Original Article

Glomerular filtration rate in patients with obstructive sleep apnea: the influence of cystatin-C-based estimations and comorbidity

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Background: Recent studies indicate that chronic kidney disease (CKD) is a comorbidity in patients with obstructive sleep apnea (OSA). We hypothesized that the use of the classical muscle-dependent, creatinine-based equation to estimate glomerular filtration rate (GFR) in patients with OSA may be inaccurate due to the extreme body mass index (BMI) of some patients. The aim of this study was to establish the role of cystatin-C-based estimation of GFR for the detection of CKD in patients with OSA and typical comorbidities.

Methods: Two hundred and forty consecutive patients with newly diagnosed OSA were enrolled into this cross-sectional study. In all patients estimated GFR (eGFR) was calculated with chronic kidney disease-epidemiology collaboration group (CKD-EPI) equations using creatinine and cystatin-C. All patients were examined for comorbidities.

Results: In obese patients with OSA significant differences between GFR estimations based on creatinine and cystatin were found: eGFR based on muscle-dependent creatinine measurement was significantly higher than the muscle-independent eGFR based on cystatin-C measurement.

Conclusions: GFR can be routinely screened for using creatinine-based estimations (eGFRcreat). In a selected group of patients with OSA with BMI over 30 kg/m^2 the addition of cystatin-C for assessment of eGFR is suggested.

Keywords: Comorbidity; cystatin-C; glomerular filtration rate (GFR); sleep apnea

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Introduction

Obstructive sleep apnea (OSA) is characterized by intermittent hypoxemia during sleep (1). Hypoxia is considered a potential initiator of the processes leading to progressive renal dysfunction (2). Many important comorbidities of OSA, such as hypertension and diabetes, have been identified so far (3,4), but the role of OSA in the development of chronic kidney disease (CKD) is still not clear. Recent studies indicate that CKD is a comorbidity in patients with OSA, although the results of research have not always been in agreement (5). Technical considerations regarding proper measurement or estimation of glomerular filtration rate (GFR) and the influence of comorbidities on the estimated GFR (eGFR) in patients with OSA are possible reasons for these diverse study results (6).

The Kidney Disease Improving Global Outcome Group (KDIGO) suggests the use of serum creatinine for initial

assessment of eGFR. The KDIGO also suggests performing additional tests, such as measurement of cystatin-C, for confirmatory kidney testing in circumstances in which eGFR based on serum creatinine is less accurate (7). According to the chronic kidney disease-epidemiology collaboration group (CKD-EPI) such specific circumstances are clinical scenarios when patients present with extreme size and extreme muscle mass (8). Both very high and very low muscle mass affect the generation of creatinine, which could affect the calculation of GFR (8). Patients with OSA often present with extreme body mass and size (9). Muscle mass does not necessary correspond directly with body mass index (BMI) in such patients (10), and in the majority of patients with OSA a shift from fat-free muscle mass to higher fat mass index is observed. All such factors added to the multiple comorbidities observed in patients with OSA can lead to clinical dilemmas as to whether to use creatinine- or cystatin-C-based equations when kidney disease is suspected. Almost all studies on assessment of CKD in OSA used classical creatinine-based equations (5,11-15). Only a few studies used cystatin-C for GFR assessment of CKD in patients with OSA (16-18).

We hypothesized that the use of the classical muscle-dependent, creatinine-based equation to estimate GFR in patients with OSA may be inaccurate due to the extreme BMI of some patients with OSA. Thus, we aimed to establish the role of cystatin-C-based eGFR in patients with OSA and typical comorbidities.

Methods

This cross-sectional study was performed in the National Institute of Tuberculosis and Lung Disease in Warsaw, at the Sleep Laboratory. During the 2-year study (2011–2012), 240 consecutive patients with newly diagnosed OSA were enrolled.

All patients were assessed according to the current guidelines of the American Academy of Sleep Medicine (AASM) and the Polish Society of Lung Disorders, and the diagnosis of OSA was based on fully attended nocturnal polysomnography (19). All study participants were carefully examined for comorbidities. A comorbidity is defined as a disease coexisting with the primary disease of interest, as suggested by Sin *et al.* (20). Diagnoses were made by a group of respiratory and internal medicine specialists and were established in accordance with current international guidelines. The list of diagnoses for each patient, including comorbidities, was recorded in an electronic database.

The diseases were counted and grouped into typical comorbidity groups as proposed by Charlson (21) and other authors investigating comorbidities in respiratory medicine (22-24).

The laboratory parameters analyzed in this study include serum creatinine, cystatin-C, albumin in urine and other typical biochemistry parameters used for routine comorbidity diagnostics. The eGFR was calculated with CKD-EPI equations (8) using creatinine and cystatin-C. For comorbidity assessment, all physicians were free to review patients' medical files and to order any additional tests including radiology. Values of eGFR <60 mL/min/1.73 m^2 were used as a threshold to separate individuals with altered eGFR (stage 3a or worse) from individuals with normal or mildly altered kidney function, following KDIGO guidelines (8).

The AASM scoring rules were applied to the polysomnography variables, which included the apnea-hypopnea index (AHI), the oxygen desaturation index (ODI), mean oxyhemoglobin saturation (mean SpO_2) and the lowest oxyhemoglobin saturation (lowest SpO_2) (25). Sleepiness was assessed using a patient-completed questionnaire—the Epworth Sleepiness Scale (ESS).

Statistical analysis

Variables are expressed as mean (SD) in the case of quantitative variables and as percentages and absolute numbers in the case of qualitative variables. A comparison of dichotomous variables was made using the χ^2 test. The Kolmogorov-Smirnov test was used to check the normality of variable distribution. Student's *t*-test was used to examine the difference between the means with normal distribution variables and the Mann-Whitney U test was used when the test of normality failed.

The Pearson or Spearman correlation coefficient was determined for selected laboratory and clinical findings and $eGFR_{cystat}$.

All results were considered to be statistically significant at $P<0.05$.

Logistic regression analyses, with eGFR <60 mL/min/1.73 m^2 as the dependent variable were calculated. A backward method was chosen in logistic regression models. Suspected predictors of CKD—age, gender, descriptive data, blood laboratory results, comorbidities and polysomnography variables (i.e., AHI, ODI, mean SpO_2 and lowest SpO_2)—were added to the model.

Statistics analyses were performed using MedCalc

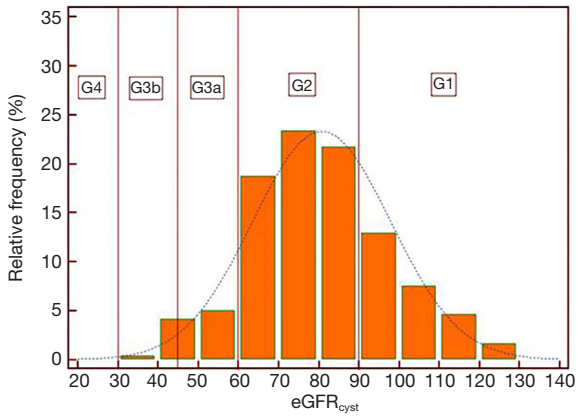

Figure 1 The relative frequency of estimated GFR measurement results when cystatin-C was used as a marker of the GFR ($eGFR_{cystat}$). Plot against normal distribution curve. Chronic kidney disease-epidemiology collaboration group (CKD-EPI) categories added. eGFR (mL/min/1.73 m^2). eGFR, estimated glomerular filtration rate.

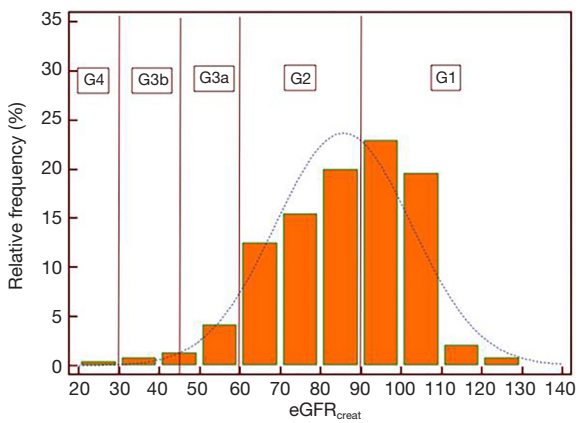

Figure 2 The relative frequency of estimated GFR measurement results when creatinine was used as a marker of GFR ($eGFR_{creat}$). Plot against normal distribution curve. Chronic kidney disease-epidemiology collaboration group (CKD-EPI) categories added. eGFR (mL/min/1.73 m^2). eGFR, estimated glomerular filtration rate.

software 16.2.1 (MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium).

Results

Two hundred and forty unselected consecutive patients with confirmed OSA were enrolled in the study: 185 men (77%) and 55 women (23%), with a mean age of 56.8 (SD, 9.9) years and a mean AHI of 38.7 (21.7) events/hour. The mean ESS score was 11.2 (5.7).

How prevalent was reduced eGFR in patients with OSA?

The total number of patients with reduced eGFR in the OSA group (defined as eGFR <60 mL/min/1.73 m^2) was 23/240 (9.6%) when the cystatin-C-based calculation ($eGFR_{cystat}$) was used and 16/240 (6.7%) when the creatinine-based calculation ($eGFR_{creat}$) was used. The difference was not statistically significant [odds ratio (OR), 1.48; 95% CI, 0.76–2.88, P=0.24].

All patients were grouped into categories of eGFR according to the CKD-EPI recommendations. The relative frequency/prevalence of CKD-EPI categories are shown for $eGFR_{cystat}$ and $eGFR_{creat}$ in *Figures 1,2*, respectively.

Anthropometrics, sleep and breathing characteristics and main blood biochemistry results in patients with OSA grouped according to $eGFR_{cystat}$ and $eGFR_{creat}$ are shown in *Tables 1,2*, respectively.

What influences eGFR in patients with OSA?

We observed a clear correlation between $eGFR_{cystat}$ and $eGFR_{creat}$ (R=0.521; 95% CI, 0.421–0.6068; P<0.0001).

A similar good correlation was observed in patients with eGFR <60 mL/min/1.73 m^2 (R=0.669; 95% CI, 0.3548–0.8476; P=0.0005). We tried to assess a link between sleep parameters, such as AHI, ODI, mean SpO_2 and lowest SpO_2, and eGFR but we did not find any correlations. Significant correlations were found between the $eGFR_{cyst}$ and pro-brain natriuretic peptide (proBNP) and the total cholesterol (*Table 3*).

In addition, a weak but statistically significant correlation was found between the ESS score and $eGFR_{cyst}$ (*Table 3*).

Cross-sectional analysis

We didn't find any significant differences between eGFR values among patients with OSA grouped by AHI according to AASM (*Table 4*).

To assess the influence of BMI on eGFR, we stratified the whole study population by World Health Organization (WHO) BMI categories as underweight, normal, overweight or obese, and compared $eGFR_{creat}$ with $eGFR_{cystat}$ in those subgroups.

There were no differences in eGFR in non-obese

Table 1 Patient characteristics in subgroups with a normal and a decreased eGFR based on serum creatinine

Characteristics	OSA $eGFR_{creat}$ ≥60	OSA $eGFR_{creat}$ <60	P value
Number (%)	224 (93.3)	16 (6.7)	<0.001
$eGFR_{creat}$ [mL/min/1.73 m^2]	88 [14]	49 [9]	<0.001
Age (years)	56.2 (9.8)	64.4 (9.7)	0.001
BMI (kg/m^2)	33.4 (5.8)	32.1 (6.3)	0.638
Male gender [No/total (%)]	173/224 [77]	12/16 [75]	0.85
ESS	12 [0–24]	7 [0–16]	0.003
AHI (events/h)	39.05 (21.8)	34.5 (20.8)	0.201
ODI (events/h)	44.7 (28.5)	40.9 (25.1)	0.615
Mean SpO_2 (%)	90.4 (5.4)	90.8 (4.2)	0.543
Lowest SpO_2 (%)	72.5 (13.9)	72.1 (13.6)	0.930
proBNP (ng/L)	183.6 (607.2)	917.1 (2,117.0)	0.011
Total cholesterol (mg/dL)	190.5 (41.0)	188.3 (48.3)	0.834
CRP (mg/L)	9.39 (10.3)	7.4 (4.1)	0.479
HBA_{1C} (%)	6.13 (1.3)	6.68 (1.7)	0.13
Tobacco smoking (pack-years)	9.8 (14.5)	3.12 (5.4)	0.068
Systemic hypertension (%)	76.8	68.7	0.413
Type 2 diabetes (%)	26.3	31.2	0.54
Chronic obstructive pulmonary disease (%)	11.2	12.5	0.87
Chronic heart failure (%)	7.2	25.0	0.013
CHD (%)	20.1	68.7	0.0001
Hyperuricemia (%)	15.6	18.8	0.735

Data expressed as mean (SD), median (min–max) or frequency depending on data type. eGFR, estimated glomerular filtration rate; OSA, obstructive sleep apnea; $eGFR_{creat}$, eGFR based on serum creatinine; BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO_2, oxyhemoglobin saturation; BNP, brain natriuretic peptide; CRP, C-reactive protein; CHD, coronary heart disease.

patients, irrespective of the type of measurement ($eGFR_{creat}$ or $eGFR_{cystat}$). But in obese and extremely obese patients significant differences between $eGFR_{creat}$ and $eGFR_{cystat}$ were found. In obese patients with OSA the muscle-dependent $eGFR_{creat}$ was significantly higher than the muscle-independent $eGFR_{cystat}$ (*Table 5*, *Figure 3*).

Logistic regression analysis

In logistic regression analyses, with $eGFR_{cystat}$ <60 mL/min/1.73 m^2 as the dependent variable, we found that only BMI, proBNP and coronary heart disease (CHD) were significant (BMI: OR, 1.1; 95% CI, 1.011–1.196; P=0.02; BNP: 1.06; 95% CI, 1.001–012; P=0.028; CHD: OR, 2.7; 95% CI, 0.96–8.04; P=0.05).

Discussion

The main finding of this study is that there is a significant difference between cystatin-C- and creatinine-based GFR estimations in obese patients with OSA. In our opinion, this observation may influence clinical practice since an increasing number of studies have confirmed CKD as a comorbidity of OSA. There is therefore likely sufficient scientific data to recommend kidney disease screening in patients with newly diagnosed OSA. The following question

Table 2 Patient characteristics in subgroups with a normal and a decreased eGFR based on serum cystatin-C

Characteristics	OSA $eGFR_{cystat}$ ≥60	OSA $eGFR_{cystat}$ <60	P value
Number (%)	217 (90.4)	23 (9.6)	<0.001
Age (years)	55.8 (9.6)	65.4 (8.2)	<0.001
$eGFR_{cystat}$ (mL/min/1.73 m^2)	84 [15]	51 [7]	<0.001
BMI (kg/m^2)	33.2 (5.8)	34.4 (6.2)	0.359
Male/female ratio (%)	78.5	65.2	–
ESS	11 [0–24]	8 [0–17]	0.013
AHI (events/h)	38.4 (21.4)	41.5 (24.5)	0.521
ODI (events/h)	43.9 (27.5)	49.4 (34.2)	0.372
Mean SpO_2 (%)	90.4 (5.5)	91.0 (3.6)	0.271
Lowest SpO_2 (%)	72.4 (13.9)	72.2 (13.0)	0.529
proBNP (ng/L)	162 (592.4)	942 (1,800.7)	0.002
Total cholesterol (mg/dL)	192.2 (41.7)	173.6 (35.4)	0.04
CRP (mg/L)	9.2 (10.9)	8.6 (5.2)	0.813
HBA_{1C} (%)	6.14 (1.3)	6.4 (1.4)	0.242
Tobacco smoking (pack-years)	9.73 (14.4)	6.1 (11.9)	0.251
Systemic hypertension (%)	75.1	87.0	0.2799
Type 2 diabetes (%)	24.4	47.5	0.0339
Chronic obstructive pulmonary disease (%)	11.1	13.0	0.816
Chronic heart failure (%)	7.2	21.0	0.0514
CHD (%)	20.7	47.0	0.0151
Hyperuricemia (%)	14.3	30.4	0.0852

Data expressed as mean (SD), median (min–max) or frequency depending on data type. eGFR, estimated glomerular filtration rate; OSA, obstructive sleep apnea; $eGFR_{creat}$, eGFR based on serum creatinine; BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO_2, oxyhemoglobin saturation; BNP, brain natriuretic peptide; CRP, C-reactive protein; CHD, coronary heart disease.

is important to discuss: is creatinine-based eGFR assessment sufficient for such screening? From a clinician's perspective, creatinine-based estimations have several advantages. Serum creatinine, which is traditionally used as a biomarker for renal function, is inexpensive and broadly used. However, it can be hugely affected by extra-renal factors, especially abnormally high body muscle mass or body size. According to KDIGO, in specific groups of patients, such as those with OSA, serum creatinine is occasionally underestimated or overestimated. Cystatin-C is a biomarker potentially less affected by muscle and that likely reflects renal function more sensitively than serum creatinine in very obese patients. As patients with OSA are characterized by a high BMI, patient mass depends mainly on fat mass. In such cases potential error linked to non-linearity or non-reliability of creatinine-based eGFR equations in individuals with extremely high BMI needs to be considered. In our study we have shown that the number of patients with OSA with suspected CKD was higher when the cystatin-C measurement was added (6.7% *vs.* 9.6%). In addition, we have shown that patients with OSA with a BMI over 30 kg/m^2 need to be assessed with the use of cystatin-C measurements, due to the possible underestimation of CKD with classical creatinine testing. In our group very obese patients showed lower mean $eGFR_{cystat}$ than $eGFR_{creat}$, confirming the non-reliability of CKD-EPI estimations in patients with extreme body mass, as suggested by CKD-

Table 3 Correlation between selected laboratory and clinical findings and eGFR based on cystatin-C

Parameters	P value	Correlation coefficient
proBNP	0.0053	–0.247
Total cholesterol	0.0438	0.13
Age	<0.0001	–0.526
Creatinine	<0.0001	–0.277
ESS	0.0121	0.162
Minimum SpO_2	0.833	0.014
ODI	0.9868	0.001
Mean SpO_2	0.9915	0.001
AHI	0.2004	0.083
BMI	0.352	0.06
Triglyceride	0.0516	0.126
CRP	0.5249	–0.047
HbA_{1C}	0.3261	–0.064
Smoking (pack-years)	0.129	0.098

eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ESS, Epworth Sleepiness Scale; SpO_2, oxyhemoglobin saturation; ODI, oxygen desaturation index; AHI, apnea-hypopnea index; BMI, body mass index; CRP, C-reactive protein.

EPI group experts. We have also tried to look at what type of comorbidities are important and could be used to guide clinicians thinking of adding cystatin-C measurements to the test panel for patients with OSA. In both correlation and regression tests we have found that patients with CHD are better suited to cystatin-C testing. In our study, we also found an increase in proBNP in patients with diminished eGFR and a correlation between $eGFR_{cystat}$ and proBNP. This finding may confirm recent data suggesting the role of cystatin-C as an emerging biomarker in cardiovascular diseases (26) or confirm the well-known data showing the role of kidney diseases in atherogenesis.

The discussion about screening for reduced eGFR in patients with OSA needs to also focus on the next question: how prevalent is reduced eGFR or CKD in patients with OSA, and is such coexistence of clinical importance?

OSA is frequently associated with other diseases. Hypertension, diabetes and obesity are typical examples of OSA comorbidities. CKD was suspected to be a comorbidity of OSA, but the pathophysiological and epidemiological interrelation between CKD and OSA is still unclear (1). Hanly *et al.* proposed that nocturnal hypoxemia may contribute to the pathogenesis of CKD and its progression to kidney failure. In addition, chronic intrarenal hypoxia may result in tubulointerstitial injury (1). Moreover, there

Table 4 eGFRs based on creatinine and cystatin-C in subgroups of patients with obstructive sleep apnea divided by AHI severity

Parameters	AHI <15 events/hour	AHI 15–30 events/hour	AHI >30 events/hour	P value for trend
$eGFR_{creat}$ (mL/min/1.73 m^2)	83 [15]	84 [18]	86 [16]	NS
$eGFR_{cystat}$ (mL/min/1.73 m^2)	80 [15]	79 [17]	81 [17]	NS

Data are mean [SD]. eGFR, estimated glomerular filtration rate; AHI, apnea-hypopnea index; $eGFR_{cystat}$, eGFR based on serum cystatin-C; $eGFR_{creat}$, eGFR based on serum creatinine.

Table 5 The mean results of GFR estimations using creatinine and cystatin-C in the whole study group stratified according the WHO BMI categories

Parameters	BMI <18.5 kg/m^2	BMI 18.5–25 kg/m^2	BMI 25–30 kg/m^2	BMI 30–40 kg/m^2	BMI >40 kg/m^2
$eGFR_{creat}$ (mL/min/1.73 m^2)	NA	81 [19]	83 [16]	86 [16]	88 [17]
$eGFR_{cystat}$ (mL/min/1.73 m^2)	NA	80 [16]	83 [18]	80 [17]	78 [17]
P value	NA	0.766	1.0	0.0195	0.0164

Data are mean [SD]. eGFR, estimated glomerular filtration rate; BMI, body mass index; $eGFR_{cystat}$, eGFR based on serum cystatin-C; $eGFR_{creat}$, eGFR based on serum creatinine.

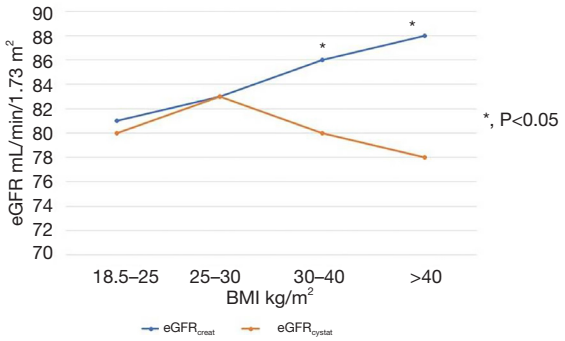

Figure 3 The mean results of GFR estimations using creatinine ($eGFR_{creat}$) and cystatin-C ($eGFR_{cystat}$) in the whole study group stratified according to the WHO BMI categories. GFR, glomerular filtration rate. BMI, body mass index; eGFR, estimated glomerular filtration rate.

are also data suggesting that chronic kidney hypoxia is a common final pathway in end-stage renal disease (2).

From a clinical point of view the relationships between CKD and OSA are of great interest due to potential epidemiological and clinical problems. The epidemiological relationships between OSA and CKD may be studied in different ways.

In our study, the prevalence of reduced GFR, defined as eGFR <60 mL/min/1.73 m^2, varied from 6.7% to 9.6% depending on the type of biomarker used. When traditional creatinine measurements were used for eGFR estimation, the prevalence of CKD was lower (6.7%), and when the newer cystatin-C measurement was used, it was higher (9.6%). Such a difference suggests that the use cystatin-C instead of creatinine may considerately influence the assessment of disease prevalence. Most other cohort OSA studies have used only one type of biomarker, most often creatinine, for CKD assessments. Marrone and collaborators gathered patients with OSA from a few European countries from the European Sleep Apnea Database (ESADA) group to study the prevalence of CKD. Similarly to our study, Marrone *et al.* used the same contemporary CKD-EPI equations. When creatinine was used as a biomarker the prevalence of CKD was found to be 6.1% (5). Across other cohort studies in patients with OSA a great variability in CKD prevalence can be seen. Reported numbers are hugely influenced by the methodology used. Kanbay *et al.* used the Cockcroft-Gault formula, and detected a significant GFR decrease when the severity of OSA increased (27). Chou *et al.* studied 40 patients referred for polysomnography to rule out sleep apnea and used a Modification of Diet in Renal Disease (MDRD) formula for GFR estimation. The prevalence of CKD in patients with OSA was 14% (12). Iseki *et al.* evaluated patients in a OSA syndrome registry of CKD, defined as an eGFR <60 mL/min/1.73 m^2, using MDRD and creatinine, and found a 30.5% CKD prevalence in patients with sleep apnea (14). Fleischmann *et al.* used the same MDRD equation and creatinine measurement for determination of eGFR in 158 consecutive patients with OSA. They found that 11.4% of patients with OSA had eGFR <60 mL/min/1.73 m^2 (13).

Very few OSA studies have used cystatin-C to determine CKD prevalence. Zhang *et al.* studied cystatin-C levels in patients with OSA, concluding that serum cystatin-C was associated with the severity of OSA in younger men (17). In a later study after introduction of continuous positive airway pressure (CPAP) treatment, the same authors concluded that CPAP can decrease cystatin-C levels among patients with severe OSA and may prevent latent renal impairment (28). Kato *et al.* studied 267 consecutive patients with OSA referred for polysomnography (29). The authors concluded that severe OSA independently increases serum cystatin-C levels in patients without CKD and that cystatin-C needs to be considered as a biomarker that reflects both clinically latent renal dysfunction and cardiovascular risk, which are influenced by OSA.

Our study has some limitations. First, our study is a single-center cross-sectional analysis. Second, the population we studied was not entirely comparable to the other populations. However, we studied consecutive and unselected patients, and therefore think that we studied a typical Polish population affected by OSA.

What's new?

In our study we discussed the role of creatinine- and cystatin-C-based estimations of eGFR in the assessment of eGFR in patients with OSA.

Conclusions

GFR in OSA can be routinely screened by using creatinine-based estimations ($eGFR_{creat}$). In a selected group of patients with OSA with BMI over 30 kg/m^2 the addition of cystatin-C for assessment of eGFR is suggested.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants and written participant consents were in accordance with the ethical standards of the institutional and/or national research committee; Committee of National Institute of Tuberculosis and Lung Diseases in Warsaw and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local Ethics Committee of the Institute of Tuberculosis and Lung Diseases (No. KB-57).

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