Obstructive sleep apnoea and metabolic impairment in severe obesity

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ABSTRACT: **Obstructive sleep apnoea (OSA) seems to worsen metabolism. This effect has not been evaluated in morbid obesity (MO). We hypothesised that the metabolic profile is more impaired in MO patients with OSA than in those without, and investigated whether any specific metabolic dysfunction is related to OSA in MO.**

A prospective multicentre cross-sectional study was conducted in consecutive subjects before bariatric surgery. OSA was defined as apnoea/hypopnoea index (AHI) $\geqslant$ 15 by overnight polysomnography. Anthropometrical, blood pressure (BP) and fasting blood measurements were obtained the morning after. Metabolic syndrome (MetS) was defined according to National Cholesterol Education Program Adult Treatment Panel III modified criteria.

159 patients were studied: 72% were female and 72% had OSA. MetS prevalence was 70% in OSA *versus* 36% in non-OSA (p<0.001). As AHI severity increased, metabolic parameters progressively worsened, even in those without type 2 diabetes (DM2). AHI was independently associated with systolic and diastolic BP, triglycerides and the percentage of glycosylated haemoglobin (HbA1c) in the total sample, and with systolic BP, high-density lipoprotein cholesterol and HbA1c in those samples without DM2. OSA increased the adjusted odds ratio of having MetS by 2.8 (95% CI 1.3–6.2; p=0.009).

In MO, OSA is associated with major metabolic impairment caused by higher BP and poorer lipid and glucose control, independent of central obesity or DM2.

KEYWORDS: Metabolic index, metabolic syndrome, morbid obesity, obstructive sleep apnoea

Metabolic abnormalities, whether assessed as metabolic syndrome (MetS) [1] or as their single components (central obesity, impaired glucose metabolism, hypertension, hypertriglyceridaemia and lower high-density lipoprotein cholesterol (cHDL)) have been shown to increase cardiovascular (CV) morbidity and mortality [2–5]. Central obesity seems to play a crucial role in the origin of metabolic disruption, but many other mechanisms have also been considered responsible [6]. Recent reports have suggested that obstructive sleep apnoea (OSA) may worsen the effect of obesity on cardiometabolic risk and that it could represent an additional burden on the metabolic dysfunction associated with obesity [7, 8].

The mechanisms through which OSA may worsen metabolism are complex. It may trigger several pathological mediating pathways (sympathetic activation, neurohumoral changes, glucose homeostasis disruption, inflammation and oxidative stress) through chronic intermittent hypoxia (CIH),

and these may ultimately cause deterioration in the metabolic function [9, 10]. Animal studies have shown reduced insulin resistance and plasma lipids, as well as increased blood pressure (BP), after exposure of lean and obese animals to CIH [11], but data in humans are more scarce.

Obesity is the main confounding factor in the investigation of the association between OSA and metabolic dysfunction [12]. Most previous reports have excluded subjects with morbid obesity (MO), possibly because the effect of OSA is expected to be little or absent in this subpopulation, due to extreme obesity. Conversely, MO patients could have a higher CV risk compared with non-MO subjects, because of the high prevalence of both metabolic dysfunction [13, 14] and OSA [15, 16]. Therefore, investigating this association in MO should contribute to a better understanding of the relative interaction between OSA, MO and metabolic dysfunction.

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We hypothesised that, in a cohort of consecutive MO patients enrolled in a bariatric surgery programme, the metabolic profile is more impaired in those with OSA than in those with no OSA. Furthermore, we attempted to detect whether there is any specific metabolic dysfunction pattern related to OSA, and whether the overall CV risk increases in parallel with OSA severity in the morbidly obese.

METHODS

Subjects and protocol

Consecutive patients prospectively included in the obesity surgery programme were studied in the corresponding Sleep Units from January 2009 through February 2010. The study protocol was approved by the local ethical committee of each hospital (PR052/08, 07/064/797, PI080277). All participants gave their informed written consent.

Inclusion criteria were the same as those for the obesity surgery programme: aged 18–60 yrs and a body mass index (BMI) of $\geqslant 40$ kg·m^{-2} or $\geqslant 35$ kg·m^{-2} with comorbidity related to obesity (resistant hypertension, established heart disease, severe degenerative osteoarthritis, respiratory failure). The following patients were excluded: those with known OSA and prior continuous positive airway pressure (CPAP) treatment, unstable CV conditions, acute or chronic inflammatory diseases during the previous 6 months, chronic immunosuppressant therapy, severe cognitive or psychiatric disorders, chronic obstructive pulmonary disease (COPD) [17], pregnancy or past or current history of alcohol abuse, and those who refused to give their consent.

Each participant completed a detailed questionnaire on medical history, cardiovascular risk factors and current medication. Exercise level and sleep duration were recorded by a self-administered International Physical Activity Questionnaire [18] and a sleep diary for 15 consecutive nights. Anthropometric characteristics included BMI, neck circumference (at the level of the laryngeal prominence), waist circumference (WC; measured midway between the lower rib and the iliac crest), waist/hip ratio and percentage of body fat mass measured by electrical bioimpedance (BIA 101; Akern Bioresearch, Florence, Italy). Clinical BP was measured by a standard mercury sphygmo-manometer while the subject was seated at rest, and taken as the mean value of at least two measurements separated by 5 min; an additional measurement was made if there was a difference of >5 mmHg between the two [19]. Respiratory functional assessment included forced spirometry and arterial blood gas analysis, taken with the subject seated breathing room air.

Sleep study

OSA was determined by a full overnight polysomnography (PSG). PSG interpretation was assessed according to standard criteria [20], as described in E1 of the online supplementary material.

As few morbidly obese patients were expected to show an apnoea/hyponoea index (AHI) <5 events·h^{-1} [16], an AHI cut-off of 15 events·h^{-1} was chosen to define the presence of OSA by the study design. The degree of nocturnal desaturation was assessed by the mean percentage of sleep time with arterial oxygen saturation measured by pulse oximetry <90% (time S_{p,O_2} <90%). Excessive daytime sleepiness (EDS), quantified by the Epworth sleepiness scale (ESS), was defined as an ESS score $\geqslant 10$.

Blood measurements and MetS definition

The morning after PSG, a venous blood sample was obtained from all patients in fasting conditions and an oral glucose tolerance test (OGTT) was performed, except in those with previously known type 2 diabetes (DM2). Fasting blood glucose (FBG), percentage of glycosylated haemoglobin (HbA1c), total cholesterol, triglycerides, cHDL, low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol levels were determined with standard laboratory methods. Patients were classified according to the OGTT: normal glucose tolerance (post-load glucose <7.8 mmol·L^{-1}), impaired glucose tolerance (post-load glucose 7.8–11.1 mmol·L^{-1}) and established DM2 (post-load glucose $\geqslant 11.1$ mmol·L^{-1}) [21].

MetS was defined in accordance with the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria [1] as the presence of three or more of the following: WC $\geqslant 88$ cm in females, $\geqslant 102$ cm in males; high BP as systolic $\geqslant 130$ and/or diastolic $\geqslant 85$ mmHg or antihypertensive treatment; high FBG as $\geqslant 5.6$ mmol·L^{-1} or anti-diabetic treatment; high triglycerides as $\geqslant 1.7$ mmol·L^{-1} or lipid-lowering treatment; reduced cHDL as <1.3 mmol·L^{-1} in males and <1 mmol·L^{-1} in females or lipid-lowering treatment. Metabolic index was established as the number of individual MetS components for each patient.

Cardiovascular risk assessment in the AHI categories

The Framingham cardiac risk score was applied to estimate the CV risk [22] in the different AHI categories. The scores consider sex, age, total cholesterol, cHDL, systolic BP and smoking, and they were used to predict the 10-yr risk of coronary events in the AHI categories.

Sample size

Power calculations indicated that 39 subjects were needed in each group to detect a difference of at least 0.32 in MetS prevalence between OSA and non-OSA, based on prior studies reporting high prevalence of MetS and OSA in MO [23] and similar MetS prevalence difference depending on OSA status [24], assuming an α risk of 0.05 and a β risk of 0.20.

Statistical methods

Data were expressed as mean±SD, median (interquartile range) or percentage for parametric, nonparametrical and categorical data, respectively. The bivariate comparisons were evaluated using the Chi-squared (categorical), t- (parametric) or Mann–Whitney (nonparametric) unpaired tests.

Multiple comparisons were evaluated using the Chi-squared test (categorical), ANOVA with Scheffe *post hoc* analysis (parametric) and the Mann–Whitney test, applying the Bonferroni method when significant differences were found by the Kruskal–Wallis test (nonparametric). The adjusted linear regression model studied the association between AHI and individual measures of metabolic dysfunction. Logistic regression assessed the relationship between MetS and OSA (AHI $\geqslant 15$). The association results were summarised using unadjusted and adjusted odds ratios and β coefficients with their 95% confidence intervals. A p-value of <0.05 was considered statistically

significant. SPSS version 15 software (SPSS Inc., Chicago, IL, USA) was used for all the analyses.

RESULTS

A total of 174 consecutive patients were evaluated. 15 patients were excluded due to inflammatory disease (n=8), COPD (n=3), pregnancy (n=1), immunosuppressant therapy (n=1) and refusal to participate (n=2). Thus, we studied 159 patients: 44 non-OSA and 115 OSA. The mean age was 43 ± 10 yrs, the mean BMI was 46.1 ± 5.8 kg·m^{-2} and 72% of them were female.

OSA versus non-OSA group

OSA subjects were older, had a larger neck and WC, and had a nonsignificant trend toward a higher BMI (table 1). No differences were observed in sex predominance and OGTT categories. When stratifying by sex, the level of physical activity did not differ between OSA and non-OSA subjects (data not shown). In terms of comorbidities, hypertension and diabetes were reported more frequently by OSA than by non-OSA patients (hypertension 48% versus 21%, p=0.002, diabetes 24% versus 11%, p=0.057, respectively). With regard to medication, angiotensin receptor antagonists and oral hypoglycaemic

TABLE 1	General and sleep characteristics of the study cohort			
	Total	**Non-OSA**	**OSA**	**p-value**
Subjects n	159	44	115	
Age yrs	43.0 ± 10.0	39.3 ± 10.6	44.9 ± 9.6	0.002
BMI kg·m^{-2}	46.1 ± 5.8	44.7 ± 4.7	46.7 ± 6.1	0.052
Sex females	72.3	75.0	71.3	0.641
Current smoking	20.0	25.0	18.3	0.635
Alcohol consumption	5.7	6.8	5.2	0.696
Body fat %	48.4 ± 8.2	47.5 ± 8.4	48.8 ± 8.1	0.396
WC cm	129.8 ± 15.7	123.2 ± 14.0	132.4 ± 15.6	0.001
Waist/hip ratio	0.93 ± 0.10	0.88 ± 0.08	0.95 ± 0.10	0.001
Neck circumference cm[#]	42.0 (40.0–46.0)	41.0 (39.0–43.0)	43.0 (40.0–48.0)	0.001
Obesity duration yrs	25.4 ± 10.4	24.5 ± 10.0	25.7 ± 10.4	0.529
Physical activity MET·min-week^{-1}	2343.8 ± 2421.9	2280.4 ± 2382.2	2368.5 ± 2447.5	0.840
Glucose tolerance assessment[¶]				
Diabetes	41 (25.8)	8 (18.2)	33 (28.7)	0.284
IGT	25 (15.7)	6 (13.6)	19 (16.5)	
Normal	84 (52.8)	27 (61.4)	57 (49.6)	
Missing data	9 (5.7)	3 (6.8)	6 (5.2)	
Arterial blood gases				
P_{a,O_2} mmHg	84.8 ± 11.0	88.1 ± 10.4	83.5 ± 11.1	0.020
P_{a,CO_2} mmHg	40.0 ± 5.0	39.0 ± 4.1	40.4 ± 5.3	0.119
Spirometry				
FVC % pred	98.5 ± 16.0	96.8 ± 15.3	99.1 ± 16.3	0.452
FEV1 % pred	99.3 ± 15.4	97.0 ± 13.5	100.1 ± 16.1	0.282
FEV1/FVC%	80.9 ± 7.6	81.5 ± 7.9	80.7 ± 7.5	0.592
TST min	351.6 ± 65.9	358.2 ± 54.3	349.1 ± 69.8	0.437
Sleep efficiency %	75.9 ± 14.0	77.5 ± 12.3	75.3 ± 14.6	0.376
Stage I[#] %	6.8 (4.0–12.0)	7.2 (4.1–10.2)	6.7 (3.6–13.4)	0.928
Stage II[#] %	57.4 (49.6–68.2)	57.3 (49.8–65.5)	57.5 (49.3–68.2)	0.847
SWS[¶] %	20.0 (12.7–28.7)	22.1 (12.1–31.3)	19.5 (12.7–27.9)	0.317
Stage REM[#] %	14.3 (9.0–18.3)	14.6 (9.6–18.7)	14.0 (9.0–18.3)	0.952
Arousal index[#] n·h^{-1}	23.1 (15.0–41.5)	11.4 (8.9–18.0)	28.9 (18.4–47.1)	0.001
AHI[#] events·h^{-1}	32.4 (14.6–53.0)	11.6 (8.0–13.9)	43.2 (29.5–64.2)	0.001
Time S_{p,O_2} <90% TST[#] %	4.65 (0.5–19.3)	0.2 (0.0–1.2)	7.5 (2.1–29.4)	0.001
Self-reported sleep duration h·night^{-1}	7.47 ± 1.63	6.75 ± 1.74	7.74 ± 1.51	0.001
ESS score	8.0 ± 5.0	7.0 ± 4.0	8.0 ± 5.0	0.427
Subjects with ESS >10	26.4	22.7	27.8	0.514

Unless otherwise stated, data are presented as mean±SD, median (range) or n (%); data are presented as % for normal, non-normal ([#]) distributed and categorical data. Unpaired t-tests, Mann–Whitney and Chi-squared tests were performed on normally, skewed and categorical data, respectively. OSA: obstructive sleep apnoea; BMI: body mass index; WC: waist circumference; MET: metabolic equivalent task; IGT: impaired glucose tolerance; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; TST: total sleep time; SWS: slow-wave sleep; REM: rapid eye movement; AHI: apnoea/hypopnoea index; time S_{p,O_2} <90% TST: mean percentage of sleep time with arterial oxygen saturation measured by pulse oximetry <90%; EES: Epworth sleepiness scale. [¶]: data according to oral glucose test tolerance results in 117 patients and previous known diabetes in 33 patients.

agents were prescribed more in the OSA than in the non-OSA group (12% *versus* 0%, p=0.015, and 22% *versus* 7%, p=0.027, respectively).

Table 1 also shows the main sleep characteristics of the total sample, and according to the presence/absence of OSA. Self-reported sleep duration was longer in OSA than in non-OSA but the PSG total sleep time was similar in both groups. OSA subjects had worse sleep parameters in terms of nocturnal oxygen desaturation levels and arousal index, but with no differences in the sleep stage percentages or in the level of EDS, according to the ESS.

Metabolic variables according to AHI categories

OSA patients had a more impaired metabolic profile than non-OSA patients (table 2). They had higher levels of systolic and diastolic BP, FBG, HbA1c and triglycerides, and lower levels of cHDL. Moreover, as the severity of OSA increased according to AHI categories, a progressive significant worsening of individual metabolic parameters was found and the metabolic index deteriorated. The Framingham cardiac risk score also increased with the OSA categories (fig. 1).

The overall prevalence of MetS was 60%, but was twice as high in the OSA group compared with the non-OSA group (70% *versus* 36%, p<0.001). The prevalence of each individual MetS component was also higher in the OSA group but did not reach significance for reduced cHDL (41% *versus* 27%, p=0.112) (fig. 2).

We also examined the relationship between individual metabolic parameters and OSA markers by linear regression analysis (table 3). In the unadjusted model, all metabolic parameters were associated with AHI and time S_{P,O_2} <90% (data not shown). After adjusting for age, sex, smoking and BMI, the association with AHI remained significant for systolic BP, diastolic BP, triglycerides and Hb1Ac, but was lost for FBG and cHDL. When adding WC to the adjustment, the associations did not change. Associations with oxygen desaturation index $\geqslant$ 3% (ODI3%) followed a similar pattern to those with AHI (data not shown). In contrast, when the same analysis was performed with time S_{P,O_2} <90%, only Hb1Ac and triglycerides were significant; but after adjusting for WC, the association only remained significant for HbA1c.

Table 4 summarises the results of binary logistic regression to assess the association of OSA and MetS in MO patients. The

TABLE 2	Metabolic syndrome components and others metabolic variables according to obstructive sleep apnoea (OSA) categories				
	Non-OSA	**OSA**			**p-value[#]**
	AHI <15	**AHI 15–30**	**AHI 30–50**	**AHI >50**	
Subjects n	44	29	42	43	
AHI[¶] events·h⁻¹	11.6 (8.0–17.3)	23.2 (19.8–27.5)	37.8 (33.3–46.4)	78.7 (58.6–114.6)	
WC cm	123.2±14.1	126.3±12.1	130.9±14.2	137.9±17.5	<0.001[+,§§]
SBP mmHg	126.8±17.3	131.6±14.7	140.0±17.0	142.1±15.5	<0.001[+,++]
DBP[¶] mmHg	78.0 (60.0–87.5)	83.0 (80.0–90.0)	84.0 (80.0–90.0)	88.0 (83.0–93.0)	0.001[+]
cHDL mmol·L⁻¹	1.32±0.27	1.34±0.59	1.20±0.34	1.07±0.26	0.004[+,ƒƒ]
TG[¶] mmol·L⁻¹	1.10 (0.90–1.53)	1.21 (0.90–1.90)	1.30 (1.00–1.90)	1.60 (1.20–2.30)	0.004[+]
FBG[¶] mmol·L⁻¹	5.45 (5.00–6.03)	5.50 (5.10–6.70)	5.80 (5.30–6.20)	6.40 (5.40–7.70)	0.007[+]
MetS	36.4	62.1	69.8	74.4	0.001
Metabolic index number of components	2.34±1.03	2.72±1.00	3.14±1.13	3.53±1.16	<0.001[+,++,§§]
Total cholesterol mmol·L⁻¹	5.01±0.82	4.97±1.02	4.82±0.78	4.93±0.90	0.796
cLDL[¶] mmol·L⁻¹	1.39 (1.15–2.71)	1.22 (1.01–1.57)	1.19 (1.05–1.66)	1.16 (0.97–1.45)	0.030[+]
cVLDL[¶] mmol·L⁻¹	0.39 (0.27–0.66)	0.40 (0.22–0.71)	0.56 (0.29–0.67)	0.65 (0.43–1.04)	0.022[+]
HbA1c[¶]	5.4 (5.0–5.8)	5.7 (5.3–6.2)	5.5 (5.3–6.0)	5.9 (5.5–7.1)	<0.001[+,ƒƒƒ]
IGT + DM2	34.1	46.2	39.5	59.0	0.137

Unless otherwise stated, data are presented as mean±SD or median (interquartile range); data are presented as % for normal, non-normal distributed ([¶]) and categorical data. AHI: apnoea/hypopnoea index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; cHDL: high-density lipoprotein cholesterol; TG: triglycerides; FBG: fasting blood glucose; MetS: metabolic syndrome; cLDL: low-density lipoprotein cholesterol; cVLDL: very low-density lipoprotein cholesterol; HbA1c: glycosylated haemoglobin; IGT: impaired glucose tolerance (metabolic syndrome definition based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria [1] and metabolic index, calculated as the sum of components of metabolic syndrome presented in each subject divided by the number of subjects in each AHI category); DM2: type 2 diabetes. [#]: comparisons among OSA categories. Chi-squared test was used for categorical variables. ANOVA with Scheffe *post hoc* analysis was used for normal continuous variables. Kruskal–Wallis test was used for non-normal distributed continuous variables using Mann–Whitney test and Bonferroni correction to compare between groups. For normal data p-values of intra-group tests were presented as follows: [+], [++], [§§] for intergroup results. [+]: p<0.001 between groups AHI <15 and AHI >50. [++]: p<0.001 between groups: AHI <15 and AHI 30–50. [§§]: p<0.001 between groups AHI 15–30 and AHI >50. [ƒƒ]: p<0.001 between groups AHI <15 and AHI 15–30. [ƒƒƒ]: p<0.001 between groups AHI 30–50 and AHI >50.
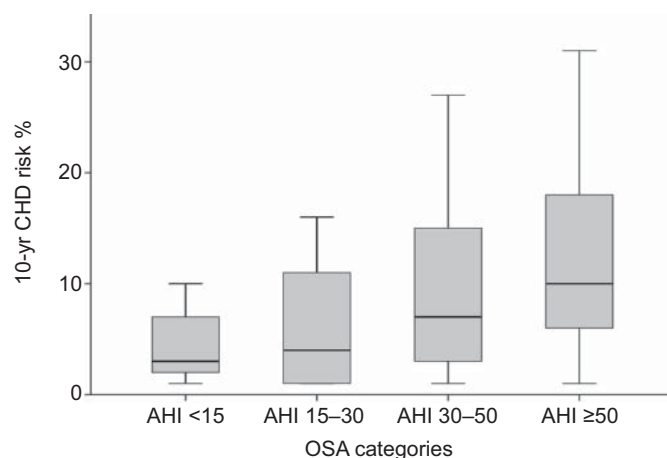
FIGURE 1. The Framingham cardiac risk score [22] was applied to estimate the 10-yr risk of coronary events in the different apnoea/hypopnoea index (AHI) categories. ANOVA with Scheffe *post hoc* analysis was used for comparisons between obstructive sleep apnoea (OSA) categories. CHD: coronary heart disease. p <0.005.

FIGURE 2. The presence of obstructive sleep apnoea (OSA) was considered when the apnoea/hypopnoea index was ⩾15 events·h^{-1}. The metabolic syndrome (MetS) definition and its components were based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria [1]. The Chi-squared test was used for comparisons. BP: blood pressure; FBG: fasting blood glucose; cHDL: high-density lipoprotein cholesterol; TG: triglycerides.

occurrence of OSA was defined as AHI ⩾15, and the severity of nocturnal hypoxia by cumulative time at S_{P,O_2} <90% as ⩾4.65% (as the median sample value). We also assessed the combination of both. After adjusting for age, sex, BMI and smoking, OSA increased the odds of having MetS threefold. The BMI did not appear to contribute to the association since its exclusion during the statistical analysis did not change the results (data not shown).

OSA status according to metabolic variables
When we compared patients with (n=96) and without (n=63) MetS, the prevalence of OSA was significantly higher in the MetS group (83% *versus* 56%, p<0.001). The distribution of the number of MetS components (according to the metabolic index) significantly shifted toward high values in OSA compared with non-OSA patients (Chi-squared test, p-value 0.002; fig. 3).

Subanalysis in patients without known DM2
As MetS is considered a pre-morbid condition for DM2, we repeated the analysis after excluding 33 patients with DM2 (reported in supplementary material E2).

Subanalysis in females
Our sample was composed mainly of females (n=115), thus we repeated the analysis for the female subgroup (reported in supplementary material E3).

DISCUSSION
To our knowledge, this is the first large cross-sectional study focusing on the association of OSA and MetS in MO. In agreement with our hypothesis, MetS was more prevalent, and the metabolic profile more impaired, in morbidly obese patients with OSA than in those without. The metabolic profile progressively worsened with increasing OSA severity, irrespective of sex. This worsening remained even after excluding those patients with DM2. Therefore, even in a population with such a high prevalence of MetS as MO patients, OSA is associated with a worse metabolic profile, suggesting a
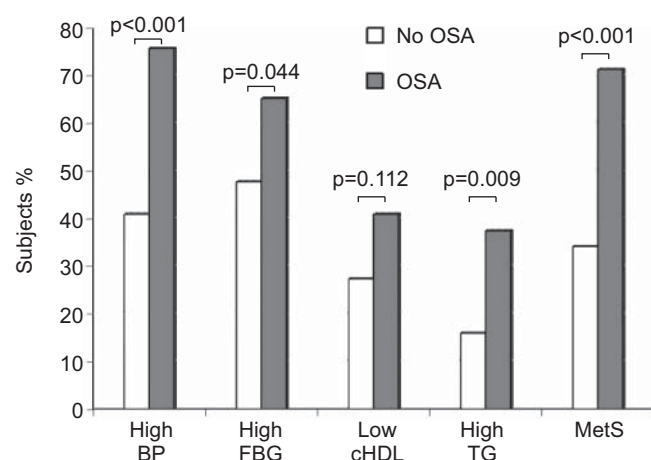
possible additional contribution to the increased CV risk associated with obesity.

The relationship between OSA and metabolic dysfunction has been studied mostly in moderately obese sleep-referred patient cohorts [9, 24–27], and more recently in specific high cardiovascular risk populations, such as MetS [7, 8, 28], hypertensive [29] and CV disease cohorts [30]. All these data agree that OSA is common in middle-aged moderately obese subjects and is associated with MetS or some of its components, independent of the BMI. We have chosen a different approach by studying severely obese patients who represent the extreme model of association between OSA, MetS and MO. Only a small retrospective study pointed out a higher prevalence of both disorders in the same bariatric cohort [23].

The comparison of OSA and non-OSA patients revealed a double prevalence of MetS (70% *versus* 36%, p<0.001) and a progressively impaired metabolic profile in line with an increased AHI. Therefore, our data do not reinforce the notion that MO overwhelms the potential contribution of OSA to metabolic aggravation. Moreover, the occurrence of OSA still increased the adjusted odds of having MetS by up to threefold, irrespective of sex. This is a novel contribution because no analysis of the metabolic effect of OSA on MO females has been addressed before (see supplementary material E3). Interestingly, in females it seems necessary to increase whole body fat in order to increase central fat; in contrast, this is not required in males. Also, the percentage of menopause state was higher in OSA, compared with non-OSA females, in keeping with three large cohort studies [31–33]; however, the association between OSA and MetS did not change after adjusting for menopause state and percentage of body fat. Thus, it is plausible to consider that in morbidly obese patients, the metabolic dysfunction may be conferred not only by MO but also by OSA, which does not seem to have a sex-specific effect.

| TABLE 3 | The association of metabolic parameters with obstructive sleep apnoea severity evaluated as apnoea/hypopnoea index (AHI) and time for arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) <90% total sleep time (TST) in the entire group |

Dependent variable	Adjusted β coefficient[#] (95% CI)	p-value	Adjusted β coefficient[¶] (95% CI)	p-value
Independent variable AHI				
WC cm	0.073 (0.021–0.124)	0.006		
SBP mmHg	0.158 (0.071–0.244)	<0.001	0.149 (0.060–0.238)	0.001
DBP mmHg	0.117 (0.037–0.196)	0.004	0.102 (0.021–0.183)	0.014
TG mmol·L^{-1}	0.007 (0.003–0.011)	0.001	0.005 (0.001–0.010)	0.009
cHDL mmol·L^{-1}	-0.002 (-0.004–0.000)	0.048	-0.002 (-0.004–0.000)	0.050
FBG mmol·L^{-1}	0.008 (-0.002–0.017)	0.119	0.007 (-0.003–0.017)	0.162
HbA1c %	0.010 (0.005–0.016)	<0.001	0.010 (0.004–0.016)	0.001
Independent variable time				
S_{p,O_2} <90% TST				
WC cm	0.082 (0.012–0.152)	0.023		
SBP mmHg	0.117 (-0.003–0.238)	0.057	0.103 (-0.020–0.226)	0.099
DBP mmHg	-0.008 (-0.119–0.102)	0.882	-0.032 (10.143–0.079)	0.569
TG mmol·L^{-1}	0.006 (0.001–0.012)	0.029	0.005 (-0.001–0.010)	0.092
cHDL mmol·L^{-1}	-0.002 (-0.005–0.001)	0.117	-0.002 (-0.005–0.001)	0.124
FBG mmol·L^{-1}	0.181 (-0.053–0.416)	0.129	0.168 (-0.071–0.407)	0.168
HbA1c %	0.011 (0.004–0.019)	0.005	0.011 (0.003–0.019)	0.008

Data were analysed using linear regression as the dependent variable of each metabolic parameter and AHI or time S_{p,O_2} <90% TST as the independent variable. WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; cHDL: high-density lipoprotein cholesterol; FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin. [#]: data adjusted by age, sex, body mass index (BMI) and smoking; [¶]: data adjusted by age, sex, BMI, WC and smoking.

| TABLE 4 | The association of metabolic syndrome with obstructive sleep apnoea (OSA) in the global sample |

Independent variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Presence of OSA AHI ⩾15 events·h^{-1}	4.00 (1.93–8.31)	<0.001	2.84 (1.30–6.22)	0.009
Age yrs			1.07 (1.03–1.11)	0.001
Sex[#]			0.42 (0.18–0.98)	0.045
BMI kg·m^{-2}			1.05 (0.98–1.13)	0.147
Smoking[¶]			0.99 (0.59–1.68)	0.972
Presence of nocturnal hypoxaemia	4.93 (2.46–9.90)	<0.001	3.34 (1.58–7.08)	0.002
Time S_{p,O_2} <90% ⩾4.65% of TST				
Age yrs			1.06 (1.02–1.10)	0.002
Sex[#]			0.53 (0.22–1.26)	0.153
BMI kg·m^{-2}			1.05 (0.98–1.13)	0.184
Smoking[¶]			0.90 (0.52–1.54)	0.694
Presence of OSA with significant nocturnal hypoxaemia AHI ⩾15 events·h^{-1} and time S_{p,O_2} <90% ⩾4.65% of TST	5.10 (2.51–10.39)	<0.001	3.29 (1.51–7.15)	0.003
Age yrs			1.06 (1.02–1.10)	0.004
Sex[#]			0.54 (0.23–1.29)	0.168
BMI kg·m^{-2}			1.04 (0.97–1.12)	0.250
Smoking[¶]			0.92 (0.54–1.58)	0.765

Data were analysed using binary logistic regression. The presence of metabolic syndrome defined by National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria [1] was considered the dependent variable. Data were adjusted for age, sex, BMI and smoking. Results were expressed as unadjusted and adjusted OR (95% CI) and p-value. AHI: apnoea/hypopnoea index; BMI: body mass index; time S_{p,O_2} <90% TST: mean percentage of total sleep time with arterial oxygen saturation measured by pulse oximetry <90% (presence of significant nocturnal hypoxaemia considering values higher or equal to the median of the variable time S_{p,O_2} <90% TST). [#]: no females, one male; [¶]: one smoker, no nonsmokers.
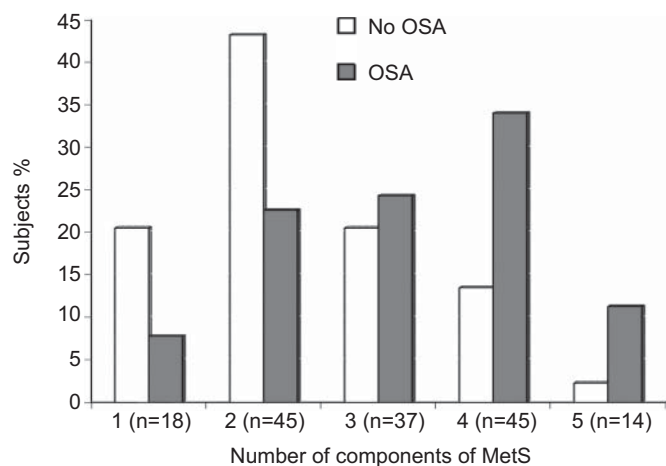
FIGURE 3. The distribution of the metabolic index according to the obstructive sleep apnoea (OSA) presence. The chi-square test was used for comparisons. MetS: metabolic syndrome. p=0.002.

Whether OSA is linked to a specific metabolic pattern has yet to be completely defined. In non-MO cohorts, OSA is associated with various metabolic abnormalities, probably due to the heterogeneity of the samples [24–27, 34, 35]. In the present study, a significant linear association was found between AHI and systolic and diastolic BP, triglycerides and HbA1c after controlling for BMI and WC. Furthermore, even in the subgroup of patients without diabetes, the association remained significant with systolic BP, cHDL and HbA1c. Thus, in MO patients, increasing severity of OSA is associated with metabolic worsening, caused mainly by higher systolic BP, lipid disruption and poorer glucose control, independent of adiposity and other confounders, and irrespective of established DM2.

Hypertension has been widely studied in OSA patients [36]. Recent guidelines on hypertension have recognised OSA as a frequent cause of secondary hypertension [37]. Our findings are consistent with previous large studies pointing to a high prevalence of hypertension among OSA patients [38–40]; more interestingly, a clear deterioration in BP levels in line with increasing OSA category was seen in this MO cohort, and higher BP is independently associated with OSA severity, regardless of sex or the degree of obesity.

With regard to glucose metabolism, most published reports have found a significant association between OSA and hyperglycaemia/insulin resistance/diabetes in moderate obese subjects [35, 41–43]. In the present study, although no differences in FBG or OGTT data were found when comparing the OSA and non-OSA groups, HbA1c was highly associated with OSA markers. So, even in the morbidly obese, our data showed a clear, graded inverse relationship between OSA severity and long-term glucose control, as assessed by HbA1c, after controlling for the degree of obesity and other confounders. This finding was also seen in patients without DM2.

The association between OSA and lipid profile has been investigated less. Overall, there is no definitive evidence regarding the effect of OSA on the lipid profile. The majority of cross-sectional studies are negative [26, 44–46], although some large sample studies found a positive association between OSA

and higher triglycerides and lower cHDL [24, 47, 48]. Our data also show, for first time in a cohort of MO patients, an independent association of AHI with higher triglycerides and lower cHDL.

Furthermore, although the Framingham study's generalisation of CV risk in MO patients should be interpreted with caution, our data suggest that OSA may contribute an additional burden to CV morbidity and mortality in this cohort, and it should be controlled in any study evaluating the consequences of MetS in the morbidly obese. Experimental studies in animals and humans have shown intermittent hypoxia to be a major determinant of metabolic dysfunction associated with OSA [49, 50]. In our cohort, OSA compared with non-OSA patients had a greater degree of nocturnal CIH due to higher AHI, time S_{P,O_2} <90% and arousal index without higher subjective EDS or differences in sleep-stage percentages. Furthermore, AHI was independently associated with most of the individual metabolic parameters, according to the linear regression analysis, whereas time S_{P,O_2} <90% was independently associated with only HbA1c. This may suggest that OSA contributes to metabolic dysfunction in MO, mostly through CIH. Moreover, adding a greater nocturnal hypoxaemia by means of greater time S_{P,O_2} <90% to a high baseline AHI leads to greater metabolic dysfunction than a high baseline AHI alone, according to the logistic regression analysis. These findings concur with those observed by POLOTSKY et al. [51], supporting the "two-hit" model hypothesis to explain the potential role of OSA in the development of steatohepatitis and insulin resistance in severe obesity. MO might act as a "first hit" initiating a metabolic dysfunction, and severe OSA through nocturnal CIH may act as a "second hit" aggravating the disorder. Despite strong evidence from experimental studies demonstrating the role of CIH [11], a definitive causal role of OSA in metabolic impairment in humans cannot be firmly established. In interventional studies, CPAP therapy lowered BP [52], while data on glucose and/or lipid control still appear to be inconclusive [53–57]. Thus, further long-term randomised controlled interventional trials are clearly needed in well-characterised samples, and also in the morbidly obese, in order to address the direction of causality.

As well as being the main energy storage organ, adipose tissue is a highly active tissue involved in the integrated metabolism regulation [58]. Ectopic fat, particularly visceral fat, could adversely modify the metabolism, decreasing the insulin sensitivity in key tissues by a paracrine effect and through the release of adipokines that promote a low-grade pro-inflammatory state [59]. OSA may worsen this state [60] by acting as an additional cardiometabolic burden risk. In the present study, we used WC as an accepted surrogate of visceral adiposity [61]. OSA patients had greater WC and neck circumference compared with non-OSA subjects despite a similar BMI and fat mass percentage, suggesting that OSA is more closely linked to a particular visceral adiposity than to the overall obesity. Conversely, the association of OSA with several metabolic abnormalities remained independent of WC and sex, supporting the notion that OSA may play an additional role in the overall metabolic dysfunction, even in MO. Unfortunately, direct analysis of visceral fat was not possible in this study and thus our findings should be considered approximate. Despite this limitation, these results concur with the hypothesis previously proposed by VGONTZAS et al. [62]: visceral fat could progressively worsen

MetS and OSA manifestations but OSA may also aggravate MetS through an increase in sympathetic activation, inflammation and insulin resistance that deteriorates the overall metabolic dysfunction.

In our cohort, OSA prevalence was notably high: 72% of patients had an AHI $\geqslant$15 and only 2% had an AHI <5. Significantly, most subjects did not complain about EDS (72% of OSA patients had ESS <10), even if they had severe OSA. Although previous studies demonstrated objectively higher EDS in obese patients, compared with healthy non-obese controls, regardless of OSA status [63, 64], the lack of sleepiness measured by EDS is concordant with previous studies evaluating patients before bariatric surgery. This point may reflect the limitations of the EDS in the MO population, as there are other potential cofactors that could affect EDS [65, 66]. Our finding of a lack of subjective sleepiness is clinically relevant, however, as it emphasises the need to perform sleep studies in this specific population, regardless of self-reported symptoms.

With regard to limitations, our cross-sectional study design does not provide cause–effect evidence, although the regression analysis showed an independent association between OSA markers and individual parameters of dysfunction. It would also have been desirable to perform abdominal computed tomography or magnetic resonance imaging to assess the amount of visceral fat, but the subjects did not fit into the machines due to their high body weights. Finally, as discussed, we did not assess objective EDS.

Conclusions

OSA is associated with a more severe metabolic profile in MO patients, independent of age, sex, BMI and smoking, suggesting an important role of OSA, in addition to obesity, in the pathogenesis of metabolic dysfunction in this population. As OSA is a treatable condition, and EDS assessed by ESS is not a good OSA marker in MO, clinicians dealing with obese subjects should appropriately assess OSA in addition to other classic known obesity-related comorbidities, in order to better treat the overall metabolic dysfunction.

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