In addition to lower survival rates, quality of life was shown to be poor in dialysis patients when compared to the general population.[5] Measurement of physical functioning is recommended twice a year by validated tools.[6]

Sleep disordered breathing, also called sleep apnea, consists of a wide spectrum of diseases, from snoring to severe hypoxemia, that lead to consequent pathophysiological changes in different organ systems.[7] The disease is characterized by transient cessation of breathing during sleep and can be with or without a compromised respiratory drive.[7] A drop in airflow of at least 90% for at least 10 s is considered apnea.[7] Hypopnea is described as a drop in airflow of at least 50% for at least 10 s and with a minimal oxygen desaturation of 3%.[7] The severity of the disease is defined by an apnea/hypopnea index, which is calculated by the total events per sleep divided by the total sleep time in hours.[7] If the number of events is between 5 and 15 per hour, it is called mild; if the number exceeds 30 per hour, it is classified as severe sleep apnea.[7]

Sleep apnea is more common in patients with kidney dysfunction[8] and requires polysomnography to make a definitive diagnosis.[9] The condition has been associated with adverse health outcomes, including mortality.[10] Thus, it is important to diagnose and provide appropriate management in a timely manner.

Although not a substitute for the gold standard, questionnaires—widely available and accessible tools—are used before more detailed exams or diagnostic procedures are employed. The Berlin Questionnaire (BQ)[11] was validated for sleep apnea screening. The Short Form 36 Quality of Life Health Survey Questions (SF-36)[12] was also validated in CKD patients, and can be used for assessment of quality of life. The aforementioned tools do not pose any risk in their application and are easily applied. Therefore, their use has been reported in numerous studies world-wide.[13–17]

Sleep apnea is one of the most common causes for sleep disorders, and can be left unrecognized due to atypical presentation in kidney patients.[18] Although the determinants of the disease are well-defined in the general population, a lack of evidence supporting the correlates in CKD patients necessitates further investigations in that area. Furthermore,

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most of the data are from the dialysis population, and identifiers of poor sleep quality in non-dialysis CKD patients also require more research. The main objective of this study was to identify factors associated with sleep apnea in kidney patients. The point prevalence of sleep apnea was also studied.

Methods

This is a cross-sectional study of adult patients with Stage 3 through 5D and 5T CKD recruited between September 2012 and December 2012. Hemodialysis (HD) patients were recruited from the Health Sciences Centre, St. Clare's Mercy, and Waterford Hospitals' HD centers in St. John's, Newfoundland, Canada. Patients with CKD, with or without a transplant, were enrolled in the Waterford Hospital outpatient nephrology clinics. Peritoneal dialysis (PD) and home HD patients were also recruited from the Waterford Hospital outpatient clinics.

Kidney dysfunction was defined by an e-GFR calculated with the Modification of Diet in Renal Disease Study equation.[19] Inclusion criteria included (i) being an adult patient ($\geq$18 years), (ii) having some degree of kidney dysfunction with an eGFR cutoff of <60 L/min/1.73m^2 and (iii) living in the St. John's area.

Exclusion criteria included (i) severe vision and/or hearing problems that interfere with the informed consent process and (ii) choosing to decline research participation.

This study was approved by the provincial Health Research Ethics Authority and Research Proposal Approval Committee of Eastern Health. Each patient was approached by a member of the care team to obtain initial consent before being approached by the researcher. The informed consent was obtained for each participant. The instruments that were employed in this study were the SF-36 and BQ.[12,20]

Data included completed questionnaires, blood pressure measurements and anthropometric measurements (weight and height). Chart review was also performed for the parameters such as parathyroid hormone (PTH), calcium (Ca), phosphate (P), albumin, glucose, hemoglobin (Hb) and e-GFR. BMI was calculated with the following formula: weight (kg)/height^2 (m^2). Obesity was defined as BMI $\geq$30 kg/m^2.

The sitting pre-dialysis blood pressure was recorded for dialysis patients. Sitting blood pressure measurements before the doctor's visit were also recorded for ambulatory care patients. Blood pressure was measured with an automated machine by a registered nurse or licensed practical nurse after a 5-min rest.

Excluding PTH, the value closest in time to the interview within the window plus/minus 3 months was collected. Values within 6 months of the interview day were recorded for PTH. However, all values excluding PTH were within a 1-month period for dialysis and transplanted patients. Serum calcium level was corrected with the following formula: serum calcium (mmol/L) + $0.02 \times$ [40-patient's serum albumin (g/L)]. PTH, Ca and P have been associated with sleep quality in CKD patients.[21,22]

The BQ was used to assess the risk status for sleep apnea.[11] The instrument indicated high or low risk for sleep apnea. A license from Quality Metric was obtained for the administration of the SF-36.[12] The Quality Metric Health Outcomes™ Scoring Software 4.5 was also provided by Quality Metric. A 4-week recall form of the SF-36 version 2 was employed in this study. Eight health domains and two summary measures were calculated with the Scoring Software 4.5.

The analytical plan included descriptive and inferential statistics. Median and interquartile ranges were used for non-normally distributed data, while mean and standard deviation (SD) were used in the normally distributed data. Classical methods were used to make statistical inferences. Significance of individual coefficients was tested by the Wald statistic technique, and odds ratios (OR) with 95% confidence intervals (CI) were obtained in the logistic regression models. Two-sided tests were employed with a significance level of 0.05. All data analyses were performed using IBM SPSS Statistics 20, Release Version 20.0 (SPSS Inc., 2011, Chicago, IL; www.spss.com).

Univariate analysis was performed for all potential confounders, including age, gender, BMI, presence of diabetes mellitus and smoking. Hb, PTH, Ca, P, eGFR, systolic blood pressure (SBP), diastolic blood pressure (DBP), SF-36 domain scores and summary scales were also tested in the model. The significance level was 0.1 for retention in the multivariate models. Age, BMI, SBP, physical component score (PCS) and mental component score (MCS) scores reached a significant level of 0.1, and those covariates were included in the multivariate analysis. PCS scores were analyzed as a continuous variable, while MCS scores were categorized into four groups. Since the linearity assumption for logistic regression was violated, we categorized MCS scores. In the reduced model, age, BMI, PCS and MCS were included.

Results

A total of 303 patients (125 females, 178 males with mean age 62.7 ± 14.5 years) were included in this cross-sectional study (Tables 1 and 2). We included 202 patients with non-dialysis dependant CKD (86 females, 116 males, mean age 63.8 ± 14.4), including 18 patients with a kidney transplant. A total of 101 patients (39 females, 62 males, mean age 60.6 ± 14.4) were on dialysis; seven patients were on PD, two patients were on home HD and 92 patients received in-center HD treatments.

The BQ indicated high risk for sleep apnea in 157 (51.8%) patients in the study cohort. In the dialysis group, 56 (55%) participants were classified as high risk while in the CKD group, 101 (50%) patients indicated high-risk status for sleep apnea. The frequency was not significantly different between the groups ($p = 0.37$) (Table 1). There was a significant difference between those with high and low risk for sleep apnea in terms of age, BMI, PCS and MCS scores (Figures 1 and 2). Additionally, eGFR was not correlated with the prevalence of sleep apnea ($p > 0.05$).

Associations between sleep apnea and covariates were tested. Those with a high risk for sleep apnea were younger and had a higher BMI values ($p = 0.02$ for age and $p = 0.0001$ for BMI). High risk for sleep apnea was also associated with low PCS and MCS domain scores (Table 3).

Table 1. Baseline characteristics of the participants divided by dialysis status.

Variable	Study cohort (mean ± SD)	Dialysis group (mean ± SD)	Non-dialysis group (mean ± SD)	*p*-Value[a]
n	303	101	202	
Age (years)	62.7 ± 14.5	60.6 ± 14.4	63.8 ± 14.4	0.07
BMI (kg/m^2)	29.8 ± 6.5	29.4 ± 5.9	30 ± 6.7	0.43
Female gender, *n* (%)	125 (41.2)	86 (43)	39 (39)	0.50
Diabetes, *n* (%)	141 (46.7)	53 (52.5)	88 (43.8)	0.15
Smoking, *n* (%)	28 (9.2)	12 (11.8)	16 (7.9)	0.26
BQ	157 (51.8)	56 (55)	101 (50)	0.37

Notes: BMI: body mass index; BQ: Berlin questionnaire
[a]*p*-Value indicates comparison between the dialysis and non-dialysis groups.

Table 2. Summary of laboratory parameters.

Variable	Study cohort (mean ± SD)	Dialysis group (mean ± SD)	Non-dialysis group (mean ± SD)	*p*-Value[a]
e-GFR (mL/min/1.73 m^2)	21 (7–41)[b]	6.2 ± 2.6	36.6 ± 16.3	0.0001
Hb (g/L)	119 ± 22.3	107 ± 20	126 ± 20	0.0001[c]
Albumin (g/L)	34.7 ± 4.9	32 ± 5	35.9 ± 4.3	0.0001
PTH (pg/mL)	200 (99–475)[b]	635 ± 570	148 ± 118	0.0001[c]
Ca[d] (mmol/L)	2.2 ± 0.67	2.38 ± 0.18	2.11 ± 0.8	0.88[c]
P (mmol/L)	1.4 ± 0.4	1.8 ± 0.5	1.2 ± 0.3	0.0001[c]
Glucose (mmol/L)	6.1 (4.9–8.6)[b]	8.6 ± 7.5	7.1 ± 3.3	0.3[c]

Notes: Ca: calcium; e-GFR: estimated glomerular filtration rate; Hb: hemoglobin; PTH: parathyroid hormone; P: phosphate.
[a]*p*-Value indicates comparison between the dialysis and non-dialysis groups.
[b]Indicates median (interquartile range).
[c]Indicates Mann–Whitney U-test.
[d]Indicates corrected calcium.

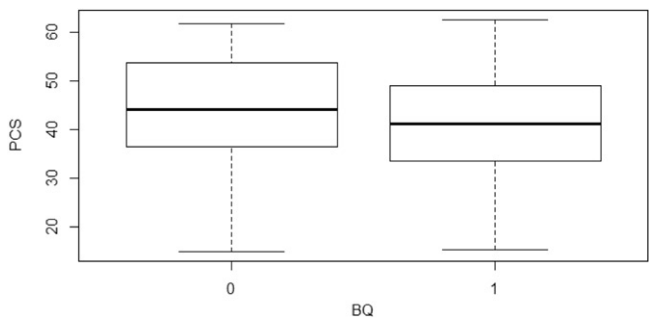

Figure 1. Box plot displaying PCS scores in patients with high and low risk for sleep apnea. Note: PCS, physical component summary.

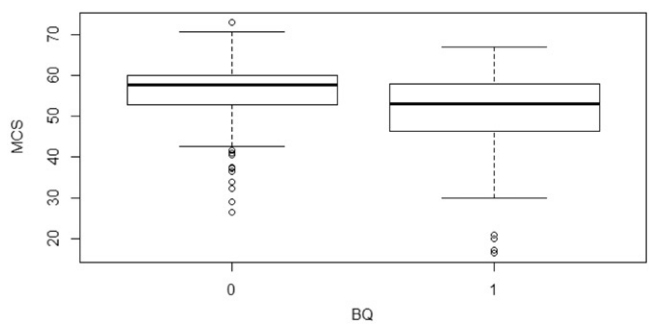

Figure 2. Box plot displaying MCS scores in patients with high and low risk for sleep apnea. Note: MCS, mental component summary.

To conclude, the results of the multivariate analyses indicated that lower age, higher BMI and lower PCS scores were associated with a higher risk for having sleep apnea (OR: 0.98, 95% CI: 0.96–1, $p = 0.05$ for age; OR: 1.08, 95% CI: 1.03–1.13, $p = 0.001$ for BMI; OR: 0.97, 95% CI: 0.94–0.99, $p = 0.03$ for PCS). Having high MCS scores was also tied to having a low risk for sleep apnea. In our study, we found that the MCS summary measure of SF-36 was correlated with risk for sleep apnea, and the most prominent effect was seen when comparisons were made between the highest percentile group and the lower percentiles (OR: 0.39, 95% CI: 0.21–0.71, $p = 0.002$) (Table 3). Consequently, worse self-reported mental health was associated with high risk for sleep apnea.

Discussion

This cross-sectional study included a total of 303 CKD patients from the St John's area. The summary of our findings are as follows: (i) the risk for sleep apnea did not differ between the dialysis and non-dialysis groups; (ii) PCS and MCS summary scales of SF-36 were lower in the dialysis group as compared to the non-dialysis group; (iii) patients with low MCS scores indicated a higher risk for sleep apnea; (iv) sleep apnea was associated with high BMI values and (v) young age and low PCS scores were also associated with sleep apnea.

Age was correlated with sleep apnea in our study cohort. Those who were at high risk for sleep apnea were significantly

Table 3. Summary of reduced models for sleep apnea.

Variable[a]	Exp (B)	95% CI	*p*-Value
Age (years)	0.98	0.96–1	0.04
BMI (kg/m^2)	1.06	1.03–1.13	0.001
PCS	0.97	0.94–0.99	0.02
MCS			0.0001
Category 1[b]	0.65	0.31–1.35	0.24
Category 2[c]	0.38	0.21–0.71	0.002
Category 3[d]	0.38	0.21–0.70	0.002

Notes: MCS, mental component summary; PCS, physical component summary.
[a]Logistic regression with enter method ($p = 0.05$) was performed to identify factors independently associated with sleep quality in the study cohort.
[b]Indicates comparison of <25% percentile with 25–50% percentile categories.
[c]Indicates comparison of 25–50% percentile with 50–75% percentile categories.
[d]Indicates comparison of 50–75% percentile with >75% percentile categories.

younger than the low-risk group. Previous reports found higher age to be a predictor for sleep apnea in the general population[23] and in the CKD population.[24–27] Our finding was different from others, and probably due to the differences in the study populations, assessment methods, and by chance alone. We included dialysis and non-dialysis patients, while others included HD patients. Additionally, one study employed polysomnography to diagnose sleep apnea in a small number of HD patients ($n = 26$).[26]

Our findings did not show any significant correlation between the prevalence of sleep apnea and eGFR. Similar results were indicated by Plantinga et al.,[28] in a large study cohort ($n = 9110$). Contrary to these findings, the CKD status was indicated as an independent predictor for sleep apnea, when compared to normal kidney functions (OR: 1.32, 95% CI: 1.13–1.55 for those with eGFR 15–29 mL/min/1.73 m^2).[29] The International Classification of Diseases (ICD-9) diagnosis codes for sleep apnea were used to identify the absence or presence of sleep apnea in this study.[29] The ICD-9 diagnosis codes include insomnia or hypersomnia with sleep apnea, and might include more major cases as compared to diagnosis of sleep apnea using the BQ. However, sleep apnea is prevalent in CKD patients.[30] A high-prevalence rate of sleep apnea was also consistent with our findings, but causality may not be inferred as this was a cross-sectional study.

We did not show a significant correlation between blood pressure parameters (SBP, DBP) and sleep apnea. Several previous reports using ambulatory blood pressure monitoring indicated that blood pressure and dipping status were associated with impaired sleep.[31–33] We only measured blood pressure on one occasion, which might make it difficult to identify any possible correlation between sleep and blood pressure.

Quality of life summary scales were also tested for an association with sleep apnea. In our study, we found that the MCS domain of SF-36 was correlated with sleep apnea, and the most prominent effect was seen when comparisons were made between the highest percentile group and the lower percentiles (OR: 0.39, 95% CI: 0.21–0.71, $p = 0.002$). We also found that the PCS and MCS scores were significantly lower in those with high risk for sleep apnea ($p = 0.05$ for PCS and $p = 0.0001$ for MCS). These findings were supported by previous studies. Guney et al.[34] indicated that PCS and MCS scores were inversely correlated with sleep quality (r: -0.41, r: -0.39, $p < 0.001$ for PCS and MCS scores, respectively).[34] The positive correlation between sleep and life quality indexes is an expected finding due to possible effects of sleep on physical and mental wellbeing. Reverse causality is also possible with those having physical or mental problems finding it harder to sleep undisturbed. Moreover, screening tools for both conditions have some overlap.

Sleep apnea has been associated with adverse short-term consequences, such as accidents, and long-term consequences, such as cardiovascular events.[35–37] As cardiovascular event rates are already high in CKD patients, a comprehensive approach to reducing the risk should be employed. Evidence suggests that continuous positive airway pressure (CPAP) treatment for sleep apnea reduces cardiovascular events and mortality.[38] Similarly, it was indicated that CPAP was associated with improved longevity and quality of life in kidney patients.[39] However, cost and patient acceptance may reduce the uptake of CPAP therapy.

This study has several strengths that need to be noted. Firstly, the sample size was large enough to accommodate patients with various levels of kidney dysfunction. As a result, comparisons were made between different levels of eGFR. Furthermore, blood pressure was measured using an automated device, which reduced the risk for measurement bias.

There are several limitations to this study. The common drawbacks of cross-sectional studies also apply to the present report. First of all, since it is a cross-sectional study, inference of causality is not possible. Therefore, we only tested associations of sleep apnea. Additionally, we had only seven cases on PD treatment, although the study included a large number of patients. Therefore, it was not possible to assess the difference between dialysis modalities, including home HD and PD. We also had 18 patients with a kidney transplant, limiting inferences for this subgroup. Additionally, we did not test the impact of dialysis modality on quality of life, since the sample size was small.

This study tested factors related to sleep apnea in CKD patients. Sleep apnea was not correlated with eGFR, blood pressure and presence of diabetes. Age, BMI, PCS and MCS scores were correlated with sleep apnea. The prevalence of sleep apnea was not higher in the group on dialysis than in those with less severe CKD.

The high-prevalence rates of sleep problems were similar to the findings of others. The findings suggest a need for more robust studies that assess the causality of these associations, as well as further work on underlying pathophysiological mechanisms. In the meantime, large-scale studies in CKD patients for predictors of sleep apnea might be recommended. Prospective cohort studies would be a reasonable choice to shed considerable light on predictors of the condition. Polysomnography needs to be employed to more firmly establish the diagnosis of sleep apnea.

Acknowledgements

We acknowledge with thanks that we received a license from the Quality Metric Incorporated to use SF-36 forms and Quality Metric Health Outcomes Scoring Software 4.5 for this study.

Declaration of interest

Authors declared that they have no conflict of interest.

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