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Original Article

Impact of CPAP treatment on leptin and adiponectin in adults with coronary artery disease and nonsleepy obstructive sleep apnoea in the RICCADSA trial

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ABSTRACT

Background: Increased leptin and decreased adiponectin levels are reported in coronary artery disease (CAD) as well as in obstructive sleep apnoea (OSA). Less is known regarding the impact of continuous positive airway pressure (CPAP) on these biomarkers. We aimed to determine variables associated with leptin and adiponectin in adults with CAD and nonsleepy OSA, and evaluate the effect of CPAP adjusted for confounding factors.

Methods: This was one of the secondary outcomes of the RICCADSA trial, conducted in Sweden between 2005 and 2013. From 244 revascularized CAD and OSA patients (apnoea–hypopnoea index >15/h) without excessive daytime sleepiness (Epworth Sleepiness Scale score <10), 196 with blood samples at baseline, after 3, and 12 months were included in the randomized controlled trial arm; of those, 98 were allocated to auto-titrating CPAP, and 98 to no-CPAP.

Results: No significant changes in leptin and adiponectin levels were observed during follow-up, whereas Body-Mass-Index and waist circumference increased in both CPAP and no-CPAP groups with no significant between-group differences. Alterations in plasma leptin were determined by changes in waist circumference (beta coefficient 2.47; 95% confidence interval 0.77–4.40), whereas none of the analyzed parameters was predictive for changes in adiponectin levels. No association was found with CPAP adherence.

Conclusions: CPAP had no significant effect on leptin and adiponectin in this cohort of nonsleepy OSA patients. An increase in waist circumference predicted an increase in plasma levels of leptin after 12 months, suggesting that lifestyle modifications should be given priority in adults with CAD and OSA regardless of CPAP treatment.

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1. Introduction

Obstructive sleep apnoea (OSA) is a disorder that is associated with a partial or complete collapse of the upper airways during sleep, resulting in intermittent hypoxia, fragmented sleep, and increased sympathetic nervous system activity [1]. Obesity is one of the main risk factors related to OSA [2]. In this context, leptin and adiponectin, which are biologically active adipokines secreted by adipose tissue [3], may play an essential role in the pathophysiological mechanisms for the development of OSA as well as its cardiometabolic complications. Leptin controls body weight and energy consumption; it also promotes oxidative distress, inflammation, and vascular hypertrophy [4]. In addition, leptin regulates ventilation through the carotid body chemoreflex mechanism. Chronic intermittent hypoxemia has shown to induce leptin

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signaling in the carotid body [5]. Increased leptin levels may induce platelet aggregation, increase blood pressure, arterial thrombosis, and atherosclerosis [6,7]. Increased levels of leptin may also predict major adverse cardiac events in patients with coronary artery disease (CAD) [8].

An association between increased leptin levels and OSA has been studied previously, and most of the studies have been conducted on subjects recruited from sleep clinic cohorts [9–16]. The majority of these studies have suggested a significant bidirectional relationship [9–14], whereas some showed no association [15,16]. Continuous positive airway pressure (CPAP) is the first-line treatment of symptomatic OSA patients, and studies examining the results of the impact of CPAP on plasma leptin levels have been contradictory [7]. It has also been suggested that adults with OSA are predisposed to weight gain [17] and reduced basal metabolic rate; a positive energy balance following CPAP treatment was suggested as one of the mechanisms involved in weight gain and increased leptin levels [18].

Adiponectin is involved in several physiological processes, among which are anti-inflammatory effects [19]. A meta-analysis of 11 studies, involving 240 patients, showed no change of adiponectin levels before and after CPAP treatment in OSA patients [3]. The role of adiponectin in CAD has also been investigated; a recent study indicated that adiponectin and its genetic variants might have an impact, particularly in myocardial infarction at a young age [20].

The Randomized Intervention with CPAP in CAD and OSA (RICCADSA) trial was designed to address the impact of CPAP on the composite of repeat revascularization, myocardial infarction, stroke, and cardiovascular mortality in patients with CAD and nonsleepy OSA [21]. The current study evaluated the effect of CPAP on circulating leptin and adiponectin levels in the same cohort as one of the secondary outcomes of the RICCADSA trial.

2. Methods

2.1. Study design and participants

The RICCADSA cohort has been described in detail previously [22]. In brief, CAD patients who underwent percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) within six months before recruitment in the Skaraborg County of West Götaland, Sweden, were requested to participate in this randomized controlled trial (RCT). The patients were recruited between 2005 and 2010, and the follow-up for the primary outcomes was completed in May 2013 [22]. As shown in Fig. 1, the CAD patients with nonsleepy OSA (apnoea-hypopnoea index [AHI] $\geq$ 15/h) on the cardiorespiratory polygraphy (CRPG) at screening and an Epworth Sleepiness Scale (ESS) < 10) were randomized to CPAP or no-CPAP (1:1 assignment, stratified by sex and revascularization type [PCI/CABG]). For the current protocol, those with nonsleepy OSA who had complete blood samples at baseline, 3, and 12-month follow-up were included in the RCT arm. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (approval nr 207-05; 09.13.2005; amendment T744-10; 11.26.2010; amendment T512-11; 06.16.2011), and written informed consent was provided from all patients. The trial was registered (FoU i Sverige – Research and development in Sweden; researchweb.org; VGSKAS-4731; 04.29.2005; and ClinicalTrials.gov; NCT 00519597).

2.2. Blood sampling

After an overnight fast of at least 10 h, venous blood samples were drawn between 07.00 and 08.00 in the morning at the time of the study inclusion for measurement of plasma glucose and serum lipids, and additional blood samples (plasma and serum) were collected using ethylenediaminetetraacetic acid and serum tubes. Blood samples were collected again after three and 12 months' follow-up. Tubes were centrifuged, and plasma/serum samples were aliquoted and stored at −70 °C until analysis. The levels of leptin were analyzed in plasma samples (undiluted) and levels of adiponectin in serum samples (diluted 1:100) using commercially available MILLIPLEX MAP (based on Luminex technology) human assay kits per the manufacturer's instructions (Merck Millipore, MA, USA). Minimum detectable concentrations (assay sensitivities) for leptin and adiponectin were 0.0854 ng/ml and 0.056 mg/mL, respectively. Maximum circulating leptin and adiponectin measurements were used respectively for the samples that had extremely high levels in order to minimize missing values. The intra-assay and inter-assay variabilities, generated from the mean of the percentage coefficient of variability from multiple reportable results across two different concentrations of analytes in one experiment, or from two results each for two different concentrations of analytes across several different experiments, were 1.4–7.9% and <21% for leptin, and 9.2% and 15.9% for adiponectin, respectively.

2.3. Sleep recordings, group assignments, and randomization

The portable CRPG was conducted with the Embletta® Portable Digital System device (Embla, Broomfield, CO, USA). As explained previously [22], the CRPG system included a nasal pressure detector, two respiratory inductance plethysmography belts (RIP) for thoraco-abdominal movements and body position, and finger pulse oximetry for detecting heart rate and oxyhemoglobin saturation (SpO_2). Apnoea was defined as at least $\geq$90% cessation of airflow, and hypopnoea was defined as at least a 50% reduction in thoraco-abdominal movement and/or in nasal pressure amplitude for $\geq$10 s [23]. Additionally, the total number of significant drops in SpO_2 ($\geq$4% from the immediately preceding baseline) was scored, and the oxygen desaturation index (ODI) was determined as the number of significant desaturations per hour of estimated sleep. Obstructive events with an evident reduction in RIP belts or in the nasal pressure amplitude for at least 10 s were also recorded as hypopnoeas if there was a significant desaturation [23].

2.4. Epworth sleepiness scale

The ESS questionnaire [24] was used to determine subjective daytime sleepiness. As previously described, the ESS questionnaire contains eight questions to address the possibility of dozing-off under eight different conditions in the past month. A cut-off value of 10 out of 24 was used for categorizing the patients with excessive daytime sleepiness.

2.5. Comorbidities

As described previously, baseline anthropometrics, smoking habits, and medical history of the entire study population were obtained from the medical records [22]. Obesity was defined as a body-mass-index (BMI) $\geq$30 kg/m^2, and abdominal obesity was defined as a waist-to-hip ratio (WHR) $\geq$ 0.9 for men and WHR $\geq$ 0.8 for women, respectively [25].

2.6. Group assignment, randomization, interventions, and follow-up

In the main RICCADSA trial, the group assignment was based on the CRPG results, and the ESS scores (Fig. 1). Nonsleepy OSA

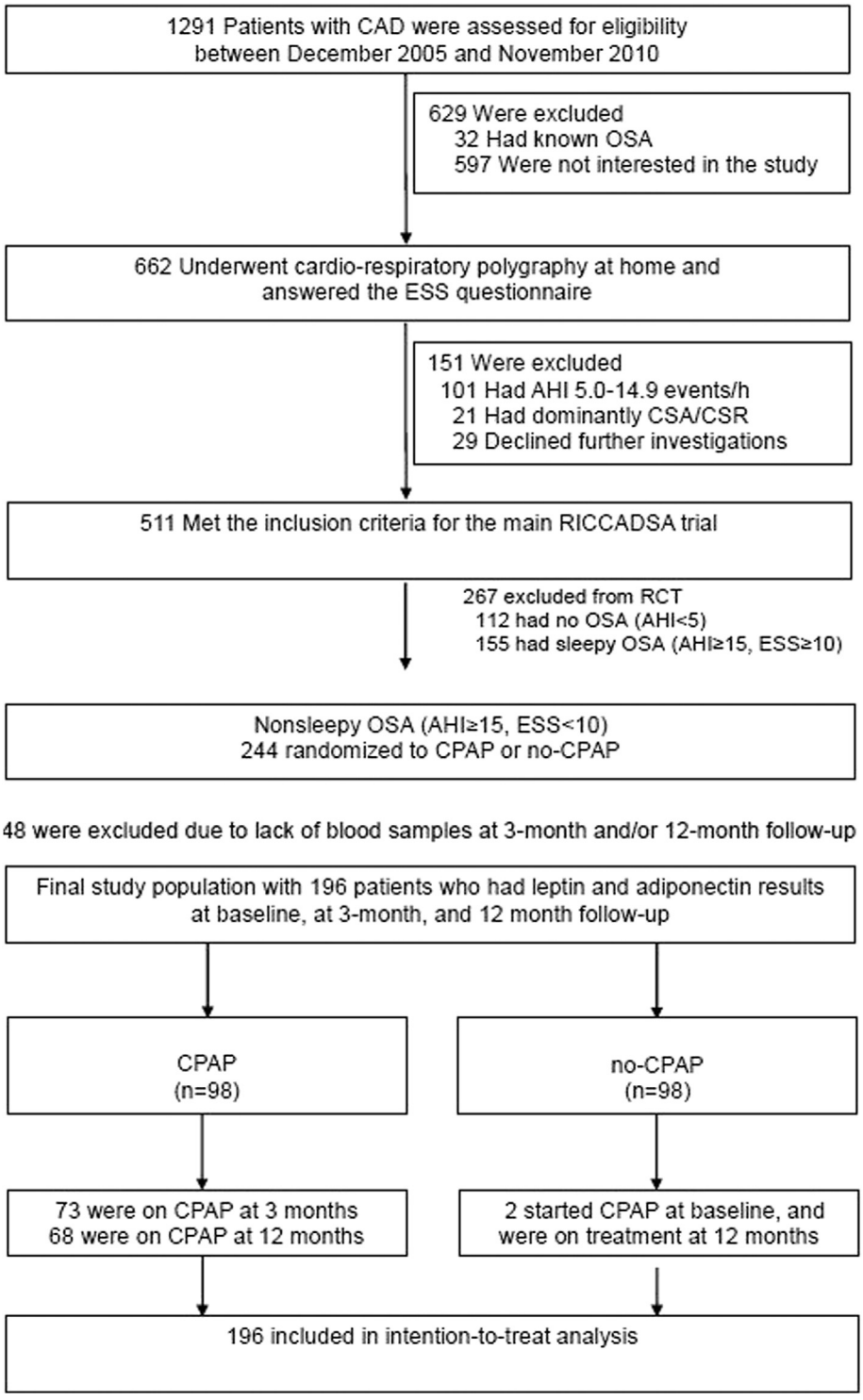


Fig. 1. Flow chart of study participants. *Definition of abbreviations*: AHI, apnoea-hypopnoea index; CAD; coronary artery disease; CPAP, continuous positive airway pressure; CSA-CSR, central sleep apnoea-Cheyne Stokes respiration; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; RCT, randomized controlled trial; RICCADSA, Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea.

patients randomized to CPAP were provided with an automatic (self-titrating) CPAP device (S8®, or S9®; San Diego, CA, USA) with a nasal or full-face mask and humidifier according to the out-patient clinical routines. As described previously, all patients allocated to CPAP were contacted by telephone after one week, and all patients were followed in the clinic after one month, three months, six months, one year, and then yearly to the end of the main study [22].

2.7. Adherence to CPAP

Hours of CPAP use were downloaded from the devices and recorded at follow-ups in all patients allocated to CPAP. All necessary technical modifications were done according to the clinical routines by the sleep medicine unit staff. Patients who stopped using the devices were followed as part of the

treatment arm, as defined in the intention-to-treat (ITT) analysis [22].

CPAP adherence at 12 months was based on the CPAP hours/night adjusted for the percentage of CPAP days per period (from the last previous visit to 12-month follow-up), and corresponding four hours of CPAP usage every night was defined as good compliance.

2.8. Outcomes

The primary outcome for the current study was the change in circulating levels of leptin and adiponectin from baseline to three and 12 months in the ITT population. On-treatment analysis of changes from baseline included secondary endpoints.

2.9. Statistical analysis

Data are shown as mean ± standard deviation (SD), median ± standard error of the mean (SEM), median interquartile range (IQR), 95% confidence interval (CI), and categorical variables as numbers (percentages). For comparison between groups, an independent sampled student T-test, or, when appropriate, Mann–Whitney U test was used. Chi-square test or, when appropriate, Fisher's exact test was used for comparison of categorical variables. Primary outcome data were analyzed on an ITT-basis. Pearson correlation coefficients were used for analyzing the association between delta BMI and delta waist circumference as well as delta leptin and adiponectin values from baseline and accumulated CPAP hours/night at one-year follow-up. A linear regression model with the bootstrap procedure was used to determine variables associated with plasma leptin and serum adiponectin values at baseline as well as with change after 12 months. Age, sex, BMI, as well as variables that were significant in univariate analyses were entered into the multivariate models. Repeated measures of leptin and adiponectin levels were analyzed using a mixed-effects model by including patient random effect. A paired t-test was used for BMI and waist circumference changes from baseline within the groups. All statistical tests were two-sided, and a p-value <0.05 was considered significant. Statistical analysis was performed using the Statistical Package for Social Sciences, version 24.0 for a Windows® system (SPSS® Inc., Chicago, Illinois, USA).

3. Results

3.1. Study population and baseline characteristics

In the main trial 244 CAD patients with nonsleepy OSA were included (Fig. 1). After excluding 48 patients who lacked blood samples at 3-month and/or 12-month follow-up, 196 (mean age 65.79 + 8.1 years; 84% men) were retained for the current protocol.

As shown in Table 1, the CPAP group (n = 98) and no-CPAP group (n = 98) had similar baseline anthropometrics, severity of OSA, clinical characteristics, medication use as well as glucose and lipid profiles. Baseline leptin levels ranged between 0.9 ng/ml and 297.4 ng/ml (five patients had extremely high values, one in the CPAP group, four in the no-CPAP group, entered as 297.4 ng/ml). Baseline adiponectin levels ranged between 0.01 mg/ml and 69.8 mg/ml (18 had extremely high values, 11 in the CPAP group, seven in no-CPAP group; entered as 69.8 mg/ml). Median values and inter-quartile ranges of leptin and adiponectin did not differ significantly between the groups at baseline (Table 1).

As illustrated in Table 2, female sex, obesity, and abdominal obesity but not AHI, ODI, and other comorbidities, were associated with increased plasma leptin levels at baseline. In the multivariate model, female sex was the only variable associated with increased baseline leptin levels (Table 2). As shown in Table 3, male sex, BMI, previous revascularization, and pulmonary disease were related to decreased serum adiponectin levels in the multivariate analysis.

Table 1
Characteristics of the entire study population with coronary artery disease and nonsleepy obstructive sleep apnoea at baseline (n = 196).

	On CPAP n = 98	No CPAP n = 98
Age, years	65.0 ± 8.1	66.4 ± 7.9
Age ≥ 65 years, %	52.0	55.1
BMI, kg/m^2	28.2 ± 3.7	28.5 ± 3.5
Obesity, %	26.5	26.5
Waist circumference, cm	100.6 ± 9.7	101.3 ± 10.3
WHR	0.97 ± 0.1	0.96 ± 0.8
Abdominal obesity, %	93.8	93.8
Male sex, %	82.7	85.7
AHI, events/h	27.9 ± 12.4	28.9 ± 13.2
ODI, events/h	16.0 ± 10.3	16.4 ± 11.5
ESS score	5.5 ± 2.3	5.6 ± 2.2
CABG before inclusion,%	24.5	26.5
Current smoker, %	17.3	11.2
AMI at the baseline,%	57.1	50.0
LVEF < 50%, %	10.2	18.4
Previous revascularization, %	19.4	14.3
Hypertension,%	69.4	56.1
Diabetes mellitus,%	26.5	18.4
Stroke,%	7.1	8.2
Pulmonary disease, %	3.1	8.2
Blood glucose, mmol/L	5.9 ± 1.4	5.5 ± 0.8
Serum LDL cholesterol, mmol/L	2.4 ± 0.7	2.4 ± 0.7
Serum HDL cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.3
Serum triglycerides, mmol/L	1.5 ± 0.8	1.4 ± 0.7
Plasma leptin, ng/mL[a]	12.3 (7.1–23.1)	11.5 (8.4–17.6)
Serum adiponectin, mg/mL[a]	11.4 (8.4–17.6)	10.9 (7.2–15.3)
Medication use		
Diuretic, %	23.4	28.1
β blocker, %	90.4	86.5
ASA, %	93.7	85.4
Clopidogrel, %	58.3	50.5
Warfarin, %	5.3	9.4
CCB, %	19.1	15.6
ACE inhibitor, %	42.6	50.0
ARB inhibitor, %	14.9	15.6
Statins, %	97.9	93.8
Anti-depressive medication, %	4.3	2.1

Definition of abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; AHI, apnoea-hypopnoea index; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass graft operation; CCB, calcium channel blocker; ESS, Epworth Sleepiness Scale; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index; WHR, waist-hip-ratio.
[a] median (inter-quartile range).

3.2. CPAP adherence

In the CPAP group, 30 (31.3%) stopped using the device within 12 months. Among 68 patients remaining on CPAP, 52 (76.5%) were using the device at least three hours/night, 45 (66.2%) at least four hours/night, and 34 (50%) at least five hours/night, respectively. In the no-CPAP group, two (2.0%) had crossed-over to the CPAP arm at baseline and remained on treatment at three and 12-month follow-up.

3.3. Outcomes

In the entire RCT population, there was a significant increase in BMI from 28.3 ± 3.7 to 28.8 ± 3.8 kg/m^2 at 12-month follow-up in the CPAP group ($p = 0.002$) with a smaller increase in the no-CPAP group (from 28.4 ± 3.5 kg/m^2 at baseline to 28.8 ± 3.7 kg/m^2 at 12-month follow-up) ($p = 0.07$). However, there was no between-group difference regarding the magnitude of change in BMI at the 12-month follow-up. Regarding the waist circumference, there was

Table 2
Association of the variables with plasma leptin levels at baseline in a linear regression model with the bootstrap procedure (n = 196).

	β coefficient	95% CI
Univariate		
Age, years	0.53	−0.29–1.40
Age ≥ 65 years	8.90	−5.77–22.05
Female sex**	52.75	21.45–94.81
BMI kg/m^2	2.44	−0.93–6.04
Obesity*	25.36	6.74–49.47
Abdominal obesity*	14.83	8.01–23.41
Waist circumference, cm	0.55	−0.19–1.48
WHR	−76.97	−223.78 – 41-16
AHI, events/h	0.68	−0.06–1.44
ODI, events/h	0.43	−0.61–1.65
ESS score	0.42	−2.52–3.55
Current smoker	0.39	−15.29–25.91
AMI at the baseline	1.57	−11.99–16.58
LVEF < 50%	−0.18	−1.42–0.67
Previous revascularization	−5.21	−15.93–4.70
Hypertension	10.03	−3.39–23.38
Diabetes mellitus	7.82	−8.85–29.32
Stroke	−7.94	−18.70–2.04
Pulmonary disease	42.39	−11.79–109.36
Multivariate		
Age, years	0.34	−0.51–1.13
Female sex*	53.78	21.96–89.66
BMI kg/m^2	2.96	−0.15–5.74

Definition of abbreviations: AMI, acute myocardial infarction; AHI, apnoea-hypopnoea index; BMI, body mass index; CABG, coronary artery bypass graft operation; CI, confidence interval; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index.
*$p < 0.05$; **$p < 0.01$.

Table 3
Association of the variables associated with serum adiponectin levels at baseline in a linear regression model with the bootstrap procedure.

	β coefficient	95% CI
Univariate		
Age, years*	0.32	0.03–0.62
Age ≥ 65 years	4.19	−1.02–9.57
Female sex**	18.12	9.74–26.44
BMI, kg/m^{2}**	−1.16	−1.90–−0.50
Obesity**	−7.46	−11.76–−3.06
Abdominal obesity	−9.12	−27.23–4.30
Waist circumference, cm**	−0.51	−0.81–−0.20
WHR*	−61.97	−106.19–−23.04
AHI, events/h	0.11	−0.08– 0.32
ODI, events/h	−11.77	−232.60–251.41
ESS	−0.88	−2.05–0.20
Current smoker*	−5302.35	−9646.82–−511.35
AMI at the baseline	−1859.00	−6560.31–2784.40
LVEF < 50%	−0.12	−0.34–0.76
Previous revascularization**	−6.19	−10.09–−2.59
Hypertension	3260.57	−1772.03–8193.01
Diabetes mellitus	−4.11	−8.89–1.13
Stroke	11.82	0.35–25.45
Pulmonary disease*	−6.07	−10.75–−1.24
Multivariate		
Age, years	0.11	−0.20–0.43
Female sex**	16.61	9.17–25.23
BMI, kg/m^{2}*	−0.95	−1.68–−0.37
Current smoker	−4.46	−9.88–0.45
Previous revascularization*	−4.84	−9.00–−1.18
Pulmonary disease**	−7.35	−12.20–−3.34

Definitions of abbreviations: AMI, acute myocardial infarction; AHI, apnoea-hypopnoea index; BMI, body mass index; CABG, coronary artery bypass graft operation; CI, confidence interval; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index; OR, odds ratio.
*$p < 0.05$; **$p < 0.01$.

a significant increase 101.6 ± 9.8 cm to 103.2 ± 10.7 cm in the CPAP group ($p = 0.01$), and from 100.9 ± 9.8 cm to 103.2 ± 10.1 cm in the no-CPAP group ($p < 0.001$) with no between-group differences.

As illustrated in Fig. 2a, plasma leptin values increased from 21.7 ng/ml (95% CI 12.5–31.0) at baseline to 31.4 ng/ml (%95 CI 22.2–40.6) after three months ($p = 0.05$), and declined to 20.2 ng/ml (%95 CI 11.0–29.5) after 12 months ($p = 0.53$) in the CPAP group intention-to-treat population. Corresponding values were 25.1 ng/ml (%95 CI 17.3–33.1) at baseline, 20.2 ng/ml (%95 CI 12.3–28.1) after three months ($p = 0.37$), and 16.8 ng/ml (%95 CI 8.9–24.7) after 12 months ($p = 0.09$) in the no-CPAP group (Fig. 2a). Serum adiponectin levels remained mainly unchanged in CPAP group (three months *vs* baseline [$p = 0.31$]; 12 months *vs* baseline [$p = 0.64$) whereas there was an increase over time within the no-CPAP group (three months *vs* baseline [$p = 0.17$]; 12 months *vs* baseline [$p = 0.01$]) (Fig. 2c).

Among tested variables, percent change in waist circumference was the only significant one associated with percent change in plasma leptin. In contrast, none of the variables was related to percent change in serum adiponectin in the intention-to-treat population (Table 4).

When comparing the groups based on CPAP adherence, there were no significant changes over time regarding leptin and adiponectin (Fig. 2b and d).

As illustrated in Fig. 3a and c, there were weak but significant associations between delta BMI and delta leptin as well as delta adiponectin at one-year follow-up; delta waist circumference was correlated with delta leptin (Fig. 3b).

4. Discussion

In this CAD cohort with nonsleepy OSA, female sex was significantly associated with increased plasma leptin, while decreased levels of adiponectin were associated with male sex, BMI, previous revascularization, and pulmonary disease. CPAP treatment had no impact on changes in leptin and adiponectin values, neither in the ITT nor in the on-treatment population. Percent change in waist circumference was the only significant variable related to percent change in leptin levels, while none of the tested variables was predictive for change in circulating adiponectin levels in the multivariate models.

To the best of our knowledge, this is the first RCT evaluating the impact of CPAP treatment on circulating leptin and adiponectin levels in a CAD cohort with nonsleepy OSA. None of the previous studies addressing the determinants of leptin and adiponectin levels in CAD cohorts considered OSA in the statistical models, and the results were not conclusive.

It has been suggested that elevated plasma leptin is a strong predictor of first AMI and that there is a strong association between leptin and development of CVD, especially in obese adults [26]. Moreover, in an early prospective, observational study of 377 adults with CAD and 783 controls, leptin was a significant predictor of incident CAD [27]. Regarding studies conducted in sleep clinic cohorts, plasma leptin levels were found to be higher in adults with OSA compared with the levels in the controls with no-OSA [9–14].

A majority of the previous studies addressing the impact of CPAP treatment on plasma leptin levels in sleep clinic cohorts have suggested beneficial effects of CPAP [18,28–31]; fewer failed to show such a benefit [32,33]. Our results confirm previous reports regarding the association between leptin and obesity measures in adults with OSA [28,33], and additionally emphasize the contributing role of female sex to leptin levels in adults with CAD. Though we found a significant increase in BMI in the CPAP group, the magnitude of the BMI change from baseline did not differ significantly between the CPAP and no-CPAP groups, and there was no

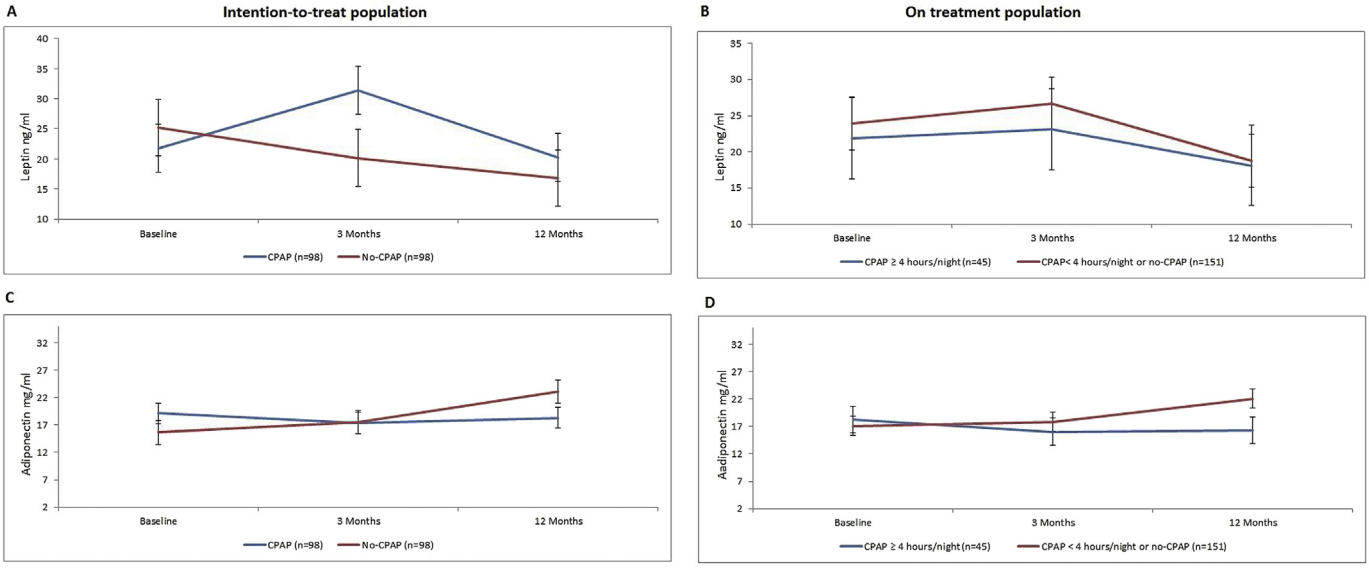


Fig. 2. a. Mean values of plasma leptin with the standard error of means at baseline, and after three, and 12 months, in the continuous positive airway pressure (CPAP) and no-CPAP (control) groups. **b.** Mean values of plasma leptin with a standard error of means at baseline, and after three and 12 months, among the patients using CPAP ≥4 h/night/all nights vs. CPAP <4 h/night or no-CPAP in the on-treatment population. **c.** Mean values of serum adiponectin with a standard error of means at baseline and after three, and 12 months, in the CPAP and no-CPAP groups. **d.** Mean values of serum adiponectin with a standard error of means at baseline, and after three and 12 months, among the patients using CPAP ≥4 h/night/all nights vs. CPAP <4 h/night or no-CPAP in the on-treatment population.

linear correlation between weight gain and CPAP use in hours/night.

Controversial results exist in the literature regarding the association between circulating levels of adiponectin and CAD. Brolin et al. [34], compared CAD subjects with non-CAD controls and reported significantly lower levels of circulating adiponectin in the CAD group. In another study conducted in a CAD population [35], lower adiponectin levels were associated with worse cardiovascular outcomes. A recent study has indicated that adiponectin and its genetic variants may have an impact, especially in myocardial infarction at a young age [20]. In a meta-analysis of 11 studies involving 240 patients in sleep clinic cohorts, no significant effect of CPAP was found in adults with OSA [3]. In our CAD cohort, lower adiponectin levels at baseline were predicted by male sex, BMI, previous revascularization, and pulmonary disease. The neutral effect of CPAP treatment on adiponectin levels is in line with the findings in sleep clinic cohorts.

In the meta-analysis mentioned above [17], comprising a total of 3181 patients from 25 RCTs, CPAP treatment was shown to be related to a significant increase in BMI. In our study, we also observed an increase in BMI and waist circumference in the CPAP group. However, there was a similar increase in the no-CPAP group, suggesting that these changes were unrelated to CPAP treatment per se. A possible explanation might be the sedentary lifestyle in this group of cardiac patients. Nevertheless, the lack of information regarding energy balance, dietary intake, and eating behavior in the RICCADSA protocol precludes further conclusions in this context.

Table 4
Association of the variables with percent change in leptin and adiponectin levels at one-year follow-up in a multivariate linear regression model with the bootstrap procedure in the intention-to-treat population.

	β coefficient	95% CI
Change in Leptin %		
Model 1		
Percent change in WC*	2.47	0.77–4.40
Age, years	0.01	−0.01–0.02
Female sex	−0.23	−0.49–0.01
CPAP assignment	0.04	−0.15–0.24
Model 2		
Percent change in BMI	0.90	−0.60–4.20
Age, years	0.01	−0.01–0.02
Female sex	−0.20	−0.44–0.03
CPAP assignment	0.04	−0.16–0.19
Change in Adiponectin %		
Model 1		
Percent change in WC	−0.20	−4.24–5.76
Age, years	−0.01	−0.01–0.03
Female sex	−0.02	−0.39–0.35
CPAP assignment	−0.46	−0.88–−0.09
Model 2		
Percent change in BMI	−0.51	−3.78–3.94
Age, years	0.01	−0.01–0.02
Female sex	−0.20	−0.44–0.03
CPAP assignment	0.04	−0.15–0.20

Definition of abbreviations: BMI, body mass index; CI, confidence interval; WC, waist circumference.
*$p < 0.05$.

4.1. Limitations

This study has several limitations. First, the group allocation was based on cardiorespiratory sleep studies, and thus, the total sleep time could not be given precisely. However, the cut off value for AHI (15/h) chosen for OSA diagnosis, was previously shown to be reliable for the Embletta system [36] used in the current trial. The adults with AHI 5.0–14.9 were described as borderline OSA [37], managed according to clinical routines, and not included in the RCT arm. Second, the RICCADSA trial was open-label and had no placebo control arm. However, as previously argued [38], there is no true sham CPAP or other proper placebo for CPAP in a long-term trial in adults with cardiovascular diseases. Thirdly, patients randomized to CPAP were treated with self-titrating CPAP devices according to the out-patient clinical routines of the study hospital. It has been suggested that auto CPAP might be less effective than fixed CPAP in improving cardiometabolic risk factors in sleep clinic cohorts [39,40]. It is unclear how the results might be different in our

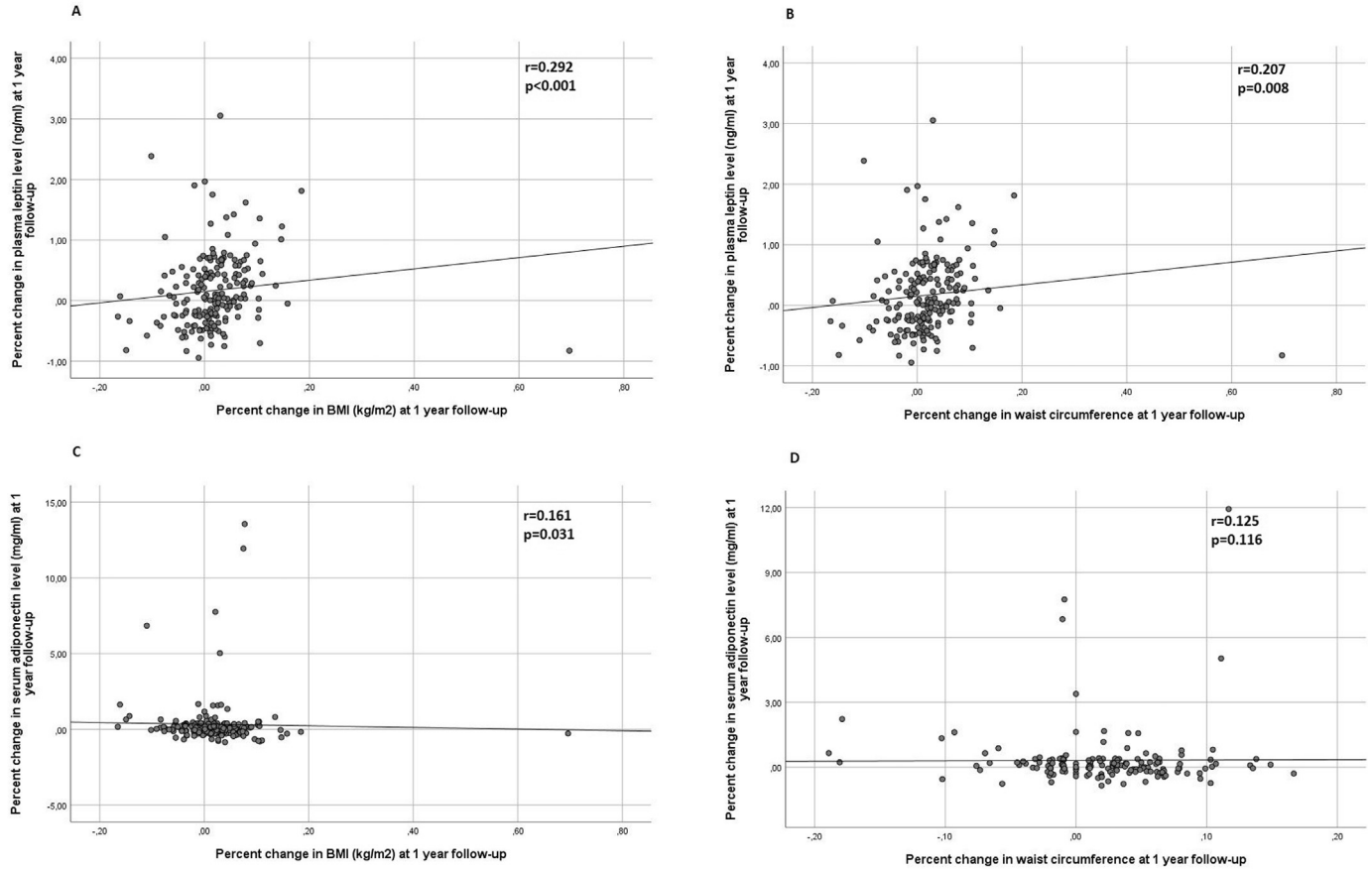


Fig. 3. a. Pearson correlation between delta plasma leptin and delta body-mass-index at the 12-month follow-up. **b.** Pearson correlation between delta plasma leptin and delta waist circumference at the 12-month follow-up. **c.** Pearson correlation between delta serum adiponectin and delta body-mass-index at the 12-month follow-up. **d.** Pearson correlation between delta serum adiponectin and delta waist circumference at the 12-month follow-up.

cardiac cohort if the fixed-pressure procedure had been conducted. Finally, our results in the current study refer to CAD patients with nonsleepy OSA, who were randomized to CPAP *vs.* no-CPAP, and are not generalizable to the sleepy phenotype. Future work comparing the RCT and observational arms of the RICCADSA population with regard to cardio-metabolic outcomes and response to CPAP treatment would hopefully give further insights into the field in this context.

5. Conclusions

We conclude that female sex was significantly associated with increased plasma leptin; male sex, BMI, previous revascularization, and pulmonary disease were the determinants of unfavorable levels of adiponectin at baseline. CPAP treatment had no effect on changes in leptin and adiponectin values, neither in the ITT nor in the on-treatment population in this cohort of nonsleepy OSA patients. An increase in waist circumference predicted an increase in plasma levels of leptin after 12 months, suggesting that lifestyle modifications should be given priority in adults with CAD and nonsleepy OSA regardless of CPAP treatment.

Disclosures

Baran Balcan, Tülay Yucel-Lindberg, Kristin Lindberg, and Pinar Ay report no conflicts of interest; Erik Thunström received consultant fees from ResMed and Pfizer (outside of the current work). Yüksel Peker declares institutional grants from ResMed Foundation and ResMed Inc for the RICCADSA trial, consultant fees from BresoTec, lecture fees from ResMed, and Philips-Respironics outside the current work.

Authors' contributions

YP designed the study. YP and ET performed patient recruitment and clinical follow-ups. TYL and KL analyzed the blood samples. BB, PA, and YP performed the statistical analysis. BB and YP prepared the manuscript and drafted the article. YP obtained study funding and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. All authors interpreted the data and approved this manuscript in its final form.

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of the study, the analysis of the data, the data collection, drafting of the manuscript, or the decision to publish.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.10.016.

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