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Obstructive sleep apnea in non-dialyzed chronic kidney disease patients: Association with body adiposity and sarcopenia

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ABSTRACT

Objectives: Obstructive sleep apnea (OSA) is a risk factor for cardiovascular disease (CVD), the main cause of mortality in chronic kidney disease (CKD). Although the prevalence of OSA in patients with CKD has not been established, a few studies suggest that it is higher than in the general population, potentially increasing the risk for CVD. Obesity increases the risk, whereas sarcopenia has been suggested as a consequence of OSA in the general population. To our knowledge, these associations have not been adequately evaluated in patients with CKD. The aim of this study was to evaluate OSA frequency and its association with total and upper body adiposity and sarcopenia in non-dialyzed CKD patients.

Methods: This cross-sectional study included 73 patients with stages 3b–4 CKD (42 men, 62.9 ± 1.1 y of age). Glomerular filtration rate was estimated by the CKD-Epidemiology Collaboration equation. Patients were assessed for OSA by Watch-PAT200 (apnea-hypopnea index ≥5 events hourly; Itamar Medical), total body adiposity by dual-energy x-ray absorptiometry (DXA) and body mass index (BMI), upper body adiposity by anthropometric parameters and by trunk and visceral fat by DXA, and sarcopenia.

Results: OSA frequency was 67% (N = 49). Both total and upper body adiposity were associated with the presence and severity of OSA. In non-obese patients (BMI <30 kg/m^2), upper body obesity increased significantly the frequency of OSA. OSA association with sarcopenia was blunted when BMI was included in regression model.

Conclusions: Results from the present study suggest that in non-dialyzed CKD patients OSA is very common and associated with total and upper body obesity, but not with sarcopenia.

Introduction

Obstructive sleep apnea (OSA) is a breathing disorder characterized by narrowing of the upper airway that impairs normal ventilation during sleep [1]. OSA is considered a public health problem due to both its high prevalence, which has been estimated as 22% in men and 17% in women in the general population [2], as well as its association with increased morbidity and mortality in the short term (traffic- and job-related accidents) [3,4] and the long term (cardiovascular diseases [CVDs]) [5,6].

To our knowledge, few studies have evaluated the prevalence of OSA in patients with chronic kidney disease (CKD) [7–11]. Some of these studies included both dialyzed and non-dialyzed patients [7,8], whereas others included only non-dialyzed patients,

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presenting a wide range of estimated glomerular filtration rate (eGFR) [9–11]. Although at the present time there is no consensus regarding the prevalence of OSA in CKD, these few studies suggest that it is higher than in the general population, exceeding 50% in some studies, and increases as eGFR declines [7–9,11,12].

Evidence suggests that the relationship between OSA and CKD is not unidirectional; OSA may favor the development and progression of CKD, whereas CKD may predispose to the occurrence of OSA [13,14]. Patients with CKD have a high risk for CVD [15,16] and the presence of OSA has the potential to further increase this risk. Therefore, it is important to identify factors that may increase the risk for OSA in CKD, as well as the clinical, laboratory, and metabolic abnormalities associated with OSA in these patients.

Obesity increases the risk for OSA and the development and progression of CKD [17,18]. The relationship between body adiposity and OSA in patients with CKD has not been adequately studied to our knowledge. The few available studies showed an association between high values of body mass index (BMI) or neck circumference (NC) with OSA [7,8,12].

Sarcopenia, a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength [19], is common in patients with CKD, especially those in stage 5 [20,21] and is associated with a worse prognosis [22]. Limited evidences suggest that sleep disturbances may impair muscle metabolism, favoring the development of sarcopenia [23,24]. However, to our knowledge, no study has evaluated the effects of OSA on sarcopenia in patients with CKD.

The present study aimed to evaluate the presence of OSA and its association with total and upper body adiposity in non-dialyzed CKD patients. As a secondary objective, we investigated the relation of OSA with sarcopenia.

Methods

This cross-sectional study was conducted with non-dialyzed CKD patients under regular treatment for ≥6 mo at the interdisciplinary outpatient nephrology clinic at Pedro Ernesto University Hospital (Rio de Janeiro State University–Rio de Janeiro, Brazil). This study followed the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the local Committee on Ethics and Research. Participants were enrolled between November 2014 and July 2016. Written informed consent was obtained from all patients.

The inclusion criteria were men and women ages 45 to 80 y with a BMI ≥20 and ≤35 kg/m^2 who were presenting CKD stages 3b and 4. The exclusion criteria were use of immunosuppressive drugs; recent changes (previous 3 mo) in body weight (≥3 kg), dietary intake, or intensity or frequency of physical exercise; diagnoses of AIDS, cancer, heart failure, liver failure, chronic pulmonary disease, autoimmune diseases, acute illness, amputation, and mental disorders; pregnant or lactating women; and inability to walk 6 m.

Participants who met eligibility criteria and agreed to take part in the study were scheduled to arrive at the Laboratory of the Discipline of Clinical and Experimental Pathophysiology between 08:00 and 10:00 a.m. after a 12-h fasting period and abstinence from alcohol for 3 d. While fasting, they were subjected to nutritional and laboratory evaluation. In sequence, participants received the portable device (Watch-PAT200; Itamar Medical) and all necessary instruction, to conduct the home sleep study. On the following day, participants returned the Watch-PAT200 to the laboratory. Sleep study was conducted over only 1 night because evidence to support performance of recording more than a single night for home sleep apnea testing is insufficient thus far [1].

Sleep study

The diagnosis of OSA was made using the wrist-worn portable device Watch-PAT200. This device, approved by the Food and Drug Administration, allows accurate and clinically effective home diagnosis of OSA, with a highly significant correlation between the apnea-hypopnea index (AHI) obtained from polysomnography [25–27].

The Watch-PAT200 is a six-channel noninvasive device. The channels of the device are peripheral arterial tonometry (PAT), pulse oximetry, actigraphy, heart rate, body position, and snoring detection [26]. The PAT signal measures the finger arterial pulsatile volume changes that are regulated by α-adrenergic innervation of the smooth muscles of the finger vasculature, and thus reflects sympathetic nervous system activity. The rise in sympathetic activity accompanies the increase in heart rate and oxygen desaturation at the termination of a respiratory event. Thus, the Watch-PAT200 indirectly detects apnea and hypopnea events by identifying surges of sympathetic activation associated with the termination of such events [27,28].

After the sleep study, the recordings were automatically downloaded and analyzed offline by the zzzPAT software. The zzzPAT algorithm detects different parameters, such as AHI, respiratory disturbance index (RDI), oxygen desaturation index (ODI), and mean and minimum oxygen saturation. AHI refers to the number of apneas and hypopneas per hour of sleep, and RDI includes both the AHI and the respiratory effort-related arousal (RERA) index. RERA is an obstructive event that does not meet the criteria for apnea or hypopnea but causes arousal from sleep. ODI expresses the number of oxygen desaturation events per hour of sleep. A desaturation event is determined as a reduction ≥4% of the oxygen saturation baseline level. In the present study, the diagnosis of OSA was made when AHI was ≥5 events hourly and its severity classified according to AHI into mild (≥5 and <15 events/h), moderate (≥5 and ≤30 events/h) and severe (>30 events/h) [29].

Anthropometric assessment

Two experienced renal dietitians performed the anthropometric measurements. Height was measured using a stadiometer accurate to ±0.5 cm and weight was obtained with a digital scale, accurate to ±0.1 kg (Filizola S.A., São Paulo, Brazil), after participants wearing light clothes without shoes attempted to empty their bladder. BMI was calculated using the standard equation (kg/m^2). Nutritional status, according to BMI (kg/m^2), was classified as eutrophic (or normal range): 18.50 to 24.99; overweight: ≥25; and obese: ≥30 [30].

Waist circumference (WC) was measured in the standing position midway between the lowest rib and the iliac crest, at midexhalation. Hip circumference (HC) was measured at the widest point over the hip/buttocks area with the tape parallel to the floor [31]. NC was measured in the midway of the neck between mid-cervical spine and mid-anterior neck, if palpable, just below the laryngeal prominence [32]. Waist-to-hip ratio (WHR) was obtained by dividing the WC (cm) by HC (cm); waist-to-height ratio (WHtR) by dividing WC (cm) by height (cm); and neck-to-height ratio by dividing NC (cm) by height (cm).

Participants with BMI ≥30 kg/m^2 were classified as obese [30]. Upper body obesity was defined according to the following criteria:

- NC ≥38.5 cm in men and ≥34.5 cm in women [32];
- WC ≥90 cm in men and ≥80 cm in women [33];
- WHR >0.90 in men and >0.85 in women [31]; and
- WHtR >0.52 in men and >0.53 in women [34].

Dual energy x-ray absorptiometry

Dual energy x-ray absorptiometry (DXA) procedure was performed by a trained technician using a GE Medical Systems Lunar (Madison, WI, USA) with the patient in the supine position. The software calculated fat mass, lean tissue, and bone mineral mass. Fat-free mass was calculated as the sum of lean tissue plus bone mineral mass. Body composition was evaluated in total body and different sites, such as trunk. Obesity according to the percent total body fat was defined as total body fat ≥25% in men and ≥32% in women [35].

Muscle mass

Muscle mass was evaluated by the skeletal muscle mass index (SMI) obtained with DXA. This index was determined by the division of the appendicular skeletal muscle mass (ASM), estimated as the sum of muscle mass of the four limbs by height (m^2), as proposed by Baumgartner et al. [36] and recommended by the European Working Group on Sarcopenia in Older People [19]. Low muscle mass was defined as SMI <7.26 kg/m^2 in men and <5.5 kg/m^2 in women [19].

Muscle strength

Muscle strength was assessed by handgrip strength (HGS), which was measured using a handheld dynamometer (Baseline Smedley Spring Dynamometer–Fabrication Enerprises Inc., White Plains, NY, USA), according to the protocol recommended by the American Association of Hand Therapists [37]. Patients were first familiarized with the device and then were examined seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral and wrist between 0 and 30° of dorsiflexion. Patients were instructed to grip the dynamometer with the maximum strength in response to a voice command. Measurements were repeated at 1-min intervals and were obtained three times for each hand in a rotational way. The highest value of three measurements in each hand was considered for the study. Low muscle strength was diagnosed as an HGS <30 kg in men and <20 kg in women [19].

Physical performance

Physical performance was evaluated by usual gait speed (m/s). Participants were asked to stand stationary with their feet behind a starting line marked with tape, then, following the examiner's command of "Go!", to walk at their usual pace over a 6-m course and to stop just past the finish line. Timing was started with the first footfall and stopped when participant's first foot completely crossed the 6-m end line. The faster of two trials (in m/s) was used for the present analyses [38]. Low physical performance was defined as usual gait speed <1 m/s [19].

Sarcopenia diagnosis

The diagnosis of sarcopenia was based on the presence of low muscle mass associated with low muscle strength and/or low physical performance [19]. Sarcopenic obesity was defined as the simultaneous presence of sarcopenia and obesity (BMI ≥30 kg/m^2).

Laboratory parameters

Laboratory analyses were performed at the Central Laboratory and at the Laboratory of Endocrine Physiology of Pedro Ernesto University Hospital. Blood samples were analyzed to measure creatinine, urea, uric acid, calcium, phosphorus, sodium, potassium, total protein, and albumin. Uric acid concentration was assessed by using enzymatic colorimetric method; serum calcium by complexometry; total protein and albumin by colorimetric technique; sodium and potassium by selective electrode method; phosphorus by phosphomolybdate method; urea by kinetic method; and creatinine by kinetic method. Creatinine was calibrated to IDMS: COBAS 6000 (Roche/Hitachi). The eGFR was obtained using CKD-Epidemiology Collaboration (CKD-EPI) equation [39].

Statistical analysis

Sample size was determined based on the study conducted by Sakaguchi et al. [9], which observed that 65% of non-dialyzed CKD patients had OSA. Considering that the total number of CKD patients eligible for the study at the outpatient nephrology clinic at Pedro Ernesto University Hospital was 100 and assuming a 95% confidence interval (CI), the minimum sample size should be 70 patients.

Participants were stratified into two groups according to their AHI. Patients with values ≥5 events/h were allocated in the OSA group and those presenting values <5 events/h were allocated in the control group [29].

Categorical variables were expressed as percentage and compared by the χ^2 test. Mean values and SEs were used to summarize continuous variables with normal distribution, whereas median and interquartile intervals were used to summarize variables with non-normal distribution. The Shapiro–Wilk normality test was used to evaluate normality. The differences between groups were analyzed using either Student's *t* test or Mann–Whitney test, as appropriate.

Spearman's correlation was performed to determine the existence of a relationship between AHI and variables used to evaluate adiposity. Partial correlation controlled for different confounders were also used. Multiple logistic regressions was performed to assess the association of OSA with the presence of obesity, upper body obesity, low muscle mass, low muscle function, and sarcopenia.

All statistical analyses were performed using STATA 12.0 software (StataCorp LP, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

We interviewed 312 volunteers, of whom 79 met the eligibility criteria and agreed to participate. Seventy-three completed all the

Table 1
Demographic and clinical characteristics of study participants according to the diagnosis of obstructive sleep apnea in non-dialyzed chronic kidney disease patients

	Total group (N = 73)	Control group (n = 24)	OSA group (n = 49)	*P*-value*
Age (y)	62.88 ± 1.06	61.17 ± 1.82	63.71 ± 1.29	0.26
Sex n (%) men/women	42 (58)/31 (42)	13 (54)/11 (46)	29 (59)/20 (41)	0.68
Physical activity (n [%])	27 (37)	7 (29)	20 (41)	0.33
Smoking habit (n [%])	4 (5)	1 (4)	3 (6)	0.73
Alcohol intake (n [%])				
Never	56 (77)	18 (75)	38 (78)	0.83
≤1 × /wk	10 (14)	3 (12.5)	7 (14)	
>1 × /wk	7 (9)	3 (12.5)	4 (8)	
Usual dietary intake				
Energy (kcal/d)	1383 (1136–1644)	1296 (1054–1544)	1481 (1199–1696)	0.07
Protein (g/d)	63.99 ± 1.99	59.15 ± 2.67	66.60 ± 2.63	0.07
Carbohydrates (g/d)	208.13 ± 9.09	185.80 ± 11.53	220.21 ± 12.18	0.07
Lipids (g/d)	37.3 (30.7–46)	34.7 (29.3–40.2)	38.6 (31.8–48.3)	0.05
Chronic kidney disease stage (n [%])				
3b	27 (37)	9 (37.5)	18 (37)	0.95
4	46 (63)	15 (62.5)	31 (63)	
Laboratory parameters				
Glomerular filtration rate (mL/min/1.73 m^2)	27.1 (22.1–35.8)	24.7 (18.8–33.5)	28.3 (23.8–35.9)	0.11
Creatinine (mg/dL)	2.2 (1.7–2.6)	2.5 (1.9–2.8)	2.1 (1.7–2.6)	0.11
Urea (mg/dL)	69 (53–87)	76.5 (54.4–86.5)	69 (53–87)	0.75
Uric acid (mg/dL)	7.3 (6.6–8.6)	7 (5.7–7.5)	7.4 (6.6–8.9)	0.11
Total proteins (g/dL)	7.52 ± 0.08	7.43 ± 0.14	7.56 ± 0.09	0.47
Albumin (g/dL)	4.38 ± 0.05	4.35 ± 0.10	4.39 ± 0.06	0.74
Sodium (mEq/L)	140.24 ± 0.39	139.83 ± 0.56	140.45 ± 0.51	0.46
Potassium (mEq/L)	4.6 (4.2–5.1)	4.8 (4.2–5.3)	4.6 (4.1–5)	0.10
Calcium (mg/dL)	9.6 (9.4–9.8)	9.6 (9.3–9.8)	9.6 (9.4–9.8)	0.85
Phosphorus (mg/dL)	3.59 ± 0.09	3.60 ± 0.14	3.59 ± 0.11	0.96
Sleep study				
Rapid eye movement sleep (%)	21.25 ± 1.05	19.95 ± 1.69	21.87 ± 1.33	0.40
Respiratory disturbance index (events/h)	12.3 (7.2–20.5)	5.5 (3.6–8)	18.0 (12.3–24.4)	<0.0001
Apnea-hypopnea index (events/h)	8.8 (3.2–19.3)	2.4 (0.3–3.2)	14.2 (8.8–22.4)	<0.0001
Oxygen desaturation index (events/h)	3.9 (1.3–13.3)	0.65 (0.2–1.5)	8.4 (3.9–15.2)	<0.0001
Minimum O_2 saturation (%)	88 (84–91)	91 (89–92.5)	85 (78–88)	<0.0001
Maximum O_2 saturation (%)	98.74 ± 0.09	98.83 ± 0.19	98.69 ± 0.11	0.49
Mean O_2 saturation (%)	94.67 ± 0.31	95.54 ± 0.39	94.24 ± 0.26	0.006
O_2 saturation time <90% (min)	0.6 (0.0–5)	0 (0–0.25)	3 (0.3–10.7)	<0.0001
Number of O_2 desaturations >4%	19.0 (7.0–67)	3 (1–7.5)	47 (16–80)	<0.0001
Minimum heart rate (bpm)	46 (41–52)	46 (40–54)	46.5 (41–51)	0.85
Maximum heart rate (bpm)	92 (83–101)	93 (86.5–102.5)	90 (81–101)	0.63
Mean heart rate (bpm)	60 (55–66)	59.0 (53.5–68.5)	62 (56–66)	0.54

OSA, obstructive sleep apnea
Values as mean ± error deviation for normal distribution or as median (interquartile interval) for not normal distribution or absolute values (%)
* Control group vs OSA group.

evaluations and were included into the statistical analysis. The participants mean age was 62.9 ± 1.1 y and 58% (n = 42) were men. The median eGFR was 27.1 (22.1–35.8) mL/min/1.73 m^2 and the majority of patients (63%, n = 46) were in stage 4 of CKD. Overall, 67% were diagnosed as OSA, with mild OSA in 34%, moderate OSA in 23%, and severe OSA in 10%.

The main characteristics of the participants, according to the presence of OSA, are summarized in Table 1. No differences were observed between groups regarding demographic, laboratory, and lifestyle characteristics. However, as expected, the OSA group presented significantly higher values of RDI, AHI, ODI, oxygen saturation time <90% and number of oxygen desaturations >4%; and lower levels of minimum oxygen saturation than the control group. No significant differences between groups in relation to other parameters assessed during sleep study were observed (Table 1).

All parameters of total and upper body adiposity, assessed by anthropometry and DXA, were significantly higher in the OSA group than in the control group in the analyses including both sexes. In the analyses stratified by sex, the results were similar except for women regarding WHtR, total body fat, and trunk body

Table 2
Parameters of body adiposity according to the diagnosis of obstructive sleep apnea in non-dialyzed chronic kidney disease patients

	Total group (n = 73)	Control group (n = 24)	OSA group (n = 49)	*P*-value*
Anthropometry				
Body mass index (kg/m^2)	27.3 (23.5–30.4)	23 (21.1–26.9)	29.3 (25–31.3)	0.0001
Men	28.6 (24.1–31)	23 (21.5–26.9)	29.3 (27–31.8)	0.001
Women	26.1 (23–30.4)	23.1 (20.8–26.9)	28.5 (24.4–30.6)	0.03
Neck circumference (cm)	37.6 (34–41)	35 (33–37.8)	39 (36–42)	0.0005
Men	40.8 (38–43)	36.8 (35–39.5)	42(40–44)	0.0003
Women	34 (33–37)	33 (31–35)	35.1 (34–37)	0.03
Waist circumference (cm)	97.8 (84–104.5)	83 (77.8–95.8)	100 (95.5–106)	0.0001
Men	100 (93.5–106.8)	84.1 (81–98)	103 (98.7–109)	0.0002
Women	85.5 (81–101.5)	81.4(76–85.5)	93.75 (83.1–101.8)	0.04
Neck-to-height ratio	0.23 ± 0.002	0.22 ± 0.003	0.24 ± 0.002	0.0005
Men	0.24 ± 0.003	0.23 ± 0.006	0.24 ± 0.03	0.004
Women	0.22 ± 0.003	0.21 ± 0.005	0.23 ± 0.003	0.03
Waist-to-hip ratio	0.9 4 ± 0.01	0.87 ± 0.02	0.97 ± 0.01	0.0001
Men	0.98 ± 0.01	0.92 ± 0.03	1.00 ± 0.01	0.0008
Women	0.90 ± 0.02	0.85 ± 0.02	0.92 ± 0.02	0.02
Waist-to-height ratio	0.58 ± 0.01	0.53 ± 0.01	0.60 ± 0.01	0.0001
Men	0.58 ± 001	0.53 ± 0.02	0.60 ± 0.01	0.0004
Women	0.57 ± 0.01	0.54 ± 0.02	0.59 ± 0.02	0.05
Classification of nutritional status according to BMI (n, %):				
Eutrophic	28 (38)	16 (67)	12 (24)	<0.001
Men	13 (31)	9 (69)	4 (14)	<0.001
Women	15 (48)	7 (64)	8 (40)	0.19
Overweight	45 (61)	8 (33)	37 (76)	<0.001
Men	29 (69)	4 (31)	25 (86)	<0.001
Women	16 (52)	4 (36)	12 (60)	0.21
Obesity	24 (33)	2 (8)	22 (45)	0.002
Men	14 (33)	1 (8)	13 (45)	0.02
Women	10 (32)	1 (9)	9 (45)	0.04
Upper body obesity (n,%) according to:				
Neck circumference	43 (59)	8 (35)	35 (71)	0.002
Men	30 (71)	5 (38)	25 (86)	0.002
Women	13 (42)	3 (27)	10 (50)	0.22
Waist circumference	56 (77)	11 (46)	45 (92)	<0.001
Men	32 (76)	5 (38)	27 (93)	<0.001
Women	24 (77)	6 (55)	18 (90)	0.02
Waist-to-hip ratio	57 (78)	12 (50)	45 (92)	<0.001
Men	37 (88)	8 (62)	29 (100)	<0.001
Women	20 (65)	4 (36)	16 (80)	0.02
Waist-to-height ratio	58 (79)	12 (50)	46 (94)	<0.001
Men	37 (88)	8 (62)	29 (100)	<0.001
Women	21 (68)	4 (36)	17 (85)	0.006
Dual energy x-ray absorptiometry				
Total body fat (kg)	24.81 ± 0.98	19.64 ± 1.40	27.17 ± 1.13	0.0002
Men	24.81 ± 1.34	18.10 ± 1.74	27.45 ± 1.47	0.0009
Women	24.80 ± 1.46	21.34 ± 2.20	26.73 ± 1.80	0.07
Trunk body fat (kg)	14.23 ± 0.69	10.42 ± 1.01	15.97 ± 0.76	0.0001
Men	15.05 ± 0.93	10.26 ± 1.35	16.93 ± 0.98	0.0006
Women	13.09 ± 0.99	10.60 ± 1.59	14.48 ± 1.18	0.06
Visceral fat (kg)	1.26 (0.62–2.23)	0.58 (0.38–1.08)	1.67 (0.91–2.33)	0.0007
Men	1.81 (1.08–2.50)	0.69 (0.38–1.80)	2.08 (1.66–2.64)	0.008
Women	0.82 (0.41–1.13)	0.46 (0.26–0.81)	0.91 (0.62–1.28)	0.04
Obesity (n [%]) according to:				
Total body fat	57 (85)	15 (71)	42 (91)	0.03
Men	34 (87)	7 (64)	27 (96)	0.006
Women	23 (82)	8 (80)	15 (83)	0.83

OSA, obstructive sleep apnea
Values as mean ± error deviation for normal distribution or as median (interquartile interval) for not normal distribution or absolute values (%)
* Control group vs OSA group.

Table 3
Correlations between apnea-hypopnea index and parameters of adiposity in non-dialyzed chronic kidney disease patients

	Correlation		Partial correlation*	
	r	*P*-value	*r*	*P*-value
Anthropometry				
Body mass index (kg/m^2)	0.40	0.0007	0.46	0.0001
Neck circumference (cm)	0.39	0.001	0.49	<0.0001
Waist circumference (cm)	0.41	0.0005	0.45	0.0002
Neck-to-height ratio	0.38	0.001	0.39	0.001
Waist-to-hip ratio	0.36	0.002	0.36	0.003
Waist-to-height ratio	0.36	0.002	0.37	0.002
Dual energy x-ray absorptiometry				
Total body fat (kg)	0.27	0.03	0.34	0.007
Trunk body fat (kg)	0.29	0.02	0.33	0.009
Visceral fat (kg)	0.42	0.0006	0.42	0.0008

* Adjusted for age, sex, and glomerular filtration rate.

fat, which presented a tendency to be higher in OSA group. It is worth mentioning that this finding may be attributed to the lower number of women than men (31 versus 42) in the study. The frequency of total and upper body obesity was higher in the OSA group (Table 2).

The AHI was directly and significantly correlated with all parameters of adiposity even after adjusting for confounding factors (sex, age, and eGFR; Table 3). Participants presenting obesity (according to BMI and percent total body fat) and upper body obesity (according to NC, WC, WHR, and WHtR) showed higher odds ratio (OR) for OSA, even after controlling for sex, age, and eGFR (Table 4). Non-obese patients, according to BMI, who presented upper body obesity according to NC, WC, WHR, and WHtR, showed a significantly higher frequency of OSA (Table 5).

The occurrence of patients presenting both low muscle mass and sarcopenia were significantly lower in OSA group. In a fully adjusted model, including BMI as a covariate, this association was no longer significant (Table 6). Sarcopenic obesity was not observed in the present study.

Discussion

In the present study, a high OSA frequency (67%) was observed, in agreement with the few studies conducted in non-dialyzed CKD patients ranging from 54% to 96% [8,9,12], but was higher than in the general population [40,41].

Although previous studies suggest that the presence or severity of OSA is associated with the stage of CKD [11,42], in the present study AHI was similar in CKD stages 3b and 4 and no significant association between AHI and eGFR was found (data not shown). The lack of association between eGFR and OSA may be explained by the fact that only patients in a narrow range of eGFR (15–45 mL/min/1.73 m^2) who were clinically stable and under regular treatment in an interdisciplinary outpatient clinic for ≥6 mo were included in this study.

We found that total and upper body adiposity was associated with the presence and severity of OSA. All parameters of total and upper body adiposity evaluated, including those obtained with DXA, were significantly higher in OSA group than in the control group and were positively and significantly correlated with AHI. Moreover, the presence of total and upper body obesity was associated with an increased frequency of OSA even after adjustment for confounders. These findings are in agreement with studies conducted in the general population [43–45] and suggest that high body adiposity (total or upper body), whether evaluated by anthropometric measures or by DXA, is a risk factor for OSA in non-dialyzed CKD patients. Therefore, anthropometric measures provide an inexpensive and easy-to-obtain way to estimate the risk for OSA in non-dialyzed CKD. We also can hypothesize that weight loss may decrease the risk for OSA in these patients, as already demonstrated in the general population in different studies including randomized clinical trials [46–48].

The frequency of OSA in the study participants classified as obese according to BMI was extremely high (92%) taking into account that we included only individuals with BMI ≤35 kg/m^2, that is, only grade 1 obesity. This frequency is higher than that observed in obese individuals of the general population presenting

Table 4
Odds ratio (95% CI) for obstructive sleep apnea according to the presence of excessive total body adiposity and upper body obesity in in non-dialyzed chronic kidney disease patients

	Cases (n) OSA (%)	Univariate analysis		Multivariate analysis*	
		Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Obesity (body mass index ≥30 kg/m^2)					
No (n = 49)	27 (55)	1.00	–	1.00	–
Yes (n = 24)	22 (92)	8.96 (1.90–42.36)	0.006	12.40 (2.45–62.78)	0.002
Overweight (body mass index ≥ 25 kg/m^2)					
No (n = 28)	12 (43)	1.00	–	1.00	–
Yes (n = 45)	37 (76)	6.17 (2.11–17.97)	0.001	11.13 (2.97–41.72)	<0.001
Obesity (total body fat ≥25% in men and ≥32% in women)					
No (n = 11)	5 (45)	1.00	–	1.00	–
Yes (n = 62)	46 (74)	4.20 (1.04–16.96)	0.04	4.75 (1.11–20.34)	0.04
Upper body obesity (neck circumference ≥38.5 cm in men and ≥34.5 cm in women)					
No (n = 30)	14 (47)	1.00	–	1.00	–
Yes (n = 43)	35 (81)	2.68 (1.75–14.30)	0.003	8.58 (2.37–31.10)	0.001
Upper body obesity (waist circumference ≥90 cm in men and ≥80 cm in women)					
No (n = 17)	4 (24)	1.00	–	1.00	–
Yes (n = 56)	45 (80)	13.30 (3.62–48.79)	<0.001	15.76 (2.87–64.21)	<0.001
Upper body obesity (waist-to-hip ratio >0.90 in men and >0.85 in women)					
No (n = 16)	4 (25)	1.00	–	1.00	–
Yes (n = 57)	45 (79)	11.25 (3.07–41.21)	<0.001	12.74 (2.91–55.75)	<0.001
Upper body obesity (waist-to-height ratio >0.52 in men and >0.53 in women)					
No (n = 15)	3 (20)	1.00	–	1.00	–
Yes (n = 58)	46 (79)	15.33 (3.72–63.16)	<0.001	9.53 (4.10–93.05)	0.001

OSA = obstructive sleep apnea
* Adjusted for age, sex and glomerular filtration rate.

Table 5
Frequency of obstructive sleep apnea according to the presence of upper body obesity and of total body obesity in non-dialyzed chronic kidney disease patients

	Non-obese individuals (BMI <30 kg/m^2) (n = 49)			Obese individuals (BMI ≥30 kg/m^2) (n = 24)		
	Upper body obesity according to neck circumference			Upper body obesity according to neck circumference		
	No (n = 28)	Yes (n = 21)	*P*-value*	No (n = 2)	Yes (n = 22)	*P*-value
OSA (n [%])	12 (43)	15 (71)	0.04	2 (100)	20 (91)	0.66
	Upper body obesity according to waist circumference			Upper body obesity according to waist circumference		
	No (n = 17)	Yes (n = 32)	*P*-value	No (n = 0)	Yes (n = 24)	*P*-value
OSA (n [%])	4 (24)	23 (72)	0.001	–	22 (91)	–
	Upper body obesity according to waist-to-hip ratio			Upper body obesity according to waist-to-hip ratio		
	No (n = 15)	Yes (n = 34)	*P*-value	No (n = 1)	Yes (n = 23)	*P*-value
OSA (n, [%])	3 (20)	24 (71)	0.001	1 (100)	21 (91)	0.76
	Upper body obesity according to waist-to-height ratio			Upper body obesity according to waist-to-height ratio		
	No (n = 15)	Yes (n = 34)	*P*-value	No (n = 0)	Yes (n = 24)	*P*-value
OSA (n %)	3 (20)	24 (71)	0.001	–	22 (92)	–

BMI, body mass index; OSA, obstructive sleep apnea;
* Upper body obesity (–) group vs upper body obesity (+) group.

BMI ≥30 and <40 kg/m^2 (62%) [49], ≥32 kg/m^2 (82%) [50], and >40 kg/m^2 (85.7%) [51]. We also observed a high frequency of OSA in overweight individuals (BMI ≥25 kg/m^2) affecting 76%, which suggests that these patients also present an increased risk for OSA.

In the present study, the correlation analyses between AHI and parameters of adiposity revealed that the highest adjusted correlation coefficient was obtained for upper body obesity according to NC. Similarly, in the logistic regression analyses, upper body obesity according to WC presented the higher adjusted OR for the presence of OSA.

To our knowledge, only three studies have evaluated the relationship between adiposity and OSA in non-dialyzed CKD patients. In two of these studies, BMI and NC were the body adiposity parameters used [7,8], and one study used solely BMI [12]. All of the studies reported a significant association between high BMI, NC, or both with OSA. In agreement with the present study, Huang et al. [8] observed a higher correlation coefficient of AHI with NC ($r = 0.67$, $P = 0.001$) than with BMI ($r = 0.48$, $P = 0.01$) in non-dialyzed CKD patients. Whereas Nicholl et al. [7] found a higher multivariate OR (95% CI) for OSA with NC (OR, 1.18; 95% CI, 1.05–1.32; $P = 0.04$) than with BMI (OR, 1.09; 95% CI, 1.02–1.16; $P = 0.08$).

Another interesting finding of the present study was that in those individuals not classified as obese according to BMI, the presence of upper body obesity, according to NC, WC, WHR, and WHtR increased significantly the frequency of OSA, suggesting that even in non-obese individuals, the evaluation of anthropometric parameters of upper body adiposity may help to identify those with increased risk for OSA.

To our knowledge, this is the first study that evaluated the association between OSA and WC, WHR, and WHtR in non-dialyzed CKD individuals. We observed that these upper body obesity parameters, which are more frequently evaluated in clinical practice than NC, also presented a good association with the presence and severity of OSA and may be used in the identification of patients at high risk for OSA. The mechanisms responsible for the development of OSA in obese individuals include narrowing of the cross-sectional area of the upper airway as fat is deposited in surrounding structures, decreased lung volume, and disturbances of respiratory control [18,52].

Among all participants, the frequency of sarcopenia was 13%, similar to that observed in previous studies in nondialytic CKD patients [53,54]. OSA was associated with lower frequency of low muscle mass and sarcopenia in unadjusted and adjusted analyses by age, sex, and eGFR. However, this association was blunted when BMI was included in regression model. This finding could be explained by the higher frequency of excess body adiposity in OSA group. Evidence indicates that individuals with excess body adiposity have higher lean mass [55,56], which can reduce the risk for muscle mass depletion and, consequently, the risk for sarcopenia. Data from the present study are in line with this hypothesis, as no obese patient (BMI ≥30 kg/m^2) presented sarcopenia; there was a positive and significant correlation of SMI with BMI ($r = 0.74$, $P < 0.001$) and NC ($r = 0.75$, $P < 0.001$); in non-obese patients according to BMI, the frequency of sarcopenia was similar in OSA and control group ($P = 0.13$); and participants presenting sarcopenia compared with those without sarcopenia presented significantly lower values of BMI and NC (data not shown).

The strength of this study pertains to the evaluation of total and upper body adiposity by anthropometric measures as well as the gold standard DXA. This approach shows for the first time, the relationship between OSA and adiposity in a non-dialyzed CKD population. It is also, to our knowledge, the first study to evaluate the relationship of OSA with muscle mass, muscle strength, physical

Table 6
Odds ratio (95% CI) for low muscle mass, low muscle function and sarcopenia according to the presence of OSA in non-dialyzed chronic kidney disease patients

	Control group (n = 24) Odds ratio	OSA group (n = 49) Odds ratio (95% CI)	*P*-value
Low muscle mass			
Cases, n (%)	6 (27)	3 (7)	
Model 1	1.00	0.19 (0.41–0.83)	0.03
Model 2	1.00	0.11 (0.02–0.58)	0.01
Model 3	1.00	0.52 (0.05–5.07)	0.58
Low muscle strength			
Cases, n (%)	13 (62)	23 (50)	
Model 1	1.00	0.62 (0.21–1.76)	0.37
Model 2	1.00	0.49 (0.15–1.57)	0.23
Model 3	1.00	0.60 (0.16–2.26)	0.45
Low physical performance			
Cases, n (%)	9 (43)	27 (63)	
Model 1*	1.00	2.25 (0.78–6.51)	0.14
Model 2†	1.00	2.40 (0.77–7.53)	0.13
Model 3‡	1.00	2.13 (0.57–7.91)	0.26
Sarcopenia			
Cases, n (%)	6 (27)	3 (7)	
Model 1*	1.00	0.19 (0.04–0.83)	0.03
Model 2†	1.00	0.11 (0.02–0.58)	0.01
Model 3‡	1.00	0.52 (0.05–5.07)	0.58

OSA, obstructive sleep apnea.
* Univariate analysis
† Adjusted for age, sex and glomerular filtration rate
‡ Model 3: adjusted for age, sex, glomerular filtration rate and body mass index

performance, and sarcopenia in CKD patients. In addition, sarcopenia was defined based on muscle mass assessment as well as by evaluating its function. The main limitation of the present study was its cross-sectional nature, implying that causality was not likely to be determined.

One important contribution of this study is the finding that simple anthropometric measures are able to identify non-dialyzed CKD patients at higher risk for OSA. It can thus be used instead of screening questionnaires, which, notwithstanding their applicability in the general population, do not accurately identify patients at high risk for OSA or rule out its presence in CKD patients [57,58]. Another important contribution, is that the use of BMI as the sole indicator of adiposity in non-dialyzed CKD patients may not be adequate for OSA screening as patients classified as non-obese according BMI had a higher risk for OSA in the presence of upper body obesity.

Conclusion

This study suggests that in non-dialyzed CKD patients, OSA is very common and its frequency is higher not only in obese but also in overweight individuals. Simple anthropometric measures of upper body adiposity may help to identify non-obese patients with increased risk for OSA. Muscle mass, muscle function, and sarcopenia do not appear to be associated with OSA in non-dialyzed CKD patients.

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