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CLINICAL RESEARCH

Asymptomatic Sleep-disordered Breathing in Premenopausal Women Awaiting Bariatric Surgery

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Abstract
Background There is a strong association between sleep-disordered breathing (SDB) and obesity. However, there are no studies addressed to determining the prevalence of SDB in morbidly obese premenopausal women, the most frequent group of patients requiring bariatric surgery. To evaluate the prevalence and characteristics of sleep apnea-hypopnea syndrome (SAHS) and obesity hypoventilation syndrome (OHS) in morbidly obese pre-menopausal women included in a program of bariatric surgery.
Methods A total of 88 consecutive morbidly obese pre-menopausal women (38.3±8.1 years, body mass index (BMI) 48.0±6.7 kg/m^2) being evaluated for bariatric surgery at the outpatient obesity unit of a university hospital were prospectively recruited. SDB examinations included a non-attended respiratory polygraphy, pulmonary function testing, and an awake arterial gasometry. SAHS was defined as an apnea-hypopnea index (AHI) ≥10 events per hour and patients were divided in non-SAHS (AHI <10), mild (AHI: 10–20), moderate (AHI: 21–30), and severe (AHI >30). OHS was defined as the presence of hypercapnia ($PaCO_2$>45). Somnolence was evaluated using the Epworth sleepiness scale.
Results A total of 66 (75.0%) obese patients had SAHS: 25 (28.4%) mild, 14 (15.9%) moderate, and 27 (30.6%) severe. Seven (7.9%) obese patients presented OHS. Excessive daily somnolence was recorded in only 11 (16.6%) of the obese women with SAHS. In multiple regression analysis, BMI was the only variable independently associated with SAHS severity.
Conclusions Due to its high prevalence and severity, it should be recommended to investigate SDB in all morbidly obese pre-menopausal women awaiting bariatric surgery even in the absence of excessive daytime sleepiness.

Keywords Obesity · Menopause · Sleep apnea · Pulmonary function · Obesity hypoventilation

The contributions of A.L. and G.S. should be considered equal.

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Introduction

With its rapid increase in prevalence during the last two decades, obesity has become one of the main threats to public health in the Western world [1]. While governments and National Health Services draw up strategies to combat obesity [2], the limited long-term effectiveness of conventional weight-reduction treatments have contributed to the

rapid increase in the number of institutions providing bariatric surgery [3]. Pre-menopausal women are the most frequent group of patients needing this surgery [4].

There is considerable evidence that obesity is the most important determinant of sleep-disordered breathing (SDB) with more than 50% of patients having a body mass index (BMI) higher than 30 Kg/m^2 [5, 6]. Sleep apnea-hypopnea syndrome (SAHS) is the most common form of SDB and has been well established as an independent risk factor for hypertension, myocardial infarction, stroke, and abnormal glucose metabolism [7–9]. In this regard, observational studies have shown how patients with SAHS have an increased risk of death, especially from cardiovascular events [9–11]. Patients with obesity hypoventilation syndrome (OHS), a combination of obesity and chronic hypercapnia accompanied by SDB, also deal with an increased morbidity and mortality mainly of cardiovascular origin [12–14]. In addition, the disruption of normal sleep as a result of recurrent and intermittent hypoxia that occurs in SDB accounts for excessive daytime sleepiness, cognitive impairment, loss in work productivity, and increased risk of driving-related accidents [15–17].

SDB has been assumed to be a condition associated primarily with men, with most population-based studies showing a male/female ratio ranging between 2:1 and 4:1 [18–20]. In addition, it has been suggested that SDB is uncommon in pre-menopausal women but increases in prevalence after menopause [20–22]. However, there is a lack of studies focusing on SDB prevalence and its clinical consequences in pre-menopausal women with morbid obesity. To shed light in this issue, we have determined the prevalence and severity of both SAHS and OHS, as well as their clinical consequences, in a large cohort of morbidly obese pre-menopausal women evaluated for bariatric surgery.

Material and Methods

Patients

A total of 97 consecutive morbidly obese pre-menopausal women being evaluated for bariatric surgery at the outpatient obesity unit of a university hospital were prospectively recruited for the study over a 2-year period. All patients met the eligibility criteria for gastrointestinal surgery established by the guidelines of the National Institutes of Health Consensus Conference [23]. Menopausal status was defined as self-reported 12-month's cessation of menstruation or hysterectomy.

A complete physical examination was performed with special attention to neurological, cardiopulmonary, ear, nose, and throat evaluations. The exclusion criteria were: chronic respiratory disease, smoking habit, clinical history of neuromuscular disease, narcolepsy, stroke, transient ischemic attack, craniofacial abnormalities, abuse of alcohol or use of sedatives, pregnancy, and other endocrinological disease apart from obesity and diabetes mellitus. Nine patients were excluded because of the following reasons: sedative intake (n=4), primary hypothyroidism (n=2), alcohol consumption >20 gr/day (n=2), and sequelae of ischemic stroke (n=1). Eighty-eight morbidly obese non-menopausal women who met none of the exclusion criteria were finally selected for the study.

Metabolic syndrome was defined according to the International Diabetes Federation guidelines [24]: central obesity (waist circumference >94 cms for men and >80 cms for women), plus two of the following factors: (1) serum triglycerides ≥150 mg/dL or specific treatment for this lipid abnormality; (2) HDL cholesterol ≤40 mg/dL in males and ≤50 mg/dL in females, or specific treatment for this lipid abnormality; (3) blood pressure ≥130/85 mmHg or specific antihypertensive medication, and (4) fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes. Type 2 diabetes was defined according to the criteria recommended by the Expert Committee on the Diagnosis and Classification of Diabetes [25].

Informed written consent was obtained from all participants and the hospital's human ethics committee approved the study.

Measurement of Sleep-disordered Breathing and Respiratory Function Data

A previously validated non-attended respiratory polygraphy was performed at patient's home with a Somnea polygraph (Compumedics, Abbotsford, Australia) which records nasal airflow (nasal cannula), respiratory effort (chest and abdominal bands), snoring, body position, and finger pulse oxymetry [26, 27]. After the performance of the study, patients were required to answer a questionnaire on self-perception of sleep quality, subjective number of hours slept, and number of awakenings. An expert scorer blinded to the study reviewed all sleep studies manually. Studies without 5 h of correct signal recording were ruled out and repeated. An apnea was defined as cessation of airflow with duration of at least 10 s. Differentiation was made between obstructive and central apneas according to the respiratory effort channels (presence or absence of thoracoabdominal movements). Hypopnea was defined as a >50% reduction in nasal cannula tracing with a duration of at least 10 s associated with a cyclical dip in SaO_2 ≥3%. The apnea-hypopnea index (AHI) was defined as the sum of apneas plus hipopneas divided by time in bed. On this basis, SAHS was defined as an AHI ≥10 events/hour, and

patients were divided in non-SAHS (AHI <10 events/hour), mild SAHS (AHI between 10 and 20 events/hour), moderate SAHS (AHI between 21 and 29 events/hour), and severe SAHS (AHI >30 events/hour). Three oxygen saturation measures were assessed: the cumulative percentage of time spent with oxygen saturations below 90% (CT90), and the lowest and the average oxygen saturations.

Forced spirometry and static pulmonary volume measurements were performed using a MasterLab apparatus (MasterLab; Jaeger; Würzburg, Germany). All tests were performed following European Respiratory Society guidelines [28]. Static pulmonary volumes were measured using the plethysmography method. The theoretical values proposed by Roca et al. [29] were applied for spirometry and values proposed by the European Respiratory Society for static volumes [28].

Room air arterial blood gas sampling was performed according standard guidelines. Briefly, after patients had been sitting for at least 10 min, samples were anaerobically drawn into preheparinized syringes following administration of local anesthesia in the area of the radial artery. Air bubbles were removed and each sample was taken immediately for analysis using an IL 682 co-oxymeter (Instrumentation Leboratories, Lexington, MA, USA). The OHS was defined as the presence of hypercapnia ($PaCO_2$ >45 mmHg).

The degree of sleepiness was evaluated by using the Epworth sleepiness scale (ESS), a widely used questionnaire assessment of the tendency to fall asleep during various daytime situations [30].

Statistical Analysis

Normal distribution of the variables was evaluated using the Kolmogorov–Smirnov test. Data were expressed either as the mean (SD) or percentage. Given their skewed distribution, AHI and oxygen saturation data were showed as median (range). For parametric tests, AHI was logarithmically transformed to achieve a normal distribution. Comparisons between groups were performed using ANOVA and student *t* tests for continuous variables and the χ^2 test for categorical variables. The relationship between the continuous variables was examined by the Pearson linear correlation test.

A stepwise multiple regression analysis was performed in order to explore the variables independently related to AIH. The variables included were those associated with SAHS in univariate analysis. All *p* values were based on a two-sided test of statistical significance. Significance was accepted at the level of $p<0.05$. Statistical analyses were performed with the SPSS statistical package (SPSS Inc, Chicago, IL, USA).

Results

The main clinical features and pulmonary parameters of the study population are presented in Table 1. According to AHI, 25 out of 88 (28.4%) obese patients included in the study presented mild, 14 (15.9%) moderate, and 27 (30.6%) severe SAHS (Table 2). Therefore, a total of 66 patients included in the study had AHI ≥10, meaning that 75.0% of the morbidly obese pre-menopausal women being evaluated for bariatric surgery had some degree of SAHS. However, somnolence (EES >11) was present only in 11 (16.6%) of the 66 obese women with SAHS (three mild, three moderate, five severe).

CT90 increased significantly with the severity of SAHS, whereas the PaO_2 and both the average and the lowest oxygen saturation levels significantly decreased (Table 2). BMI and waist circumference were related to the severity of SAHS. When morbidly obese pre-menopausal women with severe SAHS (IAH >30 events/hour) where compared with those classified as non-SAHS (IAH <10 events/hour), the former were significantly older and showed a higher EES score. In addition, subjects with metabolic syndrome spent a significantly higher percentage of time with oxygen saturation below 90% in comparison with subjects without metabolic syndrome (11.6±22.5 vs. 3.3±7.9, $p=0.017$).

Table 1 Main clinical features and pulmonary parameters of subjects included in the study

n	88
Age (years)	38.3±8.1
BMI (Kg/m^2)	48.0±6.7
Metabolic syndrome, *n* (%)	54 (62.8)
Type 2 diabetes mellitus, *n* (%)	23 (26.1)
PaO_2 (mmHg)	84.1±10.2
$PaCO_2$ (mmHg)	38.6±4.5
FVC (%)[a]	90.8±13.9
FEV1 (%)[a]	96.9±15.8
FEV1/FVC ratio (%)	84.6±6.1
TLC (%)[a]	95.4±12.2
RV (%)[a]	82.5±22.8
Epworth sleepiness scale	6.3±4.0
AHI (events/hour)	18.4 (0.7–114.0)
SAHS, *n* (%)	66 (75.0)
OHS, *n* (%)	7 (7.9)

Data are mean ± SD and median (range)

BMI body mass index, *PaO_2* arterial oxygen pressure, *$PaCO_2$* arterial carbon dioxide pressure, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *TLC* total lung capacity, *RV* residual volume, *AHI* apnea-hipoapnea index, *SAHS* sleep apnea-hypopnea syndrome, *OHS* obesity-hypoventilation syndrome

[a] Percentage of predicted

Table 2 Comparison of clinical variables and pulmonary parameters taking into account the SAHS classification

	Non-SAHS	Mild	Moderate	Severe	*p*
n (%)	22 (25.0)	25 (28.4)	14 (15.9)	27 (30.7)	–
Age (years)	36.1±7.9	38.8±9.0	36.0±7.6	40.7±7.3[b]	0.175
BMI (Kg/m^2)	44.9±4.7	48.3±6.6	46.8±5.5	50.9±7.7	0.016
T2DM, *n* (%)	4 (18.1)	7 (28.0)	4 (28.5)	8 (29.6)	0.602
METs, *n* (%)	11 (50.0)	18 (72.0)	7 (50.0)	18 (66.6)	0.461
FVC (%)[a]	96.1±12.8	88.3±13.6	92.4±13.4	88.2±14.6	0.194
EV1 (%)[a]	101.8±12.4	94.6±15.7	97.1±17.1	95.2±17.5	0.442
FEV1/FVC ratio (%)	84.8±7.6	84.8±4.9	83.5±3.9	84.7±6.8	0.924
TLC (%)[a]	98.5±13.1	92.5±12.7	96.5±12.2	95.9±14.4	0.508
RV (%)[a]	87.8±24.6	78.9±19.6	83.5±29.1	83.9±22.4	0.893
AHI (events/hour)	5.5 (0.7–9.7)	14 (10–19.8)	24.3 (20.5–29.9)	48.8 (30.1–114)	<0.001
CT90 (%)	0.70±1.40	1.27±1.89	4.52±9.37	23.67±28.08	<0.001
PaO_2 (mmHg)	88.7±7.5	85.3±10.0	84.0±10.8	80.0±10.6	0.044
$PaCO_2$ (mmHg)	37.5±4.5	38.1±3.7	38.5±3.4	39.8±5.4	0.379
Average SaO_2 (%)	96 (92–98)	95 (93–98)	94.5 (89–98)	93 (75–96)	<0.001
Lowest SaO_2 (%)	85 (73–97)	82 (60–90)	82.5 (59–86)	74 (49–95)	<0.001
EES	5.0±1.8	6.2±4.2	6.6±4.2	7.4±4.5 [c]	0.281

Data are mean±SD and median (range)

AIH apnea-hypopnea index, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *METs* metabolic syndrome, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *TLC* total lung capacity, *RV* residual volume, *CT90* percentage of time spent with oxygen saturations below 90%, *PaO_2* arterial oxygen pressure, *$PaCO_2$* arterial carbon dioxide pressure, *EES* Epworth sleepiness scale

[a] Percentage predicted

[b] Severe SAHS vs. non-SAHS, p=0.044

[c] Severe SAHS vs. non-SAHS, p=0.024

In the univariate analysis, the variables associated with SAHS severity measured by AHI (log) were age (r=0.216, p=0.043), BMI (r=0.306, p=0.004), PaO_2 (r=−0.313, p=0.007), and $paCO_2$ (r=0.269, p=0.020). However, no correlation with fasting glucose (r=0.056, p=0.605) was observed. Multiple regression analysis showed that BMI along with PaO_2 were the only variables independently associated with SAHS severity measured by AHI (Table 3).

Concerning the significant associations of BMI with the different pulmonary function and sleep parameters, a positive correlation with AHI (log; r=0.306, p=0.004), $PaCO_2$ (r=0.284, p=0.014), and somnolence score (r=0.273, p=0.013) was detected. In addition, BMI negatively correlated with forced vital capacity (percentage predicted; r=−0.321, p=0.003), lowest SaO_2 (r=−0.268, p=0.012), and average SaO_2 (r=−0.224, p=0.036; Fig. 1). However, no correlation between BMI and PaO_2 was observed (r=−0.230, p=0.144).

OHS, defined as the presence of hypercapnia (PaCo2 >45 mmHg) was detected in seven out of 88 patients (7.95%) patients included in the study. Four of them presented severe SAHS, two of them were non-SAHS women, and another one presented mild SAHS.

Table 3 Multiple regression analysis of independent variables associated with the apnea-hypopnea index (AHI)

	Beta	*p*
BMI	0.288	0.013
PaO_2	−0.239	0.038
Age	0.138	0.248
$PaCO_2$	0.056	0.650
R^2	0.164	

Beta Standardized partial regression coefficient, *BMI* body mass index, *PaO_2* arterial oxygen pressure, *$PaCO_2$* arterial carbon dioxide pressure

Discussion

In the present study, we have demonstrated that three out of four morbidly obese pre-menopausal women evaluated for bariatric surgery are affected by some degree of sleep apnea-hypopnea syndrome. In addition, severe SAHS was found in 30% of these patients. This high prevalence is particularly important if we take into account that only 16% of affected women were complaining about daily sleepiness

Although several research groups have presented prevalence estimates for SDB by age and sex, no published data

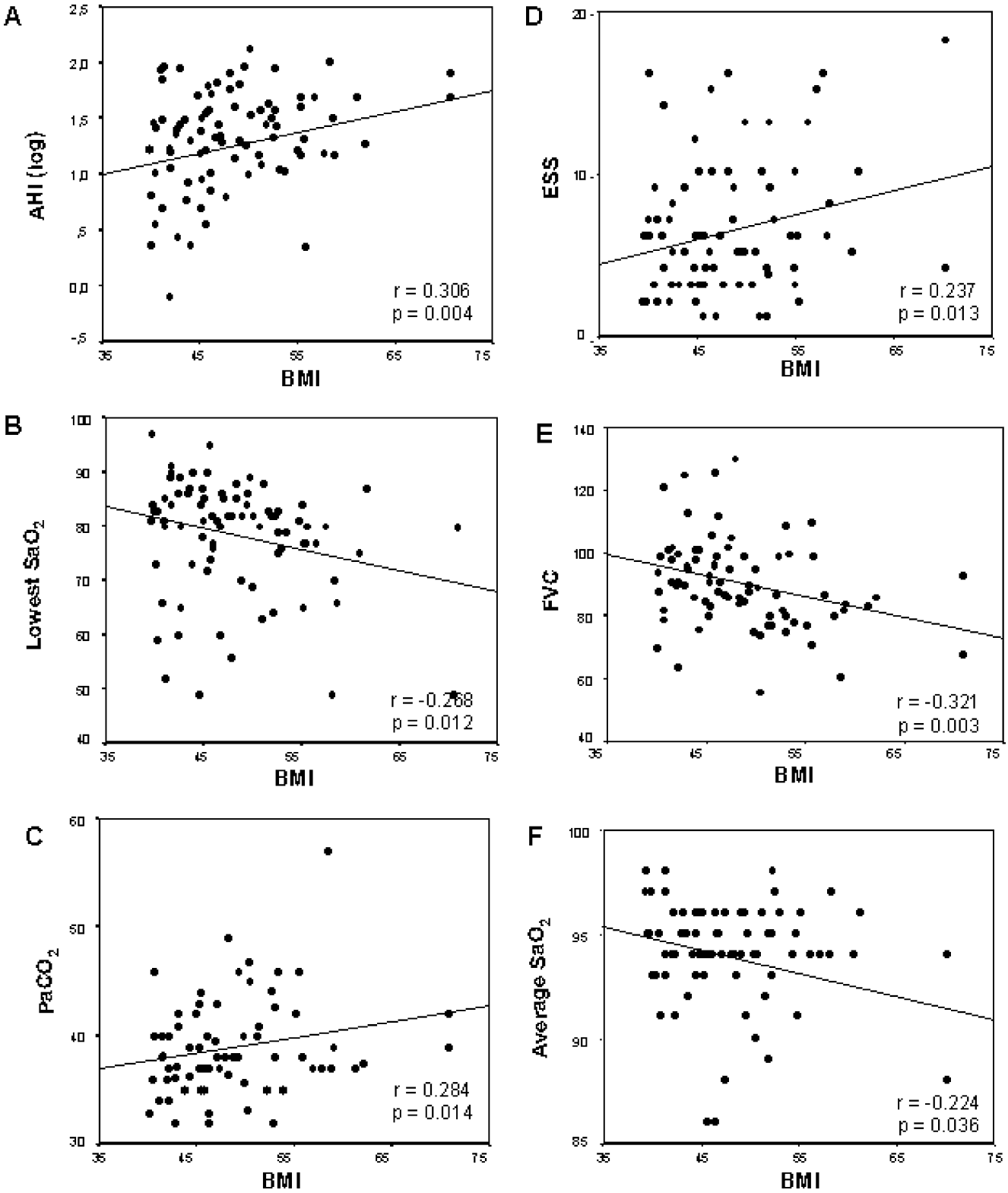

Fig. 1 Correlations of BMI with sleep-disordered breathing and respiratory function data in morbidly obese pre-menopausal women. *AHI* apnea-hypopnea index, *SaO2* oxygen saturation, *PaCO2* arterial carbon dioxide pressure, *ESS* Epworth sleepiness scale, *FVC* forced vital capacity, *BMI* body mass index

are available for pre-menopausal women with morbid obesity. Data from the 2005 "*Sleep in America*" poll of the National Sleep Foundation indicate that as many as one in four adults and 75% of individuals with BMI >40 Kg/m^2 are at high risk of SAHS [31]. This high percentage was obtained through telephone interviews, so data about height, weight, daytime sleepiness, and snoring behavior were self-reported and, therefore, could be significantly biased. Similarly, Young et al. [6], analyzing data from the *Behavioral Risk Factor Surveillance System*, the US census, and their own data from the Wisconsin Sleep Cohort, estimated a prevalence of SDB in women between 30 and 49 years old and BMI ≥40 Kg/m^2 of 39%. However, it should be noted that the authors declared that these were rough estimates that depended on sampling error variance.

In a clinical-based study, Resta et al. [32] showed that among 64 consecutive pre-menopausal women with a BMI ≥30 Kg/m^2 recruited at the outpatient obesity clinic, only 21% had sleep apnea. This is a small percentage in comparison with our results, but it should be taken into account that we have focused our study on morbid obesity and the mean of BMI in patients included in the present study was 48±6.7 Kg/m^2. Clinical observations and population studies worldwide have consistently shown a graded increase in the prevalence of SDB as BMI, and waist circumference increase [5, 6, 33–35]. In this regard, and in line with previous studies, we have found that BMI was the strongest predictor of the severity of SAHS in multiple regression analysis.

Young women are poorly represented both in clinical-based and epidemiological studies evaluating the prevalence of SDB. It has been suggested that SDB is uncommon in pre-menopausal women but increases in prevalence after menopause [21, 22]. Most hypotheses made to account for this difference suggest that depletion of estrogen and progesterone that appears after menopause increases susceptibility to SDB [6, 36]. Our results, with a very high percentage of pre-menopausal women being diagnosed with SAHS, seem to imply that severe obesity is more important than hormonal status in contributing to SDB. In this regard, it should be noted that several studies have found that pre-menopausal women with SAHS are more obese than postmenopausal women [19, 35].

Although excessive daytime sleepiness (EDS) is considered to be a cardinal feature of SDB when patients from sleep laboratories are evaluated, its association with AHI has been shown to be weak. In fact, we did not find EDS somnolence in most patients with SDB (83%) including those with severe SAHS. In support of our findings, Dixon et al. [37] failed to find a significant relationship between daily sleepiness and the polysomnographic data in a cohort of patients presenting themselves for obesity surgery. Gender-related differences in SAHS symptoms have been suggested, with women reporting EDS less frequently than men, and this might contribute to a clinical under-recognition of SAHS in females [19, 38]. However, other authors have found a similar symptom profile of men and women with SAHS [39]. The reason why some patients with high AHI do not present excessively daytime somnolence remains to be elucidated. In addition, whether or not pre-menopausal status and/or severe obesity show a lower degree of susceptibility to the effects of sleep fragmentation needs further research [40].

A high prevalence of fasting hyperglucemia, insulin resistance, and T2DM has been found among SAHS patients in comparison with healthy subjects [41, 42]. The pathogenesis of this relationship is not fully understood but a preferential activation of inflammatory pathways by intermittent hypoxia and sleep fragmentation are likely to play a central role [43]. However, in our study the presence of diabetes or metabolic syndrome were unrelated to SAHS severity measured by the AHI. This could be attributed to the fact that all patients included were morbidly obese pre-menopausal women. In this regard, it should be noted that morbid obesity is an extremely important risk factor for SAHS and this could minimize the effect of diabetes or metabolic syndrome. In fact, in a previous study, we have also failed to found higher AHI in morbid obese women with diabetes in comparison with non-diabetic control women matched by age and BMI [44]. However, the percentage of time spent at saturations below 90% (CT90) was higher in diabetic patients than in non-diabetic subjects. In addition, in the present study, we have also observed higher CT90 in patients with metabolic syndrome than in those without it. Nevertheless, a large study in order to determine whether or not type 2 diabetes or metabolic syndrome have any influence in SHAS severity in morbidly obese pre-menopausal women is needed.

Given that SAHS is an independent risk factor for cardiovascular disease [7–9], a general conclusion that could be drawn from our results is that screening for SAHS should be recommended for all morbidly obese pre-menopausal women. In addition, it should be noted that most of the obese women included in our study were candidates for bariatric surgery and it is well known that SAHS increases the risk of anesthetic and postoperative complications [45, 46]. However, specific studies addressed to demonstrating that preoperative detection of SDB would lead to a better management of these patients and to reducing those complications are needed.

Our study has some limitations. First, daytime sleepiness was measured with a subjective questionnaire and perhaps a more objective test, i.e., Multiple Sleep Latency Test, could have found a greater percentage of sleepy patients. However, the usual reason for suspecting SAHS in everyday clinical practice is the subjective perception of

sleepiness, and the ESS is the tool most widely used for evaluating daytime sleepiness in clinical practice. Second, we have not performed full polysomnographies but a home non-attended respiratory polygraphies. These imply that we have no data about other key sleep features associated with SAHS like sleep latency, changes in stage 2 sleep, and rapid eye movement sleep. In addition, the AHI was calculated from time in bed, not from sleeping time, and could underestimate the prevalence of SAHS. In addition, it should be noted that some comorbidities were excluded and, therefore, an even a higher percentage of SAHS in morbidly obese pre-menopausal women could be expected to exist in real life.

In conclusion, a high prevalence of severe SDB exists in obese premenopausal women being evaluated for bariatric surgery. In addition, most of these patients do not complain of daily sleepiness. Given that SDB is a potential life-threatening condition, further studies to define not only the potential benefits of the routine polysomnographic evaluation in obese subjects but also to determine whether or not the preoperative diagnosis of SDB could improve the management of this patients along bariatric surgery are needed.

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Conflict of interest The authors have declared that no conflicts of interest exist with the subject of the study.

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