CLINICAL STUDY

Effects of long-term continuous positive airway pressure on body composition and IGF1

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Abstract

Objective: To investigate the long-term effects of nasal continuous positive airway pressure (CPAP) ventilation in patients with obstructive sleep apnea syndrome (OSAS) on body composition (BC) and IGF1.

Design: Observational study.

Subjects: Seventy-eight (11 females and 67 males) OSAS patients who were compliant with CPAP (age 51 ± 1.1 years) participated in the study. We assessed body mass index (BMI), total body mass (TBM), total body fat (TBF; kg) and lean body mass (LBM; kg), abdominal subcutaneous (SC) and visceral (V) fat (cm^2), and waist circumference (WC; cm) by magnetic resonance imaging, and IGF1 (ng/ml) before and after 7.8 ± 1.3 months of CPAP use of an average of 5.9 ± 1.2 h.

Results: Women had a higher BMI, WC, TBM, TBF, and more SC fat. Men had a higher LBM and more V fat. CPAP increased WC ($+2.8 \pm 9.6$ cm, $P=0.02$) and LBM (2.2 ± 0.5 kg, $P=0.006$), but not IGF1. In men, CPAP increased BMI (0.5 ± 0.2 kg/m^2 , $P=0.02$), WC (1.7 ± 6.9 cm, $P=0.002$), TBM (1.7 ± 0.4 kg, $P=0.0001$), LBM (1.5 ± 0.4 kg, $P=0.0003$), SC fat (12.9 ± 5.1 cm^2 , $P=0.02$), and IGF1 (13.6 ± 4.2 ng/ml, $P=0.002$).

Compliance with CPAP increased LBM in men aged <60 years, but not in those aged >60 years, and IGF1 increased in men aged 40–60 years only.

Conclusions: Long-term CPAP increased LBM in both sexes and IGF1 in men, while fat mass remained unchanged, suggesting a sexually dimorphic response of IGF1 to CPAP. The role of the GH axis activity and age to this response is unclear. The metabolic consequences of changes in LBM are still to be determined. Future studies on the effects of CPAP on BC should include LBM as an outcome.

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Introduction

Obstructive sleep apnea syndrome (OSAS) is defined as repetitive decreases or cessations of airflow during sleep (1) and is associated with a wide array of cardiovascular (2) and metabolic risks (3, 4), and is therefore linked to an elevated cardiovascular morbidity and mortality. Interestingly, part of the risk profile appears to be shared by patients suffering from adult GH deficiency (GHD) syndrome (5). Additionally, OSAS has been associated with significant decreases in serum insulin-like growth factor 1 (IGF1) levels (6) and several metabolic disorders and alterations in body composition (BC) such as visceral (V) obesity (7). One possible explanation for the underlying mechanism in OSAS patients is the relative insensitivity of GHRH-induced GH response and a delayed IGF1 synthesis after GH injection in untreated

disease (8). The physiologic release of GH in healthy humans is stimulated by GHRH as a function of sleep depth (9). Thus, continuous positive airway pressure (CPAP) therapy may lead to a restoration of the GH axis activity to a more physiological pattern, and consecutively affect BC (6, 10–12). Adipose tissue has been associated with most of the metabolic burden associated with OSAS (7, 13, 14), and short-term CPAP reduces V fat (15). However, to date, no study has examined the effects of CPAP ventilation on lean body mass (LBM), despite potential beneficial effects of such changes on body function. During normal aging, mean GH secretion decreases mainly due to diminished amplitude of spontaneous GH peaks, whereas peak frequency usually remains unchanged (16). Aging is also associated with decreased serum IGF1 levels, which correlate well with GH secretory peaks in both women

and men (17–19). Several studies have demonstrated a significant relationship between a reduction of slow-wave sleep, decreased GH secretion rate, and peak amplitude in healthy aged individuals (16, 20), and that GH-releasing drugs can normalize sleep (21). Taken together, these data suggest that in addition to normal aging, sleep disturbances such as sleep apnea may substantially affect GH secretion and action, and thereby, have additional impact on the potential effects of CPAP treatment.

Several studies have reported a sexual dimorphic interaction of GH axis activation with sleep (22–24), and both GH administration to healthy old persons (25, 26) and GH therapy in patients with adult GHD syndrome (27) revealed that changes in LBM or adipose tissue depended on sex.

Based on the above findings, we hypothesized that long-term CPAP therapy would increase serum IGF1 levels in patients with OSAS, and that these changes would have been affected by the sex and the age of the patients. In addition, we examined the effects of CPAP on BC including total and regional fat tissues and LBM.

Patient selection

Inclusion and exclusion criteria

All women and men over the age of 18 years who were admitted as outpatients to the Kantonsspital, St Gallen, Interdisciplinary Center for Sleep Medicine between 01-01-2003 and 12-31-2005 for the evaluation of possible OSAS were invited to participate. Patients were usually referred by primary care physicians, pneumonologists, neurologists, and ear, nose and throat specialists. Patients with diabetes and hypercholesterolemia were included if they were on stable (oral) medication. There was no change in medication throughout the study period. Patients who participated in any other clinical study in the last 6 months prior to this protocol were excluded. In addition, we excluded women and men who were not able to complete German questionnaires without language support from their family members. Patients with pituitary disease, untreated thyroid disease, and medication known to interfere with the GH axis, and patients who had undergone elective surgery (such as gastric banding or hip replacement) within 6 months after enrollment were also not eligible. All patients were asked to maintain their diets and keep their level of physical activity constant during the study period. Written informed consent was obtained from all participants. The protocol had been approved by the St Gallen ethics committee.

Patients with possible OSAS were scheduled for an outpatient visit with one of the physicians in the sleep center. Prior to this appointment, all patients routinely completed a set of questionnaires. Covered domains

were socio-demographic data, assessment of smoking status and alcohol use, a validated German version of the Epworth sleepiness scale (ESS) (28) and the Stanford Sleep Disorders Questionnaire (29). During the appointment, a complete medical history of each patient was obtained to assess comorbidities (30) such as hypertension, coronary heart disease, diabetes, hypercholesterolemia, and current medication. Physical examination included inspection of the oropharynx, auscultation of lungs and heart, and abdominal palpation, followed by a brief neurological examination. Based on clinical judgement and the results of these screening questionnaires, patients who had a high likelihood to have OSAS were then scheduled for polysomnography (PSG). In the evening preceding PSG, patients were admitted to the sleep center. They were then asked to participate in the study. In the morning after the sleep study, after an overnight fast, blood samples for baseline measurements including IGF1 were drawn, independent of the result of the sleep study. Patients with OSAS who agreed to begin with CPAP were scheduled for baseline BC examination before or during a 2-week time period after initiation of CPAP therapy. Patients received an instruction in nasal CPAP ventilation followed by home CPAP. Monitoring of hours of operation of the CPAP machine was used as a measure of compliance. After at least 6 months of CPAP ventilation, all baseline examinations were repeated.

Materials and methods

Polysomnography

PSG data were recorded with a commercially available monitoring system (Mepal, MAP Medizin-Technologie, Martinsried, Germany). In the evening preceding the sleep study, each participant was offered a standardized meal at 1800 h. Lights were turned off at 2200 h. Minimum recording time was 6 h in order to meet diagnostic standards. All sleep studies were analyzed by an experienced physician. Respiration was traced with nasal pressure prongs and by piezoelectric thoracic and abdominal effort bands. Main outcome variables for the diagnosis of OSAS were apnea–hypopnea index (AHI) defined as the number of apneas (> 80% reduction of the flow signal) and hypopneas (> 50% reduction of the flow signal) per hour of sleep monitored and the desaturation index defined as the hourly rate of episodes of arterial oxygen desaturations > 3% of the stable baseline. The severity of sleep apnea was graded as mild (5–15 events per hour), moderate (16–30 events per hour), and severe (> 30 events per hour) (1). Depending on the results of this analysis, the patients were advised to commence with CPAP instruction followed by continuous home ventilation.

Nasal CPAP ventilation and assessment of compliance

Patients who were eligible for ventilation were instructed by trained nurses in the sleep center. Effectiveness of ventilation was monitored by changes in clinical symptoms, nocturnal oxygen saturation SaO₂ recordings, and an automated CPAP titration device (Sullivan Autoset T, ResMed Corp., San Diego, CA, USA). After a period of three overnight stays in the unit, patients were discharged for home ventilation. As an estimate of compliance with the CPAP machine over the entire study period, we recorded the mean hours of operation per night during 6 months of CPAP use. Ambulatory overnight oximetry (Konica–Minolta Pulsox 3, Dietikon, Switzerland) was used to measure changes of oxygen saturation while ventilated at home. In addition, one single experienced pulmonologist (O D S) reviewed all patient charts and oximetry results. Based on clinical follow-up information, overnight oximetry data, and chart information, patients were graded into two categories: non-compliant and well-compliant. We defined an average of ≥ 4 h of CPAP use per night as a minimum requirement to classify a patient as compliant (31).

Clinical assessment of BC

Weight was measured to the nearest 0.1 kg on a calibrated scale, and height was determined using a wall-mounted stadiometer. Body mass index (BMI) was calculated as the weight divided by the square of height (kg/m²).

Imaging studies for the assessment of BC

In each study participant, a dual energy X-ray absorptiometry (DEXA) determination of LBM and total and relative fat mass was performed. DEXA assessment was performed by one single experienced technician at the Kantonsspital, St Gallen, Bone Clinic with a commercially available scanner (Lunar DPX-NT, Lunar, General Electrics Healthcare, Munich, Germany). We used the scanner-installed software package (Encore Version 6.7, General Electrics Healthcare, Munich, Germany). The subjects were measured in light clothing. The scanner was calibrated every morning and three times a week; a bone phantom scan was used to determine scan quality. Internal calibration demonstrated a coefficient of variation of 0.16%. This method has been shown to precisely assess BC in several research settings (32, 33). Patients underwent magnetic resonance imaging (MRI) at the level of L4/5 for the assessment of abdominal subcutaneous (SC) and V fat areas. Abdominal MRI examinations were performed on a 1.5 T clinical imaging system (Symphony, Siemens, Munich, Germany, software version Syngo MR2004A4VA25A). Patients were scanned in the non-fasting state in supine position using

breath-holding technique and a T₁, flash-2D sequence set to optimize fat bright signal versus intermediate to dark signal adjacent tissues. Image matrix size was adapted to scan the greatest area possible. Slice thickness was 8 mm with an interslice gap of 100%. Images were analyzed on a PC using ImageJ, an NIH-developed analyzing software (Rasband, WS, ImageJ, USA National Institutes of Health, Bethesda, MD, USA, <http://rsb.info.nih.gov/ij/>, 1997–2006), as described previously (34).

Serum IGF1

After the sleep study and at follow-up, after an overnight fast, blood samples were drawn from an antecubital vein. After centrifugation, serum aliquots were stored at -80°C , and then sent to the Research Laboratory of the Division of Endocrinology at the University of Zürich for measurements of IGF1 levels. IGF-binding proteins were removed by acid Sep-Pak chromatography according to the instructions of the supplier (Waters Associates, Milford, MA, USA), and IGF1 was determined by RIA (35, 36). All samples were analyzed in a single batch by a technician who was not aware of any study data.

Data management and statistical analyses

Analyses were done with Stata (Stata Corp. 2005. Stata Statistical Software: Release 9, College Station, TX, USA). Summary statistics are described as means, medians, and S.E.M.s of the mean (S.E.M.). Baseline associations were calculated by simple linear regression. We first analyzed overall changes in the respective outcome parameters, followed by analyses for changes in non-compliant and compliant patients respectively. To examine possible sex and age effects, the compliant group was grouped by sex, and men were categorized based on the age at study entry (≤ 40 , 40–60, and > 60 years). Subsequent statistical analyses were performed in each age category separately. Differences between categorical variables within each age or sex group were assessed by χ^2 tests, and differences between continuous variables were calculated with Mann–Whitney tests or *t*-tests where appropriate. In addition, we applied ANOVA to detect possible differences between age categories at baseline. Contributions of baseline factors to changes of outcome variables of interest were entered into a stepwise linear regression model. A *P* value of <0.05 was considered as significant.

Results

Patients

Of 566 patients screened for participation, 101 patients were excluded due to language barriers. In total, 198 patients did not give informed consent for personal and work-related reasons (difficulty in leaving the job for

additional study appointments). Non-consenters and consenters did not differ by age, sex, BMI, smoking status, and socio-demographic data; however, consenters more often reported alcohol use (215/260, 82.7 vs 143/192, 74.5%, $P=0.03$) and had a slightly higher mean ESS score (11.3 ± 4.4 vs 10.6 ± 4.8 , $P=0.03$; data not shown). Using disease categories provided in the Charlson comorbidity index (30), we found an increased prevalence of chronic obstructive pulmonary disease in patients who were >60 years of age and no additional associations of age with other chronic diseases. Eight patients with diabetes on regular oral medication (sulfonylurea or metformin) were included. Patients were equally distributed between severity and age categories (χ^2 test $P=0.4$, data not shown). Here, we report data on changes in BC in 78 patients (11 women and 67 men) who were compliant and in 35 patients who were non-compliant with ventilation for a period of at least 6 months. For 73 of them (56 compliant), complete data sets of serum IGF1 were available (Fig. 1, Tables 1 and 2).

Baseline characteristics of study population

At baseline, compliant and non-compliant patients were not statistically different regarding age, waist

Figure 1 Study flow.

circumference (WC), BMI, total body mass (TBM), LBM, TFM, SC fat, V fat, and IGF1 levels, and compliance did not differ between age categories (data not shown). However, non-compliant patients had a lower AHI (difference -13.8 ± 5.7 , $P=0.02$). We studied 11 compliant women and five women who were not compliant with CPAP use. Using χ^2 analysis, women were evenly distributed among age and compliance groups ($P=0.41$; Table 1).

Compliant women and men did not differ by age, TBM, V fat, and baseline IGF1. In contrast women had a higher BMI ($+5.0 \pm 1.6$, $P=0.003$), a higher WC ($+8.6 \pm 2.8$ cm, $P=0.004$), less LBM (-12.3 ± 2.4 kg, $P=0.000001$), more total body fat (TBF) ($+21.4 \pm 3.3$ kg, $P=0.000001$), and more SC fat ($+188.9 \pm 26$ cm², $P=0.000001$).

Baseline serum IGF1

There was no sex difference between serum IGF1 levels at baseline and at follow-up. Thus, IGF1 data were pooled for analysis. IGF1 levels tended to be higher in non-compliant patients, but levels did not differ among age or compliance groups at baseline, and we found no correlation of age with IGF1 (data not shown; Table 1).

Baseline associations of IGF1 and LBM with OSAS severity

At baseline, we found no significant correlations of IGF1 with TBM, TBF, LBM, or AHI, neither overall nor across or within age categories. In addition, we found no associations of LBM with AHI or with IGF1 overall or across age categories (data not shown).

Effects of CPAP on BC and IGF1 levels in non-compliant patients

Patients underwent effective (nightly usage ≥ 4 h, mean 5.5 ± 1.2 h) CPAP ventilation therapy over a period of 7.8 ± 1.3 months. In contrast, non-compliant patients used the machine for an average of 2.4 ± 0.2 h per night ($P=0.00001$). In non-compliant patients, WC increased by $+2.7 \pm 7.3$ cm ($P=0.002$) and BMI by 0.5 ± 0.3 kg/m² ($P=0.004$). In addition, TBM increased ($+1.8 \pm 0.7$ kg, $P=0.01$), and LBM (1.3 ± 0.7 kg, $P=0.07$) and TFM ($+0.6 \pm 0.8$ kg, $P=0.5$) remained unchanged. Abdominal SC fat increased by 19 ± 9 cm² ($P=0.047$) and V fat by 12.3 ± 15.6 cm² ($P=0.4$). Serum IGF1 levels increased by $+3.2 \pm 8.4$ ng/ml ($P=0.7$; Table 2).

Effects of CPAP on BC and serum IGF1 levels in compliant patients by sex

After almost 8 months of CPAP use, we found overall increases in BMI (0.5 ± 0.2 kg/m², $P=0.006$) and WC ($+1.9 \pm 0.6$ cm, $P=0.002$), and of SC fat

Table 1 Baseline characteristics of 35 non-compliant and 78 compliant patients with continuous positive airway pressure (CPAP; means $\pm$ S.E.M).

	Non-compliant			Compliant women			Compliant men			Sex difference
	All (n=35)	Range		Mean (n=11)	Range		Mean (n=67)	Range		P
Age (years)	52.1	19.8	76.9	51.2	37.6	70.7	50.8	27.2	77.5	0.5
AHI ^a	32.5*	8.4	109.0	46.3	7.5	95.7	49.4	7.1	109.0	0.1
BMI ^b	30.4	23.8	39.7	30.9	26.2	43.4	30.0	22.1	41.7	0.004
Waist circumference (cm)	103.9	88.8	127.4	104.1	93.5	119.0	102.7	87.3	120.6	0.004
Total body mass (kg) by DEXA ^c	89.1	71.7	126.2	90.5	71.7	114.6	89.4	70.8	130.8	0.0003
Lean body mass (kg) by DEXA	55.6	38.5	75.9	56.7	39.7	50.7	58.3	45.4	75.2	0.000001
Total fat mass (kg) by DEXA	30.5	20.9	50.4	49.5	29.4	61.5	28.1	15.5	55.6	0.000001
Abdominal subcutaneous fat (cm ²)	243.3	137.9	405.3	415	268.6	546.3	226	124.0	516.0	0.000001
Abdominal visceral fat by MRI (cm ²)	211.3	72.1	367.4	163	69.3	273.1	210	60.2	443.3	0.1
IGF1 (ng/ml)	130.5	67.0	300.0	124.0	56.0	235.0	115.1	44.0	241.0	0.6
Average CPAP use per night	2.5 [†]	0.2	3.9	6.0	4.0	8.0	5.9	4.0	8.8	0.1

* $P=0.02$, $^{\dagger}P=0.0001$. Bold indicates $P<0.05$.^aApnea-hypopnea index.^bBody mass index.^cDual energy X-ray absorptiometry.

($+15 \pm 5$ cm², $P=0.008$). In addition, TBM ($+1.7 \pm 0.4$ kg, $P=0.00001$), LBM ($+1.6 \pm 2.5$ kg, $P=0.00001$), and serum IGF1 ($+10.6 \pm 4$ ng/ml, $P=0.01$) increased significantly, and there were no changes in TBF, V fat, or BMI respectively. In compliant women, CPAP increased WC ($+2.8 \pm 9.6$ cm, $P=0.02$) and LBM ($+2.2 \pm 0.5$ kg, $P=0.006$) only. In compliant men, CPAP affected BMI (0.5 ± 0.2 kg/m², $P=0.02$), WC (1.7 ± 0.7 cm, $P=0.02$), TBM (1.7 ± 0.4 kg, $P=0.001$), and LBM (1.5 ± 0.4 kg, $P=0.003$). Furthermore, SC fat ($+12.9 \pm 5.1$ cm², $P=0.02$) and IGF1 ($+13.6 \pm 4.2$ ng/ml, $P=0.002$) increased after CPAP (Table 2).

Effects of nCPAP on BC and serum IGF1 levels in compliant men by age

In men aged <40 years, BMI ($+1.0 \pm 0.4$ kg/m², $P=0.02$), TBM ($+3.4 \pm 1.2$ kg, $P=0.02$), and LBM ($+3.0 \pm 1.0$ kg, $P=0.02$) but not IGF1 ($+23.0 \pm 12.3$ ng/ml, $P=0.1$) increased significantly, and there was a trend toward an increase in WC ($P=0.07$). In patients aged 40–60 years, TBM ($+1.0 \pm 0.5$ kg, $P=0.03$), LBM ($+1.0 \pm 0.4$ kg, $P=0.02$), and IGF1 ($+12.6 \pm 5.3$ ng/ml, $P=0.02$) increased significantly. In men aged 60 years and older, we found a significant increase in TBM ($+2.3 \pm 0.8$ kg, $P=0.01$) and a trend toward an increase in BMI, but no changes in other measures of BC or IGF1 levels.

Stepwise multiple linear regression of changes in IGF1 and LBM in compliant men

Using stepwise multiple regression analysis in men with changes in IGF1 (Model 1) or changes in LBM (Model 2) as dependent variables and changes in BC, age at baseline, and hours of ventilation as independent

variables, we found no statistically significant model. However, hours of ventilation best predicted changes in LBM and IGF1 respectively.

Discussion

In this non-randomized prospective trial in patients diagnosed with sleep apnea syndrome, we found that compliance with CPAP over a period of 8 months significantly increased LBM in woman and men, and that IGF1 increased in men only. Overall, we observed small increases in WC and SC fat in all groups, despite compliance with ventilation. In contrast, in non-compliant patients, LBM remained unchanged. Serum IGF1 levels increased in compliant men, but not in women or in non-compliant patients.

Several groups have reported associations of OSAS with fat tissue as a dependent (7, 14, 37) or an independent (38, 39) metabolic risk factor. A previous study reported reductions of V fat areas after 3 months of CPAP ventilation in a cohort of men aged 50 years with a very high AHI (15). We found small increases in abdominal SC fat and WC but not in V fat using a different imaging method in a mixed patient population with a wider age range treated over a longer time period. Nevertheless, increases in WC of 1.9 cm overall in association with respective changes in SC fat warrant further discussion.

Anthropometric measures of obesity often predict the prevalence of sleep apnea. Especially, WC is a reliable predictor of OSAS severity (40, 41) and a clinically well-known parameter to assess the metabolic syndrome (42). Therefore, treatment with CPAP could be associated with a reduction in WC. Contrary to such an expectation, we found significant increases in SC fat and WC and very small increases in TBF, while TBM remained almost constant over the 8 months of

Table 2 Overall changes (means $\pm$ S.E.M.) in body composition and serum insulin-like growth factor 1 (IGF1) levels after 6 months of compliant with continuous positive airway pressure (CPAP) ventilation in non-compliant patients and in compliant women and men with obstructive sleep apnea syndrome.

	Non-compliant				Compliant				Compliant women				Compliant men			
	n=35	S.E.M.	CI	P*	n=78	S.E.M.	CI	P*	n=11	S.E.M.	CI	P*	n=67	S.E.M.	CI	P*
BMI ^a	0.5	0.3	0.1	1.0	0.04	0.51	0.18	0.86	0.006	0.6	0.4	-0.2	1.5	0.2	0.1	0.9
Waist circumference (cm)	2.7	7.3	1.2	4.3	0.002	1.90	0.59	0.72	3.09	2.8	9.6	6.1	50.1	1.7	3.0	31.0
Total body mass (kg) by DEXA ^b	1.8	0.7	0.4	3.2	0.013	1.70	0.38	0.95	2.50	1.7	1.3	-1.4	4.8	1.7	0.9	2.5
Lean body mass (kg) by DEXA	1.3	0.7	-0.1	2.8	0.1	1.59	0.34	0.91	2.28	2.2	0.5	0.9	3.6	1.5	0.7	2.3
Total fat mass (kg) by DEXA	0.6	0.8	-0.1	2.2	0.5	0.2	0.3	-	0.9	-0.4	1.0	-2.8	2.0	0.3	-0.5	1.0
Abdominal subcutaneous fat (cm ²)	19.3	9.0	8.3	41.5	0.047	15.05	5.45	4.07	26.03	24.4	2.0	-20.8	69.6	12.9	25.3	23.4
Abdominal visceral fat by MRI (cm ²)	12.3	15.2	-21.1	45.7	0.4	9.2	8.0	-	25.4	16	1.3	-16.0	47.1	7.8	-11.2	26.8
IGF1 (ng/ml)	3.2	8.4	-14.8	21.2	0.7	10.6	4.1	2.4	18.8	-4.8	12.2	-33.1	23.3	13.6	5.1	22.0

*P for paired t-test. Bold indicates $P < 0.05$.^aBody mass index.^bDual energy X-ray absorptiometry.

ventilation. It is currently unclear if such changes impact upon the metabolic burden of OSAS patients, since several alterations associated with this disease are independent of fat tissues (12, 39). Apparently, the effects of CPAP on BC in OSAS are distinct from the effects of GH in GHD, where TBF is usually decreased, in addition to an increase in IGF1 and LBM.

Although fat tissue is of clinical importance in patients with sleep apnea, the effects of CPAP use on LBM have not been examined. In man, the impact of muscle mass and exercise on glucose uptake has been known for a long time (43), and numerous studies have confirmed the roles of skeletal muscle, its oxidative capacity, and energy expenditure (EE) on insulin sensitivity, strongly supporting the role of LBM in glucose metabolism. We have recently reported that CPAP ventilation significantly improved maximal exercise capacity and heart rate recovery in our patients (44), a finding that is in line with an earlier report on the effects of 4 weeks of CPAP treatment on endurance exercise performance (45). Taken together, such data suggest that both the increases in LBM and the improvement in VO_2 max reflect changes with the potential to increase exercise performance and to decrease the metabolic and cardiovascular risks of OSAS patients.

The mechanisms by which CPAP affects LBM are currently unknown. First, ventilated patients report less daytime sleepiness and more vitality (46), which may impact upon their level of physical activity and protect against the disease (47). In addition, physical activity augments GH axis activity in young and to a lesser extent in older persons (48, 49). Thus, exercise-induced increases in GH axis activity may have additional beneficial effects on LBM. In order to control for such an effect, we have asked our patients to not change their levels of exercise or their diets during the study period. However, our protocol did not record daily activities or diets, which seemed not to be feasible for such a long study period and the clinical design. Another factor contributing to changes in BC after CPAP use is EE. Several studies have demonstrated that resting EE is closely associated with OSAS and disease severity respectively (50, 51), and one previous report demonstrated that EE is increased during sleep in OSAS patients, and that CPAP decreases EE and by this mechanism induces body weight (52) and possibly also LBM.

In contrast to healthy young or older individuals, we found no significant correlations of IGF1 with measures of body fat (53) or age (19) in our patients at baseline. These findings suggest a disruption of the GH-IGF1 axis activity based on a change in regular sleep pattern with this disease (54), or that this could be an effect of the small sample size. Although 1 month of sham ventilation induced elevated IGF1 levels (55), normalization of sleep pattern induced a restoration of the GH axis activity. Three days of CPAP ventilation induced increases in GH secretion (10), and IGF1 levels

increased after 3 months of CPAP use (6). The latter group also found an age-dependent response of IGF1 to CPAP (6). Given the fact that normal aging is associated with a decrease in GH secretion (17), the above and our results suggest that the IGF1 response to 8 months of CPAP use may also be attenuated with advanced age. Similarly, we observed increases in IGF1 and LBM in middle-aged men but not in older or younger men. The latter finding can be explained by the small number of men studied. Nevertheless, such a pattern is congruent with a reduced response in LBM after the administration of GH to healthy older individuals (56) when compared with young patients with adult GHD syndrome (57–59).

Serum IGF1 concentrations after CPAP remained unchanged in our women. While these results should be interpreted with some caution due to the small sample size, current findings suggest that GHRH impairs sleep in women (22), and that the GH secretagogue ghrelin improves sleep in young and older men (60, 61) but not in women, suggesting a sexually dimorphic response of sleep to hormone administration. While CPAP is known to decrease ghrelin in men (62), data on women are missing. Otherwise, normalization of sleep pattern by CPAP might impact upon GH secretion and IGF1 synthesis in women and men differently. Based on these observations, our data suggest that long-term CPAP activates the GH axis, and that such changes are gender dependent.

Our study has several limitations. First, our design did not allow for a true control group. Thus, the effects of CPAP on groups are comparable only to a limited extent, and the current design allows hypothesis generation rather than hypothesis testing. This is especially true for the hypothesis of a possible dose–response relationship between CPAP and changes in BC, since the primary treatment goal of CPAP is elimination of obstructive events. Nevertheless, our regression model suggested that the duration of ventilation is a potential predictor for changes in LBM. In addition, we did not record the menopausal status of our women. Postmenopausal status is associated with an increased prevalence of sleep-disordered breathing (63, 64), and circulating progesterone protects against dilation of the upper airway muscles (65). In our study, women were evenly distributed among age and compliance groups, which attenuated the effect of menopause on our results.

We were also not able to randomize patients into a placebo ventilation group, although such studies have demonstrated an improvement in function (66), endocrine axis activity (55), or control of diabetes (67). Given the study duration of at least 6 months and the high risk for cardiac events in untreated patients (68), it seemed unethical to not offer treatment for such a long period. Secondly, we were able to recruit only small numbers of patients into the respective study groups. This might have affected our results. In addition, we were not able to demonstrate direct effects of CPAP ventilation on GH axis activity by frequent GH

sampling. Given the diminished GH response to stimulation in untreated patients with OSAS (8), it seems comprehensible that ventilation would induce a more ordered 24-h GH secretion. Our study was primarily focused on changes in BC. We thus did not record changes in other clinically important measures such as blood pressure, which has been shown to decrease in several trials (69–71). Finally, using a pre-post design, we were able to detect changes within specific age categories only. This approach does not allow for inferring a direct effect of age on the main outcome variable. To approach such an effect, a regression model with a larger number of data points would have been more appropriate. However, we think that our study allows the hypothesis that CPAP treatment affects LBM by several mechanisms, one being the restoration of the GH axis activity and, furthermore, that this effect might be influenced by the age of the patients.

In summary, the results of our study suggest that an average of 8 months of CPAP ventilation in patients with newly diagnosed OSAS significantly increases LBM in women and men. The observed changes in IGF1 suggest a sexual dimorphic response pattern of GH secretion after CPAP therapy. Future studies on BC in OSAS patients should include LBM as a clinical outcome parameter. Given the increasing prevalence of sleep-disordered breathing in a growing number of older persons (64, 72) and the small number of women studied with this disease, additional trials on the effects of CPAP ventilation in women or in persons with advanced age are warranted.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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