Effects of 8 weeks of continuous positive airway pressure on abdominal adiposity in obstructive sleep apnoea

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ABSTRACT: The aim of the present study was to investigate the effect of continuous positive airway pressure (CPAP) treatment on regional adipose tissue distribution in patients with moderate or severe obstructive sleep apnoea.

Patients received both therapeutic and sham CPAP in a random order for 2 months each with an intervening 1-month washout. Abdominal subcutaneous, visceral and liver fat were quantified using magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). Liver enzymes and plasma glucose were also determined. Measurements were obtained at baseline and at the end of both treatment arms.

38 eligible patients were randomly assigned to a treatment order, with 27 patients having complete MRI/MRS data. No significant difference was observed in subcutaneous (-28.6 cm^3 ; $p=0.49$) or visceral (-16.8 cm^3 ; $p=0.59$) adipose tissue, intrahepatic lipid (-0.2% ; $p=0.21$), or fasting glucose measurements ($-0.1 \text{ mmol}\cdot\text{L}^{-1}$; $p=0.46$) between treatment modalities. Alkaline phosphatase decreased ($-3.1 \text{ U}\cdot\text{L}^{-1}$; $p=0.02$) while on therapeutic CPAP compared with sham CPAP but other liver enzymes, including aspartate aminotransferase ($0.3 \text{ U}\cdot\text{L}^{-1}$; $p=0.82$), alanine aminotransferase ($1.34 \text{ U}\cdot\text{L}^{-1}$; $p=0.59$) and γ -glutamyltransferase ($-2.3 \text{ U}\cdot\text{L}^{-1}$; $p=0.33$), remained unchanged.

In this first randomised, sham-controlled trial, there was no change in adipose tissue distribution after 8 weeks of therapeutic CPAP compared with 8 weeks of sham CPAP. Longer duration of CPAP use may be necessary to demonstrate a difference.

KEYWORDS: Fasting glucose, hepatic fat, liver function test, subcutaneous fat, visceral fat

Obstructive sleep apnoea (OSA) affects at least 4 and 2% of middle-aged males and females, respectively [1]. Central (or abdominal) obesity is a known risk factor for OSA and is strongly linked to insulin resistance. There is increasing evidence for a correlation between OSA and worsened glucose intolerance, although it remains controversial whether this relationship is entirely independent of obesity [2]. Nevertheless, several clinical trials have suggested an improvement in insulin resistance with continuous positive airway pressure (CPAP) treatment for OSA [3, 4].

Adipose tissue in the abdomen is distributed amongst the subcutaneous layer of the skin, the viscera and the liver. It is hypothesised that deposition of fat in the viscera and liver reflects the inability of the subcutaneous tissue to absorb and store excess dietary triglycerides [5]. Both visceral and subcutaneous fat are associated with increased insulin resistance; however, overweight subjects with excess visceral fat have the most

insulin resistance [5]. Furthermore, the severity of upper airway obstruction and hypoxaemia secondary to OSA appears to better correlate with the amount of visceral fat than clinical measures of obesity, including body mass index (BMI) [6].

Currently, it is unclear whether CPAP use results in a reduction of insulin resistance-associated visceral fat. Some observational studies have shown a reduction [7, 8] while others showed no change [3, 9, 10]. Factors that could contribute to the differences observed include mean CPAP compliance, duration of treatment and OSA severity. Importantly, there are presently no sham-controlled randomised trials examining central obesity in OSA and its response to CPAP. Several studies investigating the combination of improved dietary and exercise measures and weight loss-promoting medications have shown a greater reduction in visceral fat compared with subcutaneous fat [11].

OSA has also been shown to aggravate components of the metabolic syndrome, including

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hyperinsulinaemia and may, thus, indirectly contribute to the development of a fatty liver [12]. Patients with nonalcoholic fatty liver disease (NAFLD) are often asymptomatic and many have normal liver function tests. Nevertheless, patients can be diagnosed with NAFLD after mild elevations of liver enzymes are discovered [13]. Markers of hypoxia have been demonstrated to be associated with elevated serum aminotransferase levels [14]. Similarly to visceral fat, however, there are contrasting results on the effect of nasal CPAP on the biochemical markers of NAFLD in patients with OSA [12, 15, 16].

This randomised, sham-controlled crossover study investigated the effect of CPAP treatment for 8 weeks *versus* sham CPAP for 8 weeks in patients with moderate-to-severe hypoxaemic OSA on the volume and distribution of abdominal adipose tissue, liver fat, liver enzymes and glucose.

METHODS

Participants

The protocol has previously been reported in a study that assessed the effect of CPAP treatment on post-prandial lipidaemia [17]. Details of randomisation, allocation concealment and blinding, and the flow of patients through the trial are included in the original report. Briefly, we recruited patients from sleep apnoea clinics who were aged >21 yrs, with OSA severity in the upper moderate or severe range (apnoea–hypopnoea index (AHI) ≥ 25 events·h⁻¹) with a hypoxic component (oxygen desaturation index ≥ 20 events·h⁻¹). We excluded patients with BMI >35 kg·m⁻², uncontrolled type 2 diabetes and patients who had previously used CPAP. The exclusion of patients with BMI >35 kg·m⁻² was solely because such individuals cannot usually fit into a magnetic resonance imaging (MRI) scanner. Patients who consumed >140 mg of alcohol per week and those with known liver disease were also excluded. Other selection criteria are available from the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au) (identifier number ACTRN 12605000066684). The diagnosis of sleep apnoea was based on full overnight polysomnography in a clinical laboratory prior to recruitment. End-of-treatment polysomnography was performed on either therapeutic or sham CPAP. Apnoeas and hypopnoeas were scored using standard scoring techniques [18]. The study protocol was approved by the Human Research Ethics Committee of the Sydney South West Area Health Service (#X05-0128) at Royal Prince Alfred Hospital (Sydney, NSW, Australia). All subjects gave written informed consent prior to study participation.

Study design

Patients who met the inclusion/exclusion criteria were randomised to receive CPAP (Remstar Auto; Philips Respironics, Murrysville, PA, USA) or sham CPAP for 8 weeks each in a crossover design with an intervening 1-month washout period between treatments (fig. 1). Sham CPAP devices are identical in appearance to the therapeutic devices except that the pressure delivered at the mask remains at 0.5 cmH₂O, thus having no effect on sleep disordered breathing. In contrast, therapeutic CPAP was set to a pressure that prevented most sleep disordered breathing. This was determined during an at-home pressure determination study as previously described [17]. Compliance data from both devices was obtained from machine

FIGURE 1. Study protocol. CPAP: continuous positive airway pressure; MRI: magnetic resonance imaging; LFT: liver function test.

downloads at the end of each treatment arm. Subjects did not change their exercise regime, diet or medications throughout the duration of the study.

Imaging and biochemical testing

MRI and magnetic resonance spectroscopy (MRS) were used to quantify abdominal and liver fat. MRI measurements were obtained at baseline and at the end of both treatment arms (fig. 1). An average of 10 (range 5–10) T1-weighted axial images (7 mm thick, 1-mm gap) were acquired during a breath-hold starting at the level of the fourth lumbar vertebra (L4). Contiguous DICOM® (Digital Imaging and Communications in Medicine) protocol (National Electrical Manufacturer's Association, Rosslyn, VA, USA) images were analysed for quantification of subcutaneous and visceral adipose tissue using specialised validated software (Hippo Fat™; CNR Institute of Clinical Physiology, Pisa, Italy) [19]. Contours lining the inner and outer margin of subcutaneous adipose tissue and the inner margin of the abdominal muscle layer were automatically generated for each image. These were then manually adjusted by eye, as necessary [20], to encapsulate the entire subcutaneous and visceral compartments of each analysed slice. The software then performs an automated analysis of pixel intensity to discriminate tissue class (air, adipose tissue and nonadipose tissue). Investigators, including those undertaking adipose tissue quantification analysis, were blinded throughout the study to patient treatment groups.

MRS liver fat measurements were performed using a 1.5-T Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands). Following an 8-h fast, intrahepatic lipid (IHL) was measured by localised ¹H-MRS (point-resolved spectroscopy; repetition time 3,000 ms/35 ms; 3 × 3 × 3-cm voxel) (SENSE Torso Array; Philips Medical Systems). Blinded

quantification of the spectra (water and CH₂ resonances) was performed using jMRUI version 3.0 (The MRUI Project, Barcelona, Spain) [21]. Following manual first- and second-order phase correction, spectra were analysed using a nonlinear least-squares algorithm (Advanced Method for Accurate, Robust and Efficient Spectral Fitting). IHL was expressed as a percentage of liver volume, corrected for the proton densities of water and lipid [22]. Measurements of hepatic fat by spectroscopy have been validated against lipid content determined by histology [22].

Liver enzymes and glucose levels were measured in the fasting state at the end of each 8-week intervention arm.

Statistical methods

The final analyses included 27 patients who had completed the crossover trial, regardless of compliance with either therapeutic or sham CPAP. Order effect was analysed using unpaired t-tests. Main outcomes were analysed using paired t-tests. The effect of compliance with therapeutic CPAP on visceral and subcutaneous fat and IHL at the end of the CPAP period was analysed using a compliance cut-off point of 4 h with unpaired t-tests. Correlation analysis was also performed between compliance (hours) and visceral and subcutaneous fat and IHL. Order effect was examined by comparing the difference in abdominal fat between CPAP and sham CPAP for subjects who received CPAP in the first arm as opposed to the second arm.

Data was analysed with the statistical software package STATA™ version 10 (StataCorp, College Station, TX, USA).

RESULTS

A total of 29 patients completed the trial [17]. Complete MRI and laboratory data were available for 27 participants. One patient was excluded because they had poor-quality MRI images that could not be analysed using the Hippo Fat™ software, and another participant developed claustrophobia and subsequently missed the final MRI appointment, thus having incomplete data. Nine participants withdrew or were withdrawn post-randomisation, as previously reported [17].

Patient demographics, anthropometrics, diagnostic polysomnography data and baseline biochemistry data are shown in table 1, and polysomnographic, CPAP compliance and residual AHI data obtained at the end of the CPAP and sham treatment arms are outlined in table 2. No significant differences were observed in either subcutaneous or visceral fat, IHL, BMI, or fasting glucose measurements between treatment arms (table 3). The visceral/subcutaneous fat ratio was the same in the CPAP (0.44) and sham (0.44) arms. In addition, there was no significant difference in IHL when the data were reanalysed excluding the two diabetic patients (mean CPAP - sham CPAP IHL difference -0.2; $p=0.34$). There was no effect of compliant (>4 h) versus noncompliant CPAP use on the baseline-to-CPAP change in fat ($p=0.27$, 0.48 and 0.46 for subcutaneous and visceral fat and IHL, respectively), nor was there any correlation between change in subcutaneous or visceral fat, or IHL with compliance with therapeutic CPAP as a continuous variable ($r=-0.07$ ($p=0.71$), $r=0.17$ ($p=0.39$) and $r=0.24$ ($p=0.25$), respectively). In addition, there was no effect of order of CPAP treatment exposure on baseline to CPAP change in adipose tissue.

TABLE 1 Patient demographic, anthropometric and baseline data

Demographics	
Age yrs	47 ± 13
Males/females n	26/1
BMI kg·m ⁻²	31.3 ± 3.8
Medical history and medication n	
Hypertension	9
Type 2 diabetes	2
Hypercholesterolaemia	10
Antihypertensive agents	9
Oral hypoglycaemic agents	1
Insulin	0
Statins	7
Sleep apnoea	
AHI events·h ⁻¹	37.2 ± 24.7
ODI events·h ⁻¹	30.3 ± 22.6
TST with Sa,O ₂ <90% %	7.1 ± 11.7
Minimum Sa,O ₂ %	78.0 ± 11.4
ESS score	10.0 ± 4.8
LFT	
ALP [#] U·L ⁻¹	72.5 ± 13.9
AST [†] U·L ⁻¹	26.6 ± 8.1
ALT [†] U·L ⁻¹	41.1 ± 19.9
GGT [‡] U·L ⁻¹	33.9 ± 17.5
Total protein [§] g·L ⁻¹	74.0 ± 4.2
Albumin [§] g·L ⁻¹	45.3 ± 2.3
Bilirubin ^{##} μmol·L ⁻¹	12.9 ± 6.5
Fasting glucose^{††} mmol·L⁻¹	5.7 ± 1.6
Adipose tissue	
Subcutaneous fat cm ³	2784.9 ± 946.9
Visceral fat cm ³	1179.7 ± 530.9
IHL %	5.2 ± 2.1

Data are presented as mean ± SD, unless otherwise stated. BMI: body mass index; AHI: apnoea-hypopnoea index; ODI: oxygen desaturation index; TST: total sleep time; Sa,O₂: arterial oxygen saturation; ESS: Epworth Sleepiness Scale; LFT: liver function test; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; IHL: intrahepatic lipid. [#]: normal reference range 30–130 U·L⁻¹; [†]: normal reference range 5–55 U·L⁻¹; [‡]: normal reference range <35 U·L⁻¹; [§]: normal reference range 62–80 g·L⁻¹; ^{||}: normal reference range 38–48 g·L⁻¹; ^{##}: normal reference range <18 μmol·L⁻¹; ^{††}: normal reference range 3.9–5.5 mmol·L⁻¹.

As with the adipose tissue data, there was also no change in most liver enzymes. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), bilirubin, total protein and albumin remained unchanged; however, alkaline phosphatase (ALP) was lower while on CPAP compared with sham. Mean values for all baseline liver function tests were within the normal range; however, half our patients had mildly elevated liver enzyme levels. No randomised patient commenced any new medication or changed existing medication doses during the trial.

DISCUSSION

This is the first sham-controlled randomised study to test the effect of CPAP treatment for OSA on abdominal adipose tissue

TABLE 2 End-of-treatment polysomnography data

Characteristics	CPAP	Sham	p-value
AHI events·h ⁻¹	6.9±11.1	38.7±28.7	<0.00001
ODI events·h ⁻¹	5±8.4	38.1±23.4	<0.00001
TST with Sa,O ₂ <90% %	0.8±2.1	10.1±12.0	0.0005
Minimum Sa,O ₂ %	89.5±7.1	79.5±8.9	0.0001
Treatment compliance h·night ⁻¹	4.6±2.0	3.4±2.2	0.003
ESS score	7.7±4.4	9.4±4.2	0.02

Data are presented as mean±SD, unless otherwise stated. CPAP: continuous positive airway pressure; AHI: apnoea-hypopnoea index; ODI: oxygen desaturation index; TST: total sleep time; Sa,O₂: arterial oxygen saturation; ESS: Epworth Sleepiness Scale.

distribution. The study failed to demonstrate any beneficial influence of 8 weeks of therapeutic CPAP compared with sham CPAP on the reduction of subcutaneous, visceral or hepatic fat in patients with moderate-to-severe obstructive sleep apnoea. In an analysis of secondary outcomes, while there was a significant reduction in ALP, no other significant differences were observed in liver enzymes or fasting glucose measurements.

CPAP has been shown to have varying effects on abdominal subcutaneous and visceral adipose tissue distribution. Studies by our group [7] and CHIN *et al.* [8] observed a reduction in visceral fat in patients with severe OSA after 3 and 6 months of CPAP use, respectively. In the former study, this difference was only demonstrated among regular CPAP users, who had an average compliance of 6 h per night, *versus* irregular CPAP users, with a mean of 2 h use per night. The latter study showed a reduction in visceral fat in patients who either maintained a stable body weight or who lost weight while on CPAP. A decrease in

subcutaneous fat, however, was only observed in patients who had a reduction in body weight. In the present study, although our patients maintained a stable body weight throughout the trial, there was no accompanying change in visceral fat with CPAP use relative to sham CPAP. In contrast to the studies with positive findings, a more recent nonrandomised observational study by MUNZER *et al.* [9] failed to demonstrate a reduction in subcutaneous or visceral fat after 8 months of CPAP use, where compliance with CPAP averaged 6 h per night. Similar results were also shown in an observational study by VGONTZAS *et al.* [10] in which OSA patients were treated with nasal CPAP for 3 months. Although the authors stated that there was a reduction in visceral fat in a subgroup analysis of patients with high CPAP adherence (>4 h use per night; n=10), the published p-value was 0.2 [10]. This discrepancy between studies could be related to a difference in measurement techniques (computed tomography (CT) *versus* MRI); however, both MRI- and CT-determined fat analysis are proven to be accurate and reproducible [23]. An alternative explanation may be related to differences in CPAP compliance; however, previously published negative studies show no difference even in compliant patients with >5 h [3] and 6 h [9] of use. Furthermore, we could not demonstrate any correlation between compliance with CPAP and changes in fat content.

All previously published studies investigating the effects of CPAP on visceral fat [3, 7–10] involved participants with a mean AHI in the severe range, with three reporting a minimum oxygen saturation between 62 and 72% [7, 8, 10]. Subjects in four out of five studies [3, 7, 9, 10] had a mean BMI >30 kg·m⁻² while the last study had an average BMI of 28 kg·m⁻². Length of treatment did not seem to affect the outcome as there are both uncontrolled positive studies of 3 months [7] and 6 months [8] duration and negative studies with 3 months [3] and 6 months [9] treatment duration.

TABLE 3 Effects of continuous positive airway pressure (CPAP) *versus* sham CPAP

	CPAP	Sham	Mean CPAP - sham difference (95% CI)	p-value
Adipose tissue				
Subcutaneous fat cm ³	2767.8±882.6	2796.4±960.2	-28.6 (-113.4–56.1)	0.49
Visceral fat cm ³	1222.5±526.1	1239.2±563.0	-16.8 (-79.9–46.4)	0.59
IHL %	5.4±1.8	5.6±1.7	-0.2 (-0.6–0.1)	0.21
LFT				
ALP [#] U·L ⁻¹	71.5±13.4	74.6±15.2	-3.1 (-5.6–-0.6)	0.02
AST [†] U·L ⁻¹	25.8±6.7	25.5±6.8	0.3 (-2.5–3.1)	0.82
ALT [†] U·L ⁻¹	39.8±16.2	38.4±16.5	1.3 (-3.7–6.4)	0.59
GGT [‡] U·L ⁻¹	40.2±21.5	42.5±26.8	-2.3 (-6.9–2.4)	0.33
Total protein [§] g·L ⁻¹	73.3±4.1	73.3±4.7	0 (-1–0.9)	0.94
Albumin [‡] g·L ⁻¹	45.3±2.1	45.3±2.2	0 (-0.6–0.5)	0.89
Bilirubin ^{##} μmol·L ⁻¹	10.8±5.9	11.1±7.1	-0.2 (-1.7–1.2)	0.75
Fasting glucose ^{††} mmol·L ⁻¹	5.5±1.1	5.6±1.0	-0.1 (-0.4–0.2)	0.46
BMI kg·m ⁻²	31.6±3.7	31.4±3.7	0.26 (-0.28–0.80)	0.32

Data are presented as mean±SD, unless otherwise stated. IHL: intrahepatic lipid; LFT: liver function test; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; BMI: body mass index. [#]: normal reference range 30–130 U·L⁻¹; [†]: normal reference range 5–55 U·L⁻¹; [‡]: normal reference range <35 U·L⁻¹; [§]: normal reference range 62–80 g·L⁻¹; [‡]: normal reference range 38–48 g·L⁻¹; ^{##}: normal reference range <18 μmol·L⁻¹; ^{††}: normal reference range 3.9–5.5 mmol·L⁻¹.

The influence of CPAP on liver function and liver fat are equally conflicting. A study by KOHLER *et al.* [12] did not show a beneficial effect of therapeutic CPAP on liver enzymes (AST and ALT) over a 1-month period; however, CHIN *et al.* [15] demonstrated reduced overnight mean increases in amino-transferase levels after the first night of nasal CPAP treatment. Our study confirmed the lack of reduction in AST, ALT and GGT over a 2-month period; however, we did not measure short-term (overnight) changes in enzymes. The significance of an isolated reduction in ALP is also unclear, particularly as all liver enzymes were either normal or only mildly elevated. CPAP did not significantly change either albumin, total protein or bilirubin, reflecting no biochemical effect on the synthetic and detoxification function of the liver. To our knowledge, no prior studies have reported on this.

Visceral fat accumulation is an independent predictor of all-cause mortality in males [24]. Post-prandial lipidaemia has also been shown to predict incident cardiovascular-related morbidity and mortality [25]. There is also data suggesting that both visceral [26, 27] and hepatic [28] fat accumulation are important factors involved in increasing post-prandial lipidaemia, particularly in glucose-intolerant or diabetic patients. In the context of OSA, although central obesity and fasting dyslipidaemia commonly occur [2], there are no robust data to suggest that either improves with CPAP treatment. However, we have recently shown that treatment of OSA with CPAP reduces post-prandial lipids after only 8 weeks [17]. In the present study, although we could not also demonstrate significant reductions in abdominal or liver fat over a similar treatment period, an uncontrolled study using CPAP that assessed liver fat over 2–3 yrs did demonstrate a reduction in liver fat [16]. Hence, it is possible that a longer treatment period may eventually also show a benefit [17, 28].

Fasting glucose measurements obtained at baseline and after 8 weeks of CPAP use also did not improve in our study. While these do not directly indicate alterations in insulin sensitivity, they do provide a guide for altered glucose homeostasis. Nevertheless, these results are consistent with prior large randomised, sham-controlled trials that showed no significant difference in haemoglobin A1c levels and measures of insulin sensitivity with CPAP use in both diabetics [29] and nondiabetics [30]. LAM *et al.* [3] showed a reduction in insulin sensitivity as measured by a short insulin tolerance test after 1 week of nasal CPAP use in nondiabetics; however, no significant change was noted at 12 weeks in the nonobese subgroup. All subjects in these studies had severe OSA and BMI $>35 \text{ kg}\cdot\text{m}^{-2}$. Uncontrolled studies using the gold-standard hyperinsulinaemic euglycaemic clamp measurement also showed contrasting outcomes with both positive [4] and negative [31] results after 3 months.

There are several potential limitations to our study. First, we did not repeat imaging studies after the washout period and, hence, assumed that any positive effect of CPAP on fat stores would revert to baseline levels after washout. However, the length of the washout period was long (4 weeks) and we could not detect any order effect. Secondly, our sham CPAP compliance was lower than therapeutic CPAP, although the difference was small (1 h) and it would have been preferable to have longer nightly CPAP with both devices. More accurate measures of insulin sensitivity could have been added to improve the completeness

of this component of the study; however, the protocol was considerably demanding and any additional measures may have resulted in increased study withdrawals. In addition, our study may not have been adequately powered to detect a difference in central adiposity. Nevertheless, our participant numbers are comparable with other studies ($n=16$, 22 and 29) that showed a reduction in visceral fat [7, 8, 10]. Finally, we only had one female participant and, hence, our conclusions may be more applicable to the male OSA population. Future studies on females, particularly post-menopausal females, with OSA are necessary since there appears to be a preferential increase in visceral fat in this group [32].

In summary, this is the first randomised, sham-controlled study investigating the influence of CPAP on central adiposity over an 8-week period. No differences in subcutaneous, visceral and hepatic fat were observed between the therapeutic and subtherapeutic CPAP groups. This suggests that 8 weeks of CPAP do not reduce central obesity in isolation and that additional concurrent measures, such as weight reduction, are probably required for improvement in cardiovascular and metabolic wellbeing. Further sham-controlled, randomised studies using CPAP for a longer duration may be necessary to detect a significant and clinically meaningful difference.

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CLINICAL TRIAL

This study is registered with the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au), with identifier number ACTRN12605000066684.

STATEMENT OF INTEREST

None declared.

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