Impacte de la Síndrome d'Apnea-hipoapnea Obstructiva del Son en l'obesitat greu

Impact of Obstructive Sleep Apnea in Severe Obesity

Mercè Gasa Galmes

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Impact of Obstructive Sleep Apnea in Severe Obesity

Memòria presentada per

MERCÈ GASA GALMES

Directora: Dra CARMEN MONASTERIO PONSA

Dedicada a

A na Mª Magdalena Galmes, na Blanca Gasa i en Biel Gómez

(Passat, Present i Futur)

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PRODUCCIÓ CIENTÍFICA (SCIENTIFIC PRODUCTION)

Els resultats exposats en aquesta tesi doctoral han estat prèviament publicats o remesos per publicació en revistes científiques.

The exposed results in this thesis have been published or accepted for publication in scientific journals.

1. **Gasa M,** Salord N, Fortuna AM, Mayos M, Vilarrasa N, Dorca J, Montserrat JM, Bonsignore MR, Monasterio C. Obstructive sleep apnoea and metabolic impairment in severe obesity. Eur Respir J. 2011 Nov;38(5):1089-97. Epub 2011 May 26.

2. **Gasa M**, Salord N, Fortuna AM, Mayos M, Embid C, Vilarrasa N, Montserrat JM, Monasterio C. Optimizing screening of severe obstructive sleep apnea in patients undergoing bariatric surgery. Surg Obes Relat Dis. 2012 Feb 9. [Epub ahead of print].

3. **Gasa M**, Salord N, Vilarrasa N, García Ruiz de Gordejuela A, Dorca J, Montserrat JM, Monasterio C. Impact of bariatric surgery on obstructive sleep apnea severity. [Submitted].

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INTRODUCCIÓ

La síndrome d'apnea-hipoapnea obstructiva del son (SAOS) és un trastorn nocturn caracteritzat per la presència d'episodis repetits de col·lapse parcial o complet de la via aèria superior que comporten un increment progressiu de l'esforç respiratori, una desaturació intermitent d'oxigen i la fragmentació del son [1, 2]. La presència d'una SAOS no tractada pot suposar un empitjorament de la qualitat de vida [3] i un risc augmentat de patir accidents de trànsit [4]. A més a més, la SAOS està associada a una major mortalitat global [5] i d'origen cardiovascular [6]. Ara bé, la teràpia nocturna amb pressió positiva continua sobre la via aèria (Continuous Positive Airway Pressure - CPAP) corregeix el trastorn i redueix significativament el risc de patir dites conseqüències [7]. En els darrers anys, s'ha postulat que la SAOS podria contribuir a aquest risc cardiovascular a través d'actuar sobre el metabolisme. Ara bé, dita relació encara no està establerta de forma contudent i per tant, el paper causal de la SAOS en el desenvolupament de les alteracions metabòliques encara està per definir.

Les alteracions metabòliques, definides en conjunt com la presencia de la síndrome metabòlica (MetS) [8] o bé, individualment en funció dels components de la MetS presents (obesitat central, metabolisme glucídic alterat, hipertensió arterial, trastorns del metabolisme lipídic entre d'altres) incrementen la mortalitat i morbiditat cardiovascular [9-12].

L'obesitat central juga un paper fonamental en l'origen i el desenvolupament d'aquestes alteracions metabòliques però recentment s'han postulat altres mecanismes com a possibles responsables o precipitants en part de dita mortalitat i morbiditat cardiovascular [13]. En els darrers anys, diversos treballs han suggerit que la SAOS podria empitjorar el risc cardio-metabòlic atribuït a l'obesitat, de manera que podria representar una carrega addicional sobre la disfunció metabòlica relacionada amb l'obesitat [14, 15].

Els mecanismes a traves dels quals la SAOS podria empitjorar el metabolisme son complexos. La SAOS mitjançant la hipòxia crònica intermitent podria engegar diferents vies mediadores patològiques (activació simpàtica, canvis neuro-humorals, alteració en la homeòstasis glucídica, inflamació i estrés oxidatiu) que conduirien a un deteriorament metabòlic global [16]. Estudis experimentals, en ratolins tant prims com obesos, han demostrat que després de exposar-los a hipòxia crònica intermitent controlada simulant una SAOS en humans, aquests animals presenten un major grau de resistència insulínica, disfunció lipídica i elevació de la tensió arterial [17]. Ara bé, la evidència similar en humans resulta ser encara limitada.

L'obesitat és el principal factor de confusió a l'hora d'estudiar la relació entre la SAOS i les alteracions metabòliques [18]. Diversos estudis

previs han exclòs pacients amb obesitat mòrbida pressuposant que en aquesta subpoblació, l'efecte de la SAOS possiblement és nul o mínim donat que l'obesitat greu és probablement la màxima responsable del deteriorament metabòlic. Per altra banda, estudis recents avalen que la SAOS podria agreujar o empitjorar el perfil metabòlic en subpoblacions amb alt risc cardiovascular establert [14, 15]. Per aquest motiu, tenint en compte que els individus que pateixen una obesitat greu poden presentar un major risc cardiovascular que individus no obesos, és fonamental esbrinar si en aquesta població en concret, la SAOS s'associa a un major risc cardio-metabòlic independentment de l'obesitat greu.

Per altra banda, l'obesitat és el principal factor de risc per desenvolupar SAOS [19, 20]. En la població adulta general, s'ha estimat una prevalença de SAOS al voltant del 24% per homes i del 9% per dones però dits percentatges poden arribar fins al 30% en individus obesos (Índex Massa corporal >30 Kg/m^2) [21] i a prop del 90% en individus amb obesitat extrema (Índex Massa corporal >40 Kg/m^2) [22]. En aquest escenari d'obesitat extrema, la cirurgia bariàtrica (CB) s'ha convertit en una de les principals opcions terapèutiques en aquells pacients que pateixen comorbiditats greus relacionades amb dita obesitat on les mesures conservadores han estat insuficients per assolir una pèrdua de pes optima i/o mantenir aquesta pèrdua ponderal al llarg del temps. Per

aquests pacients, la CB suposa una pèrdua ponderal significativa que es manté al llarg de temps i que millora substancialment la gravetat de les comorbiditats relacionades amb l'obesitat greu tals com la hipertensió arterial, la diabetis melitus tipus 2 o la dislipemia [23].

En subjectes obesos es considera que els mecanismes fonamentals implicats en el desenvolupament d'una SAOS son el desequilibri anatòmic que es produeix al voltant de la via aèria faríngia amb un augment considerable d'estructures toves circumdants, la reducció en el volum pulmonar i l'inestabilitat del control de la respiració [20]. Tot això facilita que els pacients obesos amb una SAOS concomitant tinguin una predisposició especial a patir complicacions peri-operatòries quan se sotmeten a un acte quirúrgic major [24]. En diferents àmbits quirúrgics, s'han descrit un major nombre de complicacions peri-operatòries en pacients amb SAOS en comparació amb subjectes sense SAOS [25, 26]. Des d'un àmbit més específic com és la cirurgia abdominal, els pacients tractats amb CPAP presenten menys complicacions peri-operatòries i menys episodis d'insuficiència respiratòria després de la extubació que els pacients que no reben CPAP [27]. De fet, les guies que estableixen recomanacions generals per la optimització del maneig peri-operatori del pacient quirúrgic recomanen, en la mesura del possible, valorar pre-operatòriament la presencia d'una SAOS concomitant i iniciar teràpia amb

CPAP el més aviat possible abans, durant i posterior a l'acte quirúrgic si la gravetat de la SAOS així ho indica [28].

En relació a l'optima valoració peri-operatòria del pacient candidat a cirurgia bariàtrica amb SAOS, la evidència és encara limitada, però probablement les recomanacions generals son inclús més importants en aquests subjectes per diversos motius. Per una banda, la prevalença de SAOS en aquesta població s'estima molt més elevada que en la població general donat que presenten el principal factor de risc per desenvolupar una SAOS en edat adulta: l'obesitat per si mateixa i a més sent d'extrema gravetat. Per altra banda, és altament probable que aquests pacients presentin un major risc quirúrgic no únicament per la pròpia obesitat greu [29] sinó també per la SAOS si està present. S'ha observat que la presencia d'una SAOS no diagnosticada i per tant no tractada pot incrementar l'estada hospitalària [30] i els costos de les cures post-operatòries [31] en pacients sotmesos a CB; En canvi, la correcta detecció pre-operatòria de la SAOS juntament amb les mesures peri-operatòries de prevenció podrien ajudar a reduir els requeriments de cures intensives en aquests pacients després de la cirurgia [32]. Tant les guies Americanes [33] com Europees [34] que treballen per l'optimització del maneig mèdic del pacient obès candidat a cirurgia bariàtrica recomanen, sempre que sigui possible, un cribatge sistemàtic per detectar la SAOS abans de la

cirurgia; i en cas que es detecti, es recomana adoptar una sèrie de precaucions per tal d'evitar complicacions potencials associades a la SAOS durant el període perioperatori.

Malgrat l'evidencia científica és escassa en relació al ús sistemàtic de la CPAP pre-operatòria en l'àmbit de la cirurgia bariàtrica, sembla que la aclimatització en l'ús de la CPAP abans del procediment quirúrgic és un factor clau per facilitar la seva correcta aplicació post-operatòria. L'inici de la teràpia amb CPAP nasal una setmana abans de la cirurgia pot reduir el col·lapse faringi en incrementar l'àrea transversal de la via aèria superior [35]. A més, és altament probable que l'acceptació i la tolerància de la CPAP durant el període peri i postoperatori sigui escassa en aquells pacients amb SAOS no tractats prèviament amb CPAP, fonamentalment en els pacients asimptomàtics. Per tant, una manera de millorar dita tolerància és iniciar la teràpia amb CPAP setmanes abans del procediment quirúrgic per tal de garantir una optima aclimatització perioperatòria.

En quant al maneig postoperatori del pacient obès amb SAOS, algunes de les mesures recomanables son: garantir un estat de vigília complet després de la extubació endotraqueal evitant sempre que sigui possible l'ús de sedació profunda i seleccionar l'analgèsia més adequada per pal·liar el dolor postoperatori. És preferible l'ús d'analgèsia regional enfront de l'ús de derivats mòrfics. Aquestes ultimes drogues han

demostrat reduir la resposta ventilatoria enfront a l'hipòxia i la hipercàpnia donat que empitjoren els mecanismes neurals de control imprescindibles per preservar la via aèria superior oberta en el pacient amb SAOS, de manera que podrien provocar un retard notable en l'obertura de dita via [36, 37]. Per altra banda, cal tenir cura de la posició corporal optima post-quirúrgica d'aquests pacients. La col·locació del subjecte en sedestació o posició lateral és preferible a la posició supina donat que son posicions que no faciliten el col·lapse aeri. Val a dir que aquestes mesures generals a vegades no son suficients per preservar la patència de la via aèria superior en subjectes obesos que pateixen una SAOS de caràcter moderada-greu. En aquests casos, l'aplicació de la teràpia amb CPAP nasal durant el postoperatori pot resultar altament beneficiosa.

No obstant, el cribatge pre-quirúrgic sistemàtic per detectar la SAOS i així, poder establir un òptim maneig perioperatori del pacient candidat a cirurgia bariàtrica és un gran repte mèdic donat que sovint aquests pacients no presenten símptomes clàssics. Així, es fa difícil sospitar la presencia d'una SAOS concomitant a l'obesitat. La polisomnografia (PSG) durant una nit completa realitzada al laboratori de son és el mètode diagnòstic de referència per diagnosticar una SAOS però és un mètode car i comporta un consum de temps important. Nombrosos

autors han intentat trobar factors predictius clínics pre-operatoris que pugin ajudar a descartar pacients que presenten un baix risc i detectar aquells que tenen un alt risc de presentar SAOS; aquests últims, requeriran un maneig més complex abans de la CB [22, 38-44]. Ara bé, cap d'aquests estudis ha aconseguit trobar factors predictius clínics prou fiables recomanant enèrgicament la realització d'una PSG com a únic mètode fiable per avaluar la presència de SAOS abans de la CB malgrat ser conscients dels costos que suposa aquesta mesura sistemàtica.

Molts dels pacients sotmesos a cirurgia bariàtrica no refereixen símptomes clàssics de SAOS durant l'avaluació respiratòria pre-quirúrgica [39, 44] i en conseqüència, encara en referiran menys després de la cirurgia [45]; això fa que sovint la presència de SAOS concomitant a l'obesitat greu passi desapercebuda en ambdós períodes: abans i després de la cirurgia bariàtrica. Per això, la detecció objectiva dels pacients que presentaran una curació completa o una milloria significativa de la SAOS després de la CB torna a ser un repte important. En molts casos, en pacients que patien una SAOS greu i rebien tractament amb pressió positiva continua sobre la via aèria (CPAP - continuous positive airway pressure therapy) abans de la cirurgia, es retira el tractament amb CPAP després de la cirurgia sense una reavaluació objectiva de la SAOS. Això és degut bàsicament a que la majoria dels pacients experimenten una

pèrdua ponderal molt significativa durant el seguiment i expressen una clara milloria subjectiva dels símptomes, interpretant-se erroniàment com la resolució de la SAOS concomitant.

Però malauradament, la pèrdua ponderal significativa post-quirúrgica no garanteix la resolució completa de la SAOS en tots els casos [46]. Això, cal tenir-ho en compte perquè si la SAOS no es resolt, malgrat el pacient deixi de presentar obesitat mòrbida pot continuar patint una SAOS greu que pot suposar un risc cardio-metabòlic addicional independent de la pròpia obesitat. Dit risc addicional de la SAOS residual podria ser degut a la seva associació amb la síndrome metabòlica independentment de l'obesitat "per se". Per això, és summament important conèixer els efectes que podria suposar la cirurgia bariàtrica en la milloria/resolució de la SAOS. L'evidencia científica aportada fins ara en relació a la resolució de la SAOS després de la pèrdua ponderal post-quirúrgica encara no és prou concloent per diversos motius. Alguns dels treballs publicats presenten una grandària mostral petita [47-49], altres presenten un important biaix en el seguiment [50-52] i, a part el nombre de treballs publicats que avaluïn de forma objectiva, mitjançant la comparació de proves de son reglades abans i després de la cirurgia bariàtrica és força limitat. Això fa que els resultats d'aquests treballs previs s'hagin d'interpretar amb cautela i que les conclusions que se'n

puguin derivar no siguin prou contundents per avaluar correctament l'impacte de la pèrdua ponderal post-quirúrgica sobre la gravetat de la SAOS[53].

En conclusió, el pacient obès mòrbid candidat a cirurgia bariàtrica és un model ideal extrem que permet estudiar la relació entre la SAOS i les seves conseqüències cardio-metabòliques, associades o no a la pròpia obesitat. A part, tenint en compte que la evidencia científica fins ara presenta certes qüestions no resoltes en relació al correcte maneig respiratori d'aquests pacients abans i després de la cirurgia bariàtrica, resulta també interessant investigar si existeix alguna manera d'optimitzar la detecció dels pacients que pateixen una SAOS greu abans de la cirurgia per tal d'agilitzar-ne el seu maneig respiratori perioperatori. Per altra banda, falta coneixer a fons quin és l'efecte de la cirugia bariatrica en la resolució de la SAOS: la relacio de la SAOS residual amb un possible pitjor control metabolic, així com si existeixen factors predictius de milloria i/o resolució de la SAOS un cop establerta la pèrdua ponderal post-quirúrgica.

HIPÒTESI PRINCIPAL

La presència de la Síndrome d'apnea-hipoapnea del Son (SAOS) s'associa a un pitjor perfil metabòlic en els pacients amb obesitat mòrbida i, conseqüentment a un major risc cardio-metabòlic.

En pacients amb obesitat mòrbida candidats a cirugia bariàtrica es pot constuir un model predictiu per detectar una SAOS greu basant-se en variables clíniques senzilles que permeti evitar la necessitat d'un estudi del son pre-quirúrgic en part dels pacients.

En pacients amb obesitat mòrbida i SAOS, la perdua de pes post-quirúrgica no sempre determina la curació de la SAOS i la curació no ve determinada únicament per al pes perdut.

OBJECTIUS CONCRETS

Objectius del primer treball:

(1) Estudiar si la presencia de la SAOS s'associa a un pitjor perfil metabòlic en el pacient obès candidat a cirurgia bariàtrica i si dita associació és independent de la pròpia obesitat, particularment de l'obesitat central, considerada fonamental des del punt de vista metabòlic.

(2) Investigar si existeix un perfil concret de disfunció metabòlica característic associat a la SAOS en els pacients amb obesitat mòrbida

(3) i si el risc cardiovascular global s'incrementa en paral·lel a la gravetat de la SAOS.

Objectius del segon treball:

(1) Construir un model predictiu senzill i fàcilment aplicable per detectar els pacients amb SAOS greu en la població de obesos mòrbids abans de la cirurgia bariàtrica.

Objectius del tercer treball:

(1) Avaluar l'efecte de la pèrdua ponderal post-quirúrgica sobre la gravetat de la SAOS un any després de la cirurgia bariàtrica de manera objectiva mitjançant una prova de son reglada abans i després de la cirurgia bariàtrica.

(2) Investigar si existeixen factors preoperatoris predictius de milloria o resolució de la SAOS després de la cirurgia bariàtrica relacionats o no amb la pèrdua ponderal post-quirúrgica.

ARTICLES PUBLICATS:

1. **Gasa M,** Salord N, Fortuna AM, Mayos M, Vilarrasa N, Dorca J, Montserrat JM, Bonsignore MR, Monasterio C. Obstructive sleep apnoea and metabolic impairment in severe obesity. Eur Respir J. 2011 Nov;38(5):1089-97. Epub 2011 May 26.

2. **Gasa M**, Salord N, Fortuna AM, Mayos M, Embid C, Vilarrasa N, Montserrat JM, Monasterio C. Optimizing screening of severe obstructive sleep apnea in patients undergoing bariatric surgery. Surg Obes Relat Dis. 2012 Feb 9. [Epub ahead of print].

3. **Gasa M**, Salord N, Vilarrasa N, García Ruiz de Gordejuela A, Dorca J, Montserrat JM, Monasterio C. Impact of bariatric surgery on obstructive sleep apnea severity. [Submitted].

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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 sphygmomanometer 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$\pm$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
FEV_1 % pred	99.3±15.4	97.0±13.5	100.1±16.1	0.282
FEV_1/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; FEV_1: 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 ⩾ 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$^{+,\S\S}$
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$^{+,\dagger\dagger}$
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$^{+,++,\S\S}$
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$^{+,\dagger\dagger\dagger}$
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. ††: p<0.001 between groups AHI <15 and AHI 15–30. †††: p<0.001 between groups AHI 30–50 and AHI >50.

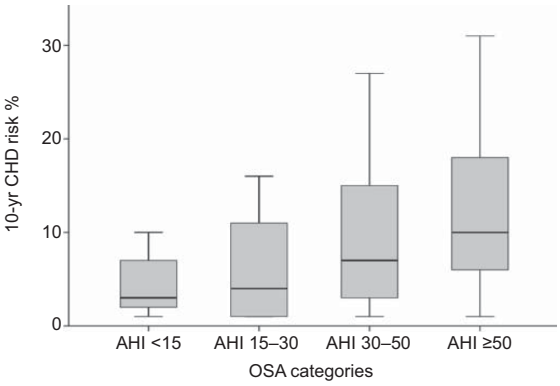

FIGURE 1. The Framingham cardiac risk score [22] was applied to estimate the 10-yr risk of coronary events in the different apnoea/hypopnoea index (AHI) categories. ANOVA with Scheffe *post hoc* analysis was used for comparisons between obstructive sleep apnoea (OSA) categories. CHD: coronary heart disease. $p < 0.005$.

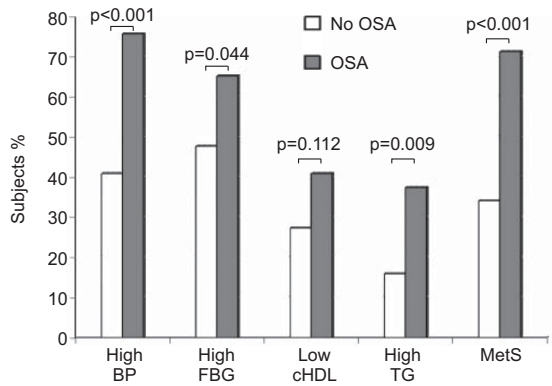

FIGURE 2. The presence of obstructive sleep apnoea (OSA) was considered when the apnoea/hypopnoea index was $\geqslant 15$ events·h^{-1}. The metabolic syndrome (MetS) definition and its components were based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III modified criteria [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 $\geqslant 15$, and the severity of nocturnal hypoxia by cumulative time at S_{P,O_2} <90% as $\geqslant 4.65\%$ (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.

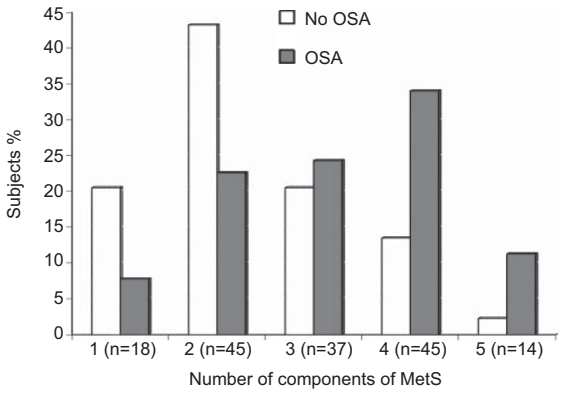

FIGURE 3. The distribution of the metabolic index according to the obstructive sleep apnoea (OSA) presence. The chi-square test was used for comparisons. MetS: metabolic syndrome. p=0.002.

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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STATEMENT OF INTEREST

None declared.

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Supplemental Material E1

Methods: Sleep Study

OSA was determined by a full overnight polysomnography (PSG). PSG (Siesta, Compumedics, Melbourne, Australia) included recording of oronasal flow (termistor and cannula), thoracoabdominal movements, electrocardiogram, sub-mental and pretibial electromyography, electrooculogram, electroencephalogram, pulse oximetry and body position sensor. Rechtstaffen and Kales' criteria were used for visual scoring of sleep stages. Apnea was defined as a cessation of flow for at least 10 seconds, and hypopnea as any flow reduction of at least 10 seconds, accompanied by a fall of ≥ 3% in SpO2 or microarousal. The apnea-hypoapnea index (AHI) and the arousal index were defined as the number of apneas/hypoapneas and arousals, respectively, per hour of sleep.

Supplemental Material E2

Sub-analysis in patients without known type 2 diabetes

Similar to the total sample, OSA subjects had higher age, WC and NC and reported more sleep hours per night. Also they had higher BMI (47 ± 6 vs 45 ± 5 Kg/m2, p 0.039) (Table e-1).

The prevalence of MetS and the metabolic profile tend to progressively worsens with increasing AHI categories but some metabolic parameters (TG, FBG, cLDL, cVLDL) loose statistically significance (Table e-2). Furthermore, the Framingham Cardiac Risk Score increased with OSA categories (Figure e-1). The adjusted linear regression analysis showed that AHI was associated with SBP, cHDL and HbA1c; by contrast, Time SpO2 < 90% was only associated with Hb1Ac (Table e-3).

Supplemental Material E3

Sub-analysis in females

OSA (n =82) were older, had higher percentage of postmenopausal state, WC, NC and reported more sleep hours per night compared to non-OSA (n = 33) (Table e-4). The percentage of MetS, even though lower than in the entire sample (57% vs 60%, was higher in OSA compared to non-OSA females (66% vs 33%, p 0.001) and showed the same differences for individual components as the total sample (Figure e-2). After adjusting for age, BMI, post-menopausal state and fat mass percentage, the association of OSA and MetS in morbidly obese women was similar to that in the whole group: binary logistic regression showed that the presence of OSA analyzed by AHI ≥ 15 events/hour, study time with SpO2<90% ≥ 3.30 and the combination of both OSA markers increased the odds of having MetS by 2.79 (p 0.033, 95% CI 1.09 – 7.17), 3.90

(p 0.003, 95% CI 1.61 – 9.46) and 2.47 (p 0.002, 95% CI 1.39 – 4.38), respectively (Table e-5). Adding smoking and obesity duration to the model did not modify significantly the results (data not shown).

Table e-1. General and Sleep characteristics of patients without known type 2 diabetes.

	Total (n=126)	**OSA -** (n=39)	**OSA +** (n=87)	**p**
Age, years mean±SD	42.0 ± 10.0	39.0 ± 10.0	44.0 ± 10.0	0.005
BMI, Kg/m^2 mean±SD	46.4 ± 6.0	44.7 ± 4.6	47.1 ± 6.4	0.039
Gender, Females %	75.4	74.4	75.9	0.856
Current smoking, %	17.5	23.1	14.9	0.532
Alcohol consumption, %	5.6	7.7	4.6	0.483
Body Fat, % mean±SD	48.8 ± 8.3	47.7 ± 8.1	49.3 ± 8.3	0.324
WC, cm mean±SD	129.1 ± 15.7	123.3 ± 13.9	131.7 ± 15.8	0.005
Waist-Hip Ratio mean±SD	0.92 ± 0.10	0.88 ± 0.08	0.94 ± 0.11	0.002
Neck circumference, cm*	42.0 (40.0 – 44.0)	41.0 (39.0 – 43.0)	42.0 (40.0 – 46.0)	0.023
Obesity Duration, years mean±SD	24.7 ± 10.4	24.0 ± 10.4	25.1 ± 10.4	0.593
Physical Activity, $METS.min.week^{-1}$, mean±SD	2319.6 ± 2491.7	2352.9 ± 2443.5	2304.4 ± 2528.0	0.921
Glucose tolerance assessment [§]**,** n (%) Diabetes IGT Normal Missing data	 10 (7.9 %) 25 (19.8 %) 82 (65.2 %) 9(7.1%)	 4 (10.3 %) 6 (15.4 %) 26 (66.6 %) 3 (7.7 %)	 6 (6.9 %) 19 (21.8 %) 56 (64.4 %) 6 (6.9 %)	0.588
Arterial blood gases mean±SD PaO_2 , mmHg $PaCO_2$, mmHg	 85.6 ± 11.3 39.9 ± 5.0	 88.5 ±10.5 39.0 ± 3.9	 84.3 ± 11.4 40.3 ± 5.4	 0.055 0.146
Spirometry, mean±SD FVC % predicted FEV_1 % predicted FEV_1/FVC%	 99.0 ± 15.1 99.9 ± 15.2 81.3 ± 6.3	 99.2 ± 13.9 98.6 ± 13.0 82.9 ± 6.6	 98.8 ± 15.6 100.5 ± 16.2 80.6 ± 6.1	 0.896 0.519 0.057
TST, minutes mean±SD	353.5 ± 66.9	363.6 ± 50.9	349.0 ± 72.8	0.196
Sleep Efficiency, % mean±SD	76.7 ± 13.9	78.7 ± 10.8	75.9 ± 15.1	0.237
Stage I*, %	6.7 (3.8 – 11.8)	6.7 (4.1 – 9.6)	6.7 (3.6 –13.4)	0.952

Stage II*, %	57.3 (50.0 – 65.0)	57.1 (49.6 – 65.0)	57.5 (50.1 –65.6)	0.806
SWS*, %	20.0 (13.4 – 28.9)	22.1 (13.0 – 31.3)	19.5 (13.8 – 28.0)	0.377
Stage REM*, %	14.5 (9.6 – 18.3)	14.7 (11.5 – 18.3)	14.0 (9.0 – 18.3)	0.977
Arousal index*, number/hour	21.0 (13.8 – 36.6)	11.2 (8.6 – 18.0)	26.8 (18.0 – 46.7)	0.001
AHI*, events/hour	30.9 (14.3 – 49.0)	12.2 (9.2 – 13.9)	39.1 (29.4 – 60.1)	0.001
Time SpO_2 <90%TST*, %	3.0 (0.3 – 14.0)	0.3 (0.0 – 1.4)	6.5 (1.6 – 22.9)	0.001
Self-reported sleep duration, hours/night mean±SD	7.59 ± 1.591.63	6.92 ±1.67	7.89 ± 1.47	0.002
Epworth sleepiness scale score mean±SD	7.0 ± 5.0	7.0 ± 4.0	8.0 ± 5.0	0.575
Subjects with ESS >10, %	27.0	25.6	27.6	0.820

Definitions of abbreviations: BMI, body mass index; WC, waist circumference; IGT, impaired glucose tolerance; PaO_2, partial arterial pressure of oxygen; $PaCO_2$, partial arterial pressure of carbon dioxide; FVC%, predicted percentage of forced vital capacity; FEV%, predicted percentage of forced expiratory volume in the first second; FEV1/FVC, FEV1/FVC ratio; TST, Total sleep time; SWS, slow-wave sleep; AHI, apnea-hipoapnea index; SpO_2, arterial oxygen saturation by pulse oximetry; Time SpO_2 <90% TST, mean percentage of sleep time with SpO_2 below 90%; Subjects with EES > 10: Percentage of patients with an Epworth sleepiness scale score above 10.

Data are presented as mean ± SD, median (percentile 25 – percentile 75) and percentage for normal, non-normal (*) distributed and categorical data, respectively.

Unpaired t-student, Mann-Whitney and chi-square test were performed on normally, skewed and categorical data, respectively.

[§] Data according to Oral glucose test tolerance (OGTT) results in 117 patients.

Table e-2. Metabolic syndrome components and others metabolic variables according to OSA categories of patients without known type 2 diabetes.

	OSA -	OSA +			
	AHI < 15 (n = 39)	**AHI 15 – 30 (n=23)**	**AHI 30 – 50 (n=34)**	**AHI > 50 (n = 30)**	**p**
AHI [*], events/hour	12.2 (9.2 – 13.9)	23.2 (19.3 – 28.4)	36.2 (33.1 – 44.8)	78.2 (57.3 – 94.7)	-
WC, cm mean±SD	123.3 ± 13.9	126.4 ± 12.2	131.7 ± 14.0	135.8 ± 19.3	0.005[*]
SBP, mmHg mean±SD	128.3 ± 17.1	131.3 ± 15.5	139.8 ± 17.6	140.7 ± 16.0	<0.001[*,**]
DBP [*], mmHg	80.0 (60.0 – 90.0)	83.0 (70.0 – 90.0)	84.0 (80.0 – 90.0)	87.5 (83.0 – 90.0)	0.024[*,**]
cHDL, mmol/l mean±SD	1.30 ± 0.25	1.40 ± 0.64	1.23 ± 0.35	1.07 ± 0.24	0.012[§]
TG [*], mmol/l	1.15 (0.90 – 1.53)	1.21 (0.89 – 1.62)	1.21 (1.00 – 1.90)	1.50 (1.10 – 2.01)	0.203
FBG[*], mmol/l	5.40 (5.00 – 6.00)	5.40 (5.00 – 5.70)	5.70 (5.27 – 6.10)	5.60 (5.30 – 6.40)	0.158
Metabolic syndrome, %	33.3	52.2	61.8	63.3	0.040
Metabolic Index, number of components mean±SD	2.26 ± 1.02	2.52 ± 0.99	2.91 ± 1.08	3.23 ± 1.17	0.002[*]
Total Cholesterol, mmol/l mean±SD	5.04 ± 0.85	4.99 ± 1.07	4.88 ± 0.81	4.87 ± 0.97	0.844
cLDL[*], mmol/l	1.36 (1.15 – 3.06)	1.32 (1.01 – 1.80)	1.17 (1.05 – 1.47)	1.26 (0.98 – 1.54)	0.155
cVLDL [*], mmol/l	0.37 (0.25 – 0.66)	0.40 (0.23 – 0.61)	0.56 (0.27 – 0.65)	0.58 (0.34 – 0.92)	0.279
HbA1c[*], %	5.4 (5.0 – 5.7)	5.5 (5.1 – 5.8)	5.4 (5.2 – 5.8)	5.8 (5.5 – 6.4)	0.007[*,**,¶¶]
IGT + DM[∞], %	25.6	35.0	23.5	33.0	0.594

Definitions of abbreviations: AHI, apnea-hipoapnea index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; cHDL, high-density lipoprotein cholesterol, TG, triglycerides; FBG; fasting blood glucose; cLDL, low-density lipoprotein cholesterol; cVLDL, very low-density lipoprotein cholesterol; HbA1c, the percentage of

glycosylated hemoglobin; IGT, impaired glucose tolerance; Metabolic syndrome definition based on NCEP ATPIII modified criteria (Circulation 2009; 120: 1640-1645) and metabolic index calculated as the sum of components of MetS presented in each subject divided by the number of subjects in each AHI category.

Data are presented as mean ± SD, median (percentile 25 – percentile 75) and percentage for normal, non-normal distributed* and categorical data, respectively.

p-value: comparisons among OSA categories. Chi-sqare test was used for categorical variables. ANOVA with Scheffe post-hoc analysis was used for normal continuous variables. Kruskall-Wallis test was used for not normal distributed continuous variables using Mann-Whitney test and Bonferroni correction to compare between groups.

$^{\infty}$**:** Data according to Oral glucose test tolerance (OGTT) results in 117 patients with 9 missing data (2, 3 and 4 patients from groups AHI <15, AHI 15-30 and AHI>50, respectively).

For normal data p values of intra-group tests were presented as following: *, **, §, §§ for inter-group 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.

§§ p<0.001 between groups: AHI 15-30 and AHI 30-50.

¶ p<0.001 between groups: AHI <15 and AHI 15-30.

¶¶ p<0.001 between groups: AHI 30-50 and AHI >50.

Table e-3. The association of metabolic parameters with OSA severity evaluated as AHI and Time SpO_2 <90% TST in patients without known type 2 diabetes.

Dependent variable	Adjusted ß coefficient * (95% CI)	p	Adjusted ß coefficient ** (95% CI)	p
Independent variable: AHI				
WC, cm	0.047 (-0.017 – 0.110)	0.146	-	-
SBP, mmHg	0.133 (0.025 – 0.242)	0.017	0.121 (0.013 – 0.23)	0.029
DBP, mmHg	0.106 (0.006 – 0.206)	0.038	0.093 (-0.007 – 0.193)	0.067
TG, mmol/l	0.004 (-0.001 – 0.009)	0.090	0.003 (-0.001 – 0.008)	0.153
cHDL, mmol/l	-0.003 (-0.005 – -0.000)	0.045	-0.003 (-0.005 - 0.000)	0.041
FBG, mmol/l	0.002 (-0.005 – 0.009)	0.548	0.001 (-0.005 – 0.008)	0.668
HbA1c, %	0.006 (0.002 – 0.010)	0.006	0.006 (0.002 – 0.010)	0.006
Independent variable: Time SpO_2 <90% TST				
WC, cm	0.064 (-0.014 – 0.141)	0.108	-	-
SBP, mmHg	0.110 (-0.025 – 0.245)	0.108	0.093 (-0.042 – 0.228)	0.176
DBP, mmHg	-0.023 (-0.148 – 0.102)	0.713	-0.044 (-0.168 – 0.080)	0.485
TG, mmol/l	0.003 (-0.003 – 0.009)	0.313	0.002 (-0.004 – 0.008)	0.495
cHDL, mmol/l	-0.002 (-0.099 – 0.202)	0.245	-0.002 (-0.005 - 0.001)	0.239
FBG, mmol/l	0.052 (-0.005 – 0.009)	0.497	0.038 (-0.114 – 0.190)	0.624
HbA1c, %	0.007 (0.002 – 0.012)	0.009	0.007 (0.002 – 0.012)	0.009

Definitions of abbreviations: WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; cHDL, high density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, the percentage of glycosylated hemoglobin;

Data was analyzed using linear regression being the dependent variable each of metabolic parameters and the independent variable apnea-hypoapnea index or Time SpO_2 <90%

TST. Results were expressed as unadjusted and adjusted ß coefficient (95% confidence interval) and p-value.

* data adjusted by age, gender, BMI and smoking

** data adjusted by age, gender, waist circumference and smoking

Table e-4. General and Sleep characteristics of the female group.

	Total (n=115)	**IAH < 15** (n=33)	**IAH ≥ 15** (n=82)	**P**
Age, years mean±SD	44.0 ± 10.0	41.0 ± 10.0	45.0 ± 10.0	0.032
BMI, Kg/m^2 mean±SD	46.0 ± 5.3	44.9 ± 4.6	46.5 ± 5.6	0.149
Postmenopausal state, %	24.3	15.2	34.6	0.038
Current smoking, %	18.3	27.3	14.6	0.147
Alcohol consumption, %	3.5	6.1	2.4	0.338
Body Fat, % mean±SD	50.7 ± 7.4	48.0 ± 8.3	51.8 ± 6.7	0.025
WC, cm mean±SD	126.3 ± 14.2	102.6 ± 14.5	128.6 ± 13.5	0.006
Waist-Hip Ratio mean±SD	0.90 ± 0.08	0.86 ± 0.05	0.92 ± 0.08	0.001
Neck circumference, cm*	41.0 (39.0 – 43.0)	40.0 (39.0 – 42.0)	42.0 (40.0 – 43.5)	0.020
Obesity Duration, years mean±SD	25.5 ± 10.3	24.9 ± 9.3	25.7 ± 10.7	0.045
Physical Activity, $METS.min.week^{-1}$, mean±SD	2358.4 ± 2442.2	2103.1 ± 2411.5	2464.6 ± 2462.6	0.484
Glucose tolerance assessment [§]**,** n (%)				
Diabetes	27 (23.5%)	7 (21.2%)	20 (24.4%)	0.512
IGT	17 (14.8%)	4 (12.1%)	13 (15.9%)	
Normal	65 (56.5%)	20 (60.6%)	45 (54.9%)	
Missing data	6 (5.2%)	2 (6.1%)	4 (4.8%)	
Arterial blood gases mean±SD				
PaO_2, mmHg	85.7 (10.5)	86.4 (10.2)	85.5 (10.7)	0.693
$PaCO_2$, mmHg	39.4 (4.5)	38.6 (4.1)	39.7 (4.7)	0.240
Spirometry, mean±SD				
FVC % predicted	100.3 ± 15.1	95.3 ± 16.1	102.3 ± 14.3	0.030
FEV_1 % predicted	101.2 ± 14.8	96.2 ± 13.6	103.2 ± 14.9	0.026
FEV_1/FVC%	81.2 ± 7.1	79.5 ± 6.3	81.8 ± 7.2	0.125
TST, minutes mean±SD	349.6 ± 65.6	351.7 ± 51.1	348.7 ± 70.9	0.806
Sleep Efficiency, % mean±SD	75.3 ± 13.7	76.0 ± 12.1	74.9 ± 14.4	0.721
Stage I*, %	6.5 (3.8 – 11.0)	7.4 (5.0 – 9.5)	5.9 (3.5–13.4)	0.551
Stage II, % mean±SD	58.6 ± 15.5	57.6 ± 10.3	59.0 ± 17.2	0.657
SWS*, %	21.5 (14.2 – 28.9)	21.6 (13.4 – 30.0)	21.1 (15.6 – 28.9)	0.359

Stage REM*, %	14.5 (9.3 – 19.0)	14.7 (11.5 – 18.3)	14.3 (9.1 – 19.0)	0.588
Arousal index*, number/hour	22.7 (13.8 – 38.3)	11.0 (8.6 – 18.0)	27.9 (17.4 – 45.2)	< 0.001
AHI*, events/hour	30.8 (14.3 – 48.0)	11.7 (7.7 – 13.6)	36.9 (28.9 – 56.1)	< 0.001
Time SpO_2 <90%TST*, %	3.2 (0.4 – 13.8)	0.2 (0.0 – 1.1)	5.7 (1.5 – 16.1)	< 0.001
Self-reported sleep duration, hours/night mean±SD	7.61 ± 1.76	6.72 ± 1.74	7.77 ± 1.57	0.003
Epworth sleepiness scale score mean±SD	7.0 ± 5.0	7.0 ± 4.0	7.0 ± 5.0	0.642
Subjects with ESS >10, %	29 (25.2)	7 (21.2)	22 (26.8)	0.039

Definitions of abbreviations: BMI, body mass index; WC, waist circumference; IGT, impaired glucose tolerance; PaO_2, partial arterial pressure of oxygen; $PaCO_2$, partial arterial pressure of carbon dioxide; FVC%, predicted percentage of forced vital capacity; FEV%, predicted percentage of forced expiratory volume in the first second; FEV1/FVC, FEV1/FVC ratio; TST, Total sleep time; SWS, slow-wave sleep; AHI, apnea-hipoapnea index; SpO_2, arterial oxygen saturation by pulse oximetry; Time SpO_2 <90% TST, mean percentage of sleep time with SpO_2 below 90%; Subjects with EES > 10: Percentage of patients with an Epworth sleepiness scale score above 10.

Data are presented as mean ± SD, median (percentile 25 – percentile 75) and percentage for normal, non-normal distributed (*) and categorical data, respectively.

Unpaired t-student, Mann-Whitney and chi-square test were performed on normally, skewed and categorical data, respectively.

[§] Data according to OGTT results in 89 patients and previous known diabetes in 20 patients.

Table e- 5. The association of metabolic syndrome with obstructive sleep apnea in females

Independent Variable	Unadjusted Odds Ratio (95% CI)	p	Adjusted Odds Ratio (95% CI)	p
Presence of OSA AHI ≥ 15 events/hour	3.86 (1.64-9.08)	0.002	2.79 (1.09-7.17)	0.033
Age, years			1.03 (0.97-1.10)	0.319
BMI, Kg/m^2			1.08 (0.99-1.17)	0.073
Postmenopausal state, %			1.98 (0.51-7.65)	0.322
Body Fat, %			1.02 (0.96-1.09)	0.490
Independent Variable	**Unadjusted Odds Ratio (95% CI)**	**p**	**Adjusted Odds Ratio (95% CI)**	**p**
Presence of nocturnal hypoxemia Time SpO_2 <90% ≥ 3.30% of TST	4.67 (2.11-10.45)	<0.001	3.90 (1.61-9.46)	0.003
Age, years			1.02 (0.96-1.09)	0.529
BMI, Kg/m^2			1.09 (1.00-1.19)	0.056
Postmenopausal state, %			2.17 (0.54-8.68)	0.274
Body Fat, %			1.02 (0.95-1.08)	0.640
Independent Variable	**Unadjusted Odds Ratio (95% CI)**	**p**	**Adjusted Odds Ratio (95% CI)**	**p**
Presence of OSA with significant nocturnal hypoxemia AHI≥15 events/hour and Time SpO_2 <90% ≥ 3.30% of TST	2.79 (1.68-4.64)	<0.001	2.47 (1.39-4.38)	0.002
Age, years			1.02 (0.96-1.09)	0.564
BMI, Kg/m^2			1.08 (0.99-1.18)	0.073
Postmenopausal state, %			2.02 (0.50-8.13)	0.321
Body Fat, %			1.01 (0.94-1.08)	0.847

Definitions of abbreviations: AHI, apnea-hypoapnea index; Presence of OSA defined as an AHI ≥ 15 events/hour; Time SpO_2 <90% TST, mean percentage of sleep time with SpO_2 below 90%; Presence of significant nocturnal hypoxemia considering values higher or equal to the median of the variable Time SpO_2 <90%TST; BMI, body mass index.

Data were analyzed using binary logistic regression. The presence of metabolic syndrome defined by NCEP ATPIII modified criteria (Circulation 2009; 120: 1640-1645) was considered the dependent variable. Data were adjusted for age, BMI, postmenopausal state and Body Fat. Results were expressed as unadjusted and adjusted odds ratio (95% confidence interval) and p-value.

Figure e-1. Framingham Cardiac Risk Score according to OSA categories in patients without known type 2 diabetes.

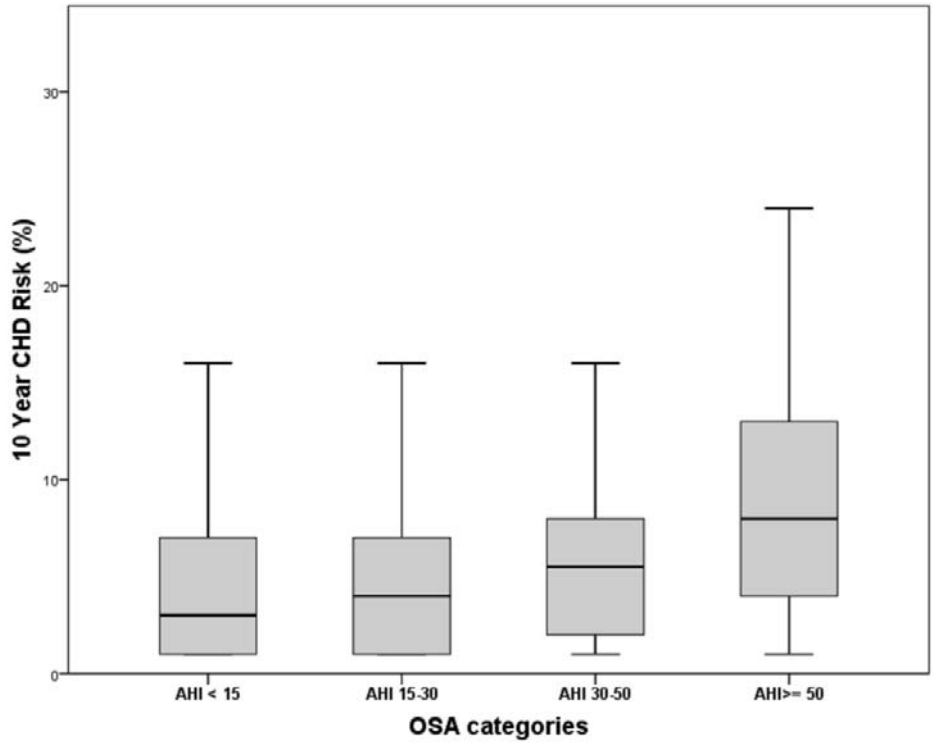
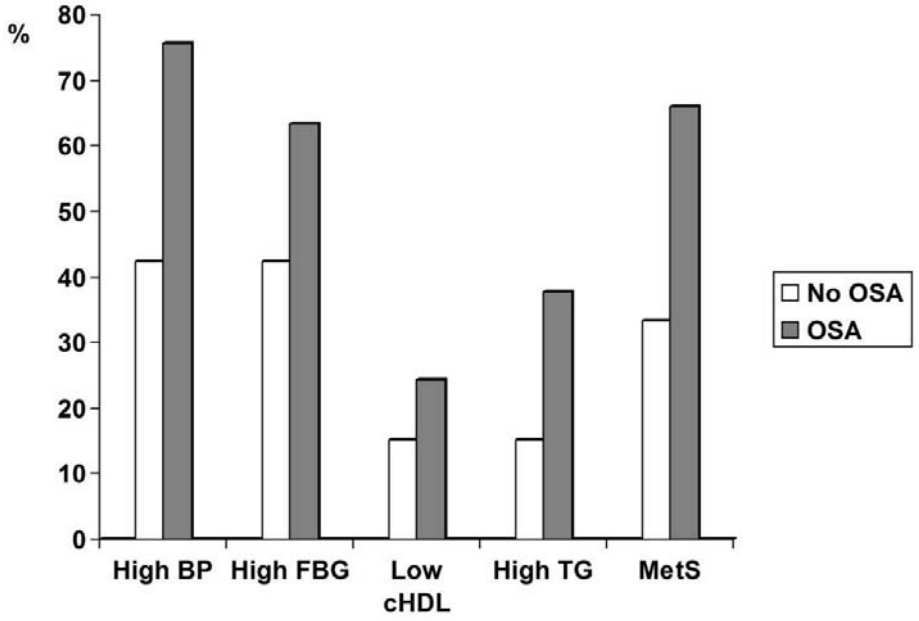


Figure legend: The Framingham Cardiac Risk Score (Wilson P.W. et al. *Circulation* 1998:97(18): 1837-1847) was applied to estimate the 10-year risk of coronary events in the different AHI categories. ANOVA with Scheffe post-hoc analysis was used for comparisons between OSA categories. * p-value <0.005.

Figure e-2. Prevalence of each component of metabolic syndrome according OSA status in the female group .



Legend: Figure. The presence of OSA was considered when AHI ≥15 events /hour. The metabolic syndrome definition and its components were based on NCEP ATPIII modified criteria (Circulation 2009; 120: 1640-1645). Chi-square test was used for comparisons.

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SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Optimizing screening of severe obstructive sleep apnea in patients undergoing bariatric surgery

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Abstract

Background: Obstructive sleep apnea is common in patients waiting for bariatric surgery (BS). International consensuses have recommended assessment of obstructive sleep apnea in the preoperative evaluation to avoid perioperative complications. Polysomnography is the standard diagnostic method but is expensive and time-consuming. The aim of our study was to detect those patients who merit treatment before BS using a simple predictor model. The study was conducted at 3 university hospitals (Hospital de Bellvitge, Hospital de la Santa Creu i Sant Pau, Hospital Clinic de Barcelona).
Methods: A prospective cross-sectional study was conducted of 136 consecutive bariatric subjects. The outcome variable was severe obstructive sleep apnea, defined as an apnea-hypoapnea index of ≥30 events/hr by polysomnography. The predictors evaluated were anthropometric and clinical in the first model, with an oxygen desaturation index of ≥3% added to the second model. Predictive models were constructed using multivariate logistic regression analysis. The best model was selected according to the area under the receiver operating characteristic curve.
Results: The first model identified 4 independent factors: age, waist circumference, systolic blood pressure, and witnessed apnea episodes, with a sensitivity of 78%, specificity of 68%, and area under the receiver operating characteristic curve of .83 (95% confidence interval .76–.90, $P < .001$). The second model identified 2 independent factors (witness apnea episodes, oxygen desaturation index of ≥3%), with a sensitivity of 91%, specificity of 85%, and area under the receiver operating characteristic curve of .94 (95% confidence interval .89–.98, $P < .001$). The 2-step model predictive values were sensitivity of 90%, specificity of 91%, and accuracy of 90% (95% confidence interval 84–94%). After applying the first model and then the second, 45% of subjects would have been ruled out (15% and 30%, respectively) and 55% would require additional sleep management before BS.

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Conclusion: The proposed model could be useful for improving the management of complex patients before BS and optimizing limited polysomnography resources. (Surg Obes Relat Dis 2012; xx:xxx.)

Keywords: Obstructive sleep apnea; Bariatric surgery; Apnea-hypoapnea index; Oxygen desaturation index; Morbid obesity

Obstructive sleep apnea (OSA), defined as the presence of an apnea/hypopnea index (AHI) of >5 events/hr of sleep, is a prevalent condition and is increasing in parallel with obesity [1]. In the general population, the estimated prevalence is about 24% in men and 9% in women [2]; however, it can reach rates of >30% in obese subjects [3]. More particularly, in morbidly obese patients scheduled for bariatric surgery (BS), the prevalence of OSA could reach rates >90% and more than one half (53%) might present with a severe form of the disease (AHI of ≥30 events/hr) [4].

Subjects with OSA have an especial predisposition to develop perioperative complications [5]. In several surgical settings, patients with OSA had more perioperative complications than those without OSA [6,7]. During abdominal surgery, those who were treated with continuous positive airway pressure (CPAP) had fewer perioperative complications and a lower rate of postextubation respiratory failure than those who were not [8]. Recent guidelines for patients scheduled for elective major surgery have recommended considering a preoperative assessment of OSA and introducing CPAP therapy, if required [9].

Although the evidence is limited in the bariatric setting, this assessment could be even more important, because these subjects have a greater anesthetic risk owing to their extreme obesity [10], and they also tend to present with concomitant OSA. Unrecognized and untreated OSA could increase the length of hospital stay [11] and the costs of postoperative care [12]. Also, its identification and subsequent precautionary measures during the perioperative period might help avoiding intensive care after BS [13]. The American [14] and European [15] guidelines of the management of bariatric patients recommend screening for OSA before surgery whenever possible. Furthermore, if OSA is detected, several perioperative precautions should be undertaken to avoid potential OSA-related complications, and CPAP treatment is recommended, if severe OSA is present.

However, systematic OSA screening in the BS setting is a major healthcare challenge, owing to the frequent lack of symptoms, even for patients with severe OSA. Full overnight polysomnography (PSG) is the standard diagnostic test but is costly and time-consuming. Various investigators have attempted to determine clinical predictors to rule out patients with a low risk of OSA and to detect those at high risk who would require additional sleep management before BS [16–24]. Most, however, were unable to find any reliable predictive factor, and, thus, they strongly recommended PSG for all patients undergoing BS [17–24]. The aim of the present study was to create a concise and easy-to-use predictor model to detect patients with severe OSA to be able to treat those with OSA with CPAP before surgery.

Methods

Study population

Consecutive patients prospectively included in the multidisciplinary BS program of the 3 university hospitals were studied in the corresponding sleep units from January 2009 to February 2010. The study protocol was approved by the local ethics committee of each hospital (PR052/08, 07/064/797, and PI080277). All participants gave informed written consent. The inclusion criteria were age 18–60 years and body mass index (BMI) of ≥40 kg/m^2 or BMI of ≥35 kg/m^2 with obesity-related co-morbidity. The exclusion criteria were previously treated OSA, unstable cardiovascular disease, inflammatory disease during the previous 6 months, immunosuppressant therapy, severe cognitive or psychiatric disorder, chronic obstructive pulmonary disease, pregnancy, alcohol abuse, and a refusal to participate.

Definition of study variables

Dependent/outcome variable. All subjects underwent full overnight PSG testing (Siesta, Compumedics, Melbourne, Australia), including a recording of the oronasal flow (termistor and cannula), thoracoabdominal movements, electrocardiogram, submental and pretibial electromyogram, electrooculogram, electroencephalogram, pulse oximetry, and body position sensor. The sleep stages were manually scored using the Rechtschaffen and Kales criteria. PSG interpretation was assessed using the standard criteria [25]. Apnea was defined as the absence of airflow lasting a minimum of 10 seconds, hypopnea as any reduction in airflow lasting a minimum of 10 seconds accompanied by a decrease of ≥3% in oxygen saturation recorded with a digital pulse oximeter or microarousal, and the AHI as the number of apnea events or hypoapnea events/hr of sleep. The outcome of interest in the analysis was the presence of severe OSA established by an AHI of ≥30 events/hr.

Independent/potentially predictive variables. The independent variables considered for the analysis included demographic (age and gender), and anthropometric (BMI; neck circumference, measured at the level of the laryngeal prominence; waist circumference [WC], measured midway between the lower rib and the iliac crest; waist/hip ratio) factors. Also, each subject was asked to answer 6 questions related to OSA symptoms (habitual snoring, observed sleep

apnea, nocturia, nocturnal choking, waking unrefreshed, and morning headaches). Each question was evaluated in terms of the frequency of the occurrence as "usually," "sometimes," "rarely," and "never." Next, each 4-point answer was converted into a yes/no (1/0) format as follows: "never" and "rarely" were dichotomized as 0 and "sometimes" and "usually" as 1. The clinical blood pressure was measured by a standard mercury sphygmomanometer at least twice, with 5 minutes between each recording [26]. The subjects' subjective daytime sleepiness was quantified using the Epworth Sleepiness Scale (ESS), a widely used 8-item questionnaire that evaluates the likelihood of dozing in various daytime situations and includes a 4-point scale for each item [27]. Excessive daytime sleepiness (EDS) was considered present when the ESS score was ≥10. An oxygen desaturation index of ≥3% (ODI3%), defined as the number of oxygen desaturations ≥3%/hr was recorded using a finger pulse-oximeter during a full-night intralaboratory PSG study.

Statistical analysis

The data are presented as the mean ± standard deviation, median (interquartile range), or percentages for the parametric, nonparametric, and categorical data, respectively. Predictor models were constructed using multivariate logistic regression analysis to estimate the probability of the outcome variable: the presence of severe OSA (AHI ≥30 events/hr). Our first option was to construct a clinical model, including all the variables, except for ODI3%, because this variable implies performing a simplified sleep study. A second predictive model was created that included the variable ODI3%. The initial model included all the variables that were statistically significant on univariate logistic regression analysis ($P < .05$). Next, a backward elimination procedure was used; variables with $P > .05$ were removed from the model step by step according to their P value. Once the final predictive variables were identified, receiver operating characteristic curve analyses were performed to assess the accuracy of the proposed models and to determine their ability to correctly classify patients as having severe or nonsevere OSA using the area under the curve for each model with the 95% confidence interval (CI). The classification variable was the probability of severe OSA predicted by the model, and the reference variable was the presence or absence of severe OSA according to the PSG findings (AHI ≥30 events/hr). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall test accuracy were calculated for each model to determine the optimal cutoff values and maximize diagnostic efficiency. Each model led to a given predictive formula with a specific sum value that represents the neperian log transformation of the probability of having severe OSA. This sum value, termed "Logit(p)," can be easily converted to a probability concept by the following function: $\text{Logit}(p) = ln(p/1 - p)$, where p is the chosen cutoff for each model. Then, for each model with a fixed cutoff, the probability of having severe OSA can be calculated as follows: if the sum value of the formula is greater than the Logit(p) value, the patient is considered at greater risk and if it is less than the Logit(p) value, the patient is considered at lower risk. The Homer-Lemershow test was used to check the internal validity of the models (goodness-of-fit when $P > .05$). Cross-validation was performed to check the overfitting of the data, using the 10-fold validation method. SPSS, version 15 (SPSS, Chicago, IL) was used for logistic regression analysis and receiver operating characteristic analysis, and the R Development Core Team 2010 was used for cross-validation (10-fold method) [28].

Results

Patient characteristics

The data from 136 subjects were studied. The main characteristics of the overall sample are listed in Table 1. The mean age and BMI was 43 ± 10 years and 46 ± 6 kg/m^2, respectively. Most of the patients were women (71%). Regarding symptoms, 90% snored but the other complaints were only observed infrequently. The median overall AHI was 33.2/h (interquartile range 15.5–56.7). The OSA severity was no OSA (AHI <5/hr) in 1 patient (1%), mild OSA (AHI 5–15/hr) in 32 (23%), moderate OSA (AHI 15–30/hr) in 27 subjects (20%), and severe OSA (AHI ≥30/hr) in 76 subjects (56%). The overall mean ESS value was 7 ± 5, and EDS was reported by only 23% of the patients. No differences were found in the ESS or EDS between those with severe and nonsevere OSA.

Clinical model: screening questionnaire

On univariate logistic regression analysis, no independent association was found between an AHI of ≥30/hr and male gender, ESS, or EDS.

The multivariate analysis identified 4 independent predictive factors for the presence of severe OSA: age, WC, systolic blood pressure, and witnessed apnea events (Table 2). According to the model, the probability of severe OSA for a given patient can be obtained by applying the formula: $-15.78 + .069 \times \text{age} + .071 \times \text{WC} + .026 \times$ systolic blood pressure $+ 1.11 \times 1$ if observed apnea present or 0 if observed apnea absent (see Table 2). The area under the curve for the model was .83 (95% CI .76–.90, $P < .001$; Fig. 1). Assuming the standard cutoff (.5) for the classification, the model had the following predictive values: sensitivity 78%, specificity 68%, PPV 76%, and NPV 71%. A cutoff of .23 was chosen to maximize the sensitivity of the model, obtaining the following predictive values: sensitivity

Table 1
General patient characteristics

Variable	Total (n = 136)	AHI <30 (n = 60)	AHI ≥30 (n = 76)	P value
Demographic, anthropometric				
Age (yr)	43 ± 10	40 ± 11	46 ± 9	.001
Gender (% female)	96 (71)	47 (78)	49 (65)	.078
BMI (kg/m^2)	46.4 ± 6.0	45.0 ± 4.9	47.6 ± 6.7	.01
NC* (cm)				<.001
Median	43.0	41.0	44.0	
Interquartile range	40.0 – 47.5	40.0 – 44.0	41.0 – 50.0	
WC (cm)	130.9 ± 15.2	124.3 ± 11.7	136.1 ± 15.6	<.001
WHR (cm)	.94 ± .10	.90 ± .09	.97 ± .10	<.001
SBP (mm Hg)	136.5 ± 17.9	129.9 ± 17.3	141.8 ± 16.7	<.001
DBP* (mm Hg)				.034
Median	85.0	83.0	88.0	
Interquartile range	80.0 – 92.0	70.0 – 92.0	80.0 – 91.5	
Clinical				
Habitual snoring	123 (90%)	52 (87)	71 (93)	.183
Observed apnea	35 (26%)	7 (12)	28 (37)	.001
Nocturia	59 (43%)	20 (33)	39 (51)	.036
Nocturnal choking	21 (15%)	7 (12)	14 (18)	.279
Waking unrefreshed	70 (52%)	29 (48)	41 (54)	.515
Morning headache	45 (33%)	19 (32)	26 (34)	.754
Sleep				
EES score	7 ± 5	6 ± 4	8 ± 5	.07
EDS	31 (23)	10 (17)	21 (28)	.13
AHI* (events/hr)				<.001
Median	33.2	14.4	51.1	
Interquartile range	15.5 – 56.7	11.6 – 21.2	37.7 – 80.7	
ODI3%* (desaturations/hr)				<.001
Median	25.4	11.6	42.0	
Interquartile range	12.0 – 46.5	6.4 – 17.4	30.5 – 63.0	
CT90%* (%)				<.001
Median	4.7	.40	14.9	
Interquartile range	.5 – 19.3	.00 – 2.05	5.7 – 40.5	
AHI category				
<5	1 (1)	1 (2)	—	
5–15	32 (23)	32 (53)	—	
15–30	27 (20)	27 (45)	—	
30–50	37 (27)	—	37 (49)	
≥50	39 (29)	—	39 (51)	

AHI = apnea-hypoapnea index; BMI = body mass index; NC = neck circumference; WC = waist circumference; WHR = waist/hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; ESS = Epworth Sleepiness Scale; EDS = excessive daytime sleepiness (ESS >10); ODI3% = oxygen desaturation index >3%; CT90% = mean percentage of sleep time with oxygen saturation recorded with digital pulse-oximeter below 90%.

Data presented as mean ± standard deviation, numbers, with percentages in parentheses, or median and interquartile range.

Bivariate comparisons evaluated using chi-square (categorical), Student's *t* (parametric), or Mann-Whitney *U* (nonparametric) tests.

* Nonparametric.

100%, specificity 35%, PPV 66%, and NPV 100% (Fig. 1). The Logit(p) was $ln(.23/.77) = -1.208$. Thus, after applying the predictive formula, the patient was considered at greater risk of having severe OSA if the sum value was greater than −1.208 and at lower risk, if the sum value was less than −1.208 (Table 2).

Second step: clinical plus ODI3% model

The data from the patients classified as being at high risk of having severe OSA according to the clinical model (n = 115) were used to create the second model, which included the same variables plus the ODI3%. The multivariate analysis identified 2 independent predictive factors for the presence of severe OSA: witnessed apnea episodes and ODI3% (Table 3). According to the model, the probability of severe OSA could be calculated by $-3.653 + 1.290 \times$ (1 if witnessed apnea present and 0 if witnessed apnea absent) + $.159 \times$ ODI3%. The area under the curve for the model was .94 (95% CI .89–.98, $P < .001$; Fig. 2). For a standard cutoff (.5), the model had the following predictive values: sensitivity 91%, specificity 85%, PPV 92%, and NPV 83% (Fig. 2). The Logit(p) was $ln(.5/.5) = ln(1) = 0$. Thus, after applying the formula derived from this second model, the patient was considered at greater risk of having severe OSA if the sum value was >0, and at lower risk, if the sum value was <0 (Table 3).

Table 2
Significant independent predictors of AHI ≥30 identified in final clinical model (n = 136)

Variable	β	Odds ratio (95% CI)	P value
Age (yr)	.069	1.072 (1.024–1.122)	.003
WC (cm)	.071	1.074 (1.035–1.114)	<.001
SBP (mm Hg)	.026	1.027 (1.000–1.053)	.047
Observed apnea (yes/no)	1.105	3.018 (1.064–8.559)	.038
Constant	−15.776		

AHI = apnea-hypoapnea index; CI = confidence interval; WC = waist circumference; SBP = systolic blood pressure; OSA = obstructive sleep apnea.

Multiple logistic regression analysis.

Predictive formula of clinical model: $-15.776 + .069 \times \text{age} + .071 \times \text{WC} + .026 \times \text{SBP} + 1.105 \times 1$ if witnessed apnea episodes present or 0 if absent; if < -1.208, low probability of having severe OSA, no additional study needed; if ≥ -1.208, high probability of having severe OSA, perform pulse oximetry.

Two-stage predictive model

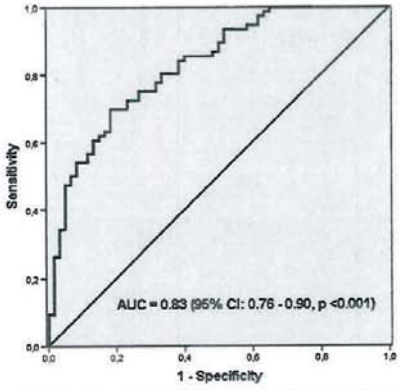
Using this 2-step model in the overall sample (n = 136), we could rule out 21 patients (15%) by applying the first formula with no false-negative findings. Next, with the remaining subjects (n = 115) and applying the second formula, we could rule out another 40 patients (35%; Fig. 3). Thus, the number of additional sleep evaluations would be reduced from 136 to 75 (a reduction of 45%), with an acceptable percentage of misclassification rates: false negative of 9% and false positive of 10%.

The final predictive values of the 2-step model for identifying severe OSA (sensitivity 91%, specificity 90%, PPV 92%, NPV 89%, and overall accuracy of .90 (95% CI .84–.94) are listed in Table 4. After using the 10-fold cross-validation method, the predictive values of the final 2-step model were a sensitivity of 88% and specificity of 90%.

Discussion

For a screening tool for severe OSA to be suitable for widespread use in the bariatric setting, it should largely record high sensitivity and NPV values. A model should allow us to correctly detect most of the subjects with severe OSA to refer them for additional sleep management before BS. However, we also should be reasonably sure that those who are identified as being at low risk are unlikely to have severe OSA. Applying the first clinical step, we obtained sufficiently high values of sensitivity and NPV but an unacceptably low specificity. This means that we would perform PSG on subjects identified as at high risk of severe OSA who did not have such a severe degree of OSA. Nevertheless, 15% of the sample could be excluded without any sleep study, which is important. To increase the specificity and reduce additional PSG studies, we performed a second step, applying the clinical factors plus ODI3% in a model for those subjects categorized by the first model as being at high risk of severe OSA.

Using this 2-step model of screening in the overall sample would allow us to optimize the use of PSG resources: 45% (61 of 136) of the patients would not require additional sleep studies before surgery: 15% using only clinical parameters and 35% requiring additional pulse-oximetry. The number of additional sleep evaluations would be reduced from 136 to 75 (a reduction of 45%), with an acceptable



	AHI ≥ 30 PROBABILITY (Predicted)		
PSG (Observed)	LOW	HIGH	
AHI < 30	21 (TN)	39 (FP)	Sp 35%
AHI ≥ 30	0 (FN)	76 (TP)	Se 100%
ROC cut-off: 0.23	NPV 100%	PPV 66%	GP 71%

AUC, area under the curve; 95% CI, 95% confidence interval; AHI, apnea-hypoapnea index; PSG, polisomnography; Se, Sensitivity; Sp, Specificity; PPV, Positive predictive value; NPV, Negative predictive value; GP, global accuracy; TN, true negative; FP, false positive; FN, false negative; TP, true positive; ROC, receiver operating curve.

Fig. 1. Receiver operating characteristic (ROC) curve for clinical predictive model and contingency table for modified clinical model (n = 136). AUC = area under curve; Se = sensitivity; Sp = specificity; GP = global accuracy; TN = true negative; FP = false positive; FN = false negative; TP = true positive.

Table 3
Significant independent predictors of AHI ≥30 events/hr identified in clinical plus ODI3% model (n = 115)

Variable	β	Odds ratio (95% CI)	P value
ODI3% (desaturations/hr)	.159	1.172 (1.102–1.246)	<.001
Observed apnea (yes/no)	1.290	3.633 (.909–14.522)	.060
Constant	−3.656		

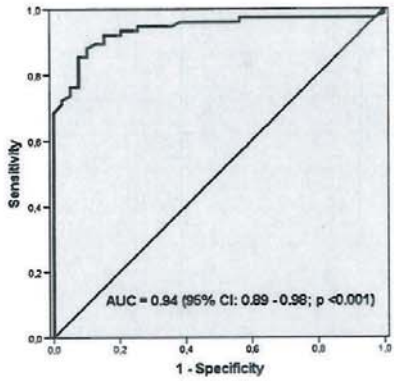
AHI = apnea-hypoapnea index; CI = confidence interval; ODI3% = oxygen desaturation index >3%; OSA = obstructive sleep apnea.

Predictive formula of clinical plus oximetry model: −3.653 + 1.290 × 1 if witnessed apnea present or 0 if absent + .159 × ODI3%; if <0, low probability of having severe OSA, screening finished; if ≥0, high probability of having severe OSA, additional sleep management needed.

percentage of misdiagnosed cases (total false-negative rate 9% and false-positive rate 10%). The application of the second formula (ODI3% and witnessed apnea episodes) at the beginning for all patients would lead to predictive values as great as those with the 2-step model, but the main objective of our study would not be achieved: ruling out patients who do not have severe OSA to avoid any additional sleep study (from complex PSG to simple pulse-oximetry).

The results of the present study support the notion reported by previous investigators [16,19–22] that typical OSA-related symptoms (e.g., snoring and daytime sleepiness, as assessed by the ESS) do not predict for OSA in bariatric cohorts, although OSA is highly prevalent. That could explain the limited usefulness of previously published models. Male gender did not predict for severe OSA in the present cohort, although it is a typical predictive factor of OSA in the general population and in some bariatric cohorts with a lower percentage of men [19,23]. Moreover, in contrast to earlier models, our proposal includes new, more discriminating clinical variables (e.g., WC and systolic blood pressure), in addition to age and observed apnea episodes. However, even so, just as in previous studies, the overall accuracy of the present clinical model alone was insufficient to predict severe OSA, making it necessary to increase the overall specificity by adding a second step using additional data (ODI3%) from a simplified sleep study.

The study published by Sareli et al. [19] attempted to predict OSA (AHI ≥5/hr) and severe OSA (AHI ≥30/hr), as confirmed by an overnight PSG study, in 342 consecutive bariatric patients by developing a model that included BMI, age, gender, and OSA-related respiratory symptoms. They concluded that even with the most stringent possible cutoff value, their model could not predict OSA with sufficient certainty. They also suggested, however—in line with our data—that their model could predict with relatively high certainty severe OSA. Dixon et al. [16] also constructed a clinical-analytical model to predict OSA in 99 symptomatic patients waiting for BS, determined by the number of observed apnea episodes, male gender, greater BMI, age, fasting insulin, and the percentage of glycosylated hemoglobin, with high sensitivity and moderate specificity (96% and 71% for AHI ≥30/hr, respectively). However, in contrast to our study of consecutive patients, these investigators studied only those with a clinical suspicion of OSA. Recently, Kolotkin et al. [23] evaluated the model proposed by Dixon et al. [16], as well as a new alternative model that included 10 predictive variables from 310 consecutive bariatric pa-



	AHI ≥ 30 PROBABILITY (Predicted)		
PSG (Observed)	LOW	HIGH	
AHI < 30	33 (TN)	6 (FP)	Sp 85%
AHI ≥ 30	7 (FN)	69 (TP)	Se 91%
ROC cut-off: 0.50	NPV 83%	PPV 92%	GP 89%

AUC, area under the curve; 95% CI, 95% confidence interval; AHI, apnea-hypoapnea index; PSG, polisomnography; Se, Sensitivity; Sp, Specificity; PPV, Positive predictive value; NPV, Negative predictive value; GP, global accuracy; TN, true negative; FP, false positive; FN, false negative; TP, true positive; ROC, receiver operating curve.

Fig. 2. Receiver operator characteristic (ROC) curve for clinical plus oximetry predictive model and contingency table for clinical plus oximetry model (n = 115). AUC = area under curve; Se = sensitivity; Sp = specificity; GP = global accuracy; TN = true negative; FP = false positive; FN = false negative; TP = true positive.

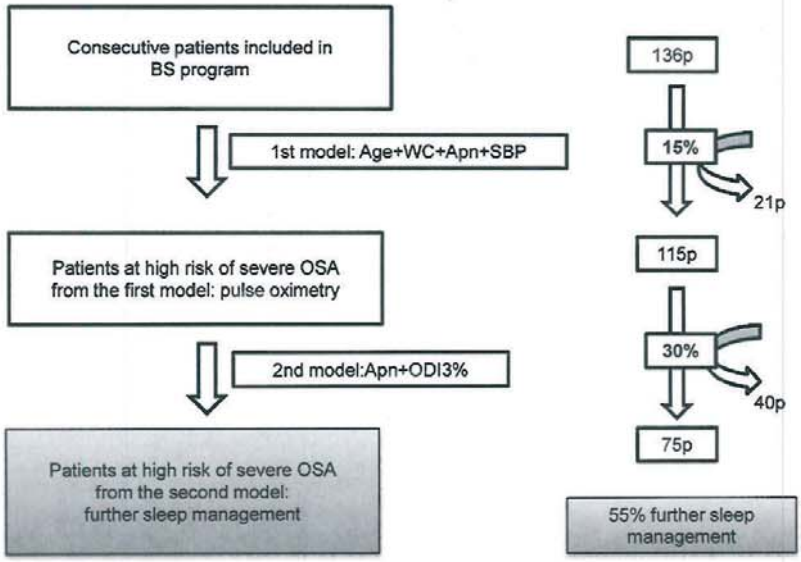


Fig. 3. Algorithm for proposed 2-step screening model. Apn = observed apnea episodes; SBP = systolic blood pressure.

tients, regardless of symptoms. However, the sensitivity and specificity values observed were <80% in any of the 2 models. Therefore, all those previous works could not find any reliable predictive factor to assess OSA in the bariatric population before BS.

The present model could therefore become a first step toward the optimization of sleep resources in the management of bariatric patients, without compromising their perioperative security. The general measures for OSA perioperative management, such as the use of the reverse Trendelenburg position, anticipation of a possible difficult airway, use of short-acting anesthetic agents, avoidance of opioids, and extubation while awake in a nonsupine position [5], should be applied to every patient who undergoes BS, because the prevalence of OSA (AHI ≥5/hr) is extremely high in bariatric populations [4,19,24,29]. Thus, the major efforts related to OSA preoperative diagnosis should be concentrated toward the detection of those with severe disease who would greatly benefit from CPAP therapy before the surgical procedure. Obviously, many others studies could be performed to help even more with the sleep management of these patients, such as the evaluation of auto-CPAP use as the first choice treatment of patients with OSA in a BS program, which would simplify CPAP titration before surgery. It would also be useful to automatically adjust the pressure changes required over time, as patients experience progressive weight loss after surgery.

Some limitations should be mentioned. First, our study did not include an external validation group, although we used the 10-fold cross-validation method to check the presence of overfitting data. Second, ODI3% data were obtained from the PSG, not from an ambulatory study with a home pulse-oximeter. Additional studies are needed to validate this model in a new cohort of consecutive bariatric patients with both tests used: intralaboratory PSG and home pulse-oximetry.

Conclusion

OSA is extremely prevalent in morbidly obese patients waiting for BS. Clinical predictors alone are not enough to

Table 4
Accuracy of proposed 2-stage diagnostic model for identifying severe OSA (AHI ≥30/h; n = 136)

Variable	Estimate (95% CI)
Sensitivity	.91 (.82–.95)
Specificity	.90 (.80–.95)
PPV	.92 (.84–.96)
NPV	.89 (.78–.94)
LR+	9.77 (4.80–19.89)
LR−	.11 (.05–.24)
Accuracy	.90 (.84–.94)

OSA = obstructive sleep apnea; AHI = apnea-hypoapnea index; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio LR− = negative likelihood ratio.

properly screen for OSA in this population. The proposed 2-step predictive model could be a useful first screening tool to rule out patients at lower risk of having severe OSA and detect those at greater risk and to optimize the sleep laboratory resources and improve the management of severe OSA in bariatric cohorts.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Impact of Bariatric Surgery on Obstructive Sleep Apnea Severity

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Running title: BS impact on OSA severity

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ABSTRACT

Background: Obstructive Sleep Apnea (OSA) is prevalent in patients undergoing bariatric surgery (BS). Lack of symptoms and optimal weight lost may not guarantee OSA resolution after BS. **Objectives:** To analyze impact of weight loss on OSA severity one year post-BS. **Methods:** Patients with a preoperative apnea-hypoapnea index (AHI pre-BS) >15 events/h were studied one year after BS. OSA diagnosis based on polysomnography or polygraphy, body mass index (BMI) and Epworth sleepiness scale (ESS) were collected before and after BS. OSA resolution was defined by a postoperative AHI <5 events/h and OSA improvement by a reduction in AHI greater than 50%. **Results:** 59 patients out of 61 were evaluated (period between BS and sleep reassessment: 15 ± 6 months). AHI decreased from 56 ± 33 to 15 ± 14 events/h ($p<0.001$) and BMI reduced from 52 ± 7 to 33 ± 5 Kg/m^2 ($p<0.001$). Severe cases (AHI ≥30 events/h) were reduced from 70% to 12%, with a CPAP withdrawal rate of 96% (46/48). 19% experienced complete OSA resolution and 42% had mild OSA (AHI 5-15 events/h) but 27% still had moderate OSA (AHI 15-30 events/h). Patients who experienced OSA improvement were younger and had higher AHI pre-BS but they did not differ as regards BMI or ESS changes. **Conclusions:** Bariatric weight loss results in significant OSA improvement after medium-term follow-up in most patients. OSA improvement cannot be reliably predicted by changes in BMI or clinical symptoms. Therefore, OSA patients should perform an objective post-BS sleep assessment to guarantee OSA resolution.

INTRODUCTION

Obesity is the major risk factor for the development of obstructive sleep apnea (OSA)[1,2], as the latter is highly prevalent in morbidly obese patients (at rates from 40% to 97%) [3,4]. Bariatric surgery (BS) is the recommended weight loss option for morbidly obese patients who suffer from serious co-morbidities related to obesity and have failed to lose weight with conservative approaches. BS results in sustained weight loss, which, in turn, reverses the severity of many obesity-related disorders such as diabetes, dyslipemia and hypertension [5].

Most standard guidelines recommend OSA screening before BS as OSA is considered a highly prevalent concomitant condition with respect to obesity and it may induce perioperative complications if left untreated. In general practice, however, this measure is not fully implemented in many bariatric centers. Moreover, most bariatric patients do not report OSA-related symptoms during the preoperative assessment [6,7] and they report even fewer symptoms after surgery [8]. This may mean that the presence of OSA is overlooked in both of these periods: before and after BS. In many cases of severe OSA patients treated with continuous positive airway pressure therapy (CPAP) before surgery have this therapy withdrawn once they experience a significant weight loss after BS, without any reassessment of objective OSA improvement. However, optimal surgical weight loss may not always guarantee OSA resolution [9] and these subjects could still suffer from OSA and its cardiometabolic burden, even though they may not complain about any OSA-related symptoms.

The presence of residual OSA after BS may worsen the deleterious consequences of obesity due to the association of OSA with the metabolic syndrome [4]. It is thus important to know the specific outcomes of bariatric surgery with respect to OSA improvement. The current literature on OSA resolution after BS is still inconclusive, for several reasons. Many published works had small sample sizes [10-12] and/or significant follow-up bias [13-15], and so their results should be interpreted with caution.

In the present work, all the patients studied for OSA before BS were reassessed after surgery via an objective sleep study, regardless of OSA symptoms. The aim of this study was to analyze the objective impact of BS on OSA severity after one year of surgery and also attempt to find clinical predictors of OSA improvement.

METHODS

Study design and setting

The present study included patients from Bellvitge Hospital's Multidisciplinary BS program who underwent this surgical procedure during the period February 2007-December 2009. The protocol was approved by our institution's scientific research review committee.

Study population

The BS inclusion criteria were: (1) Age between 18 and 60 years; (2) BMI
(Body Mass Index) $\geq$ 40 Kg/m^2 or BMI $\geq$ 35 Kg/m^2 with severe comorbidities (hypertension, diabetes mellitus, cardiovascular

disease, OSA, severe degenerative arthropathy) and (3) failure to lose weight with conservative approaches. Patients were eligible for the study if they fulfilled the BS inclusion criteria and had been diagnosed as having OSA prior to surgery. The preoperative sleep evaluation was conducted in all patients with a BMI >50 Kg/m^2, and after reports of any OSA-related symptom (including mild snoring) in patients with a BMI ≤50 Kg/m^2. One year after BS, patients who had had a preoperative apnea-hypoapnea index (AHI pre-BS) >15 events/hour were invited to perform the postoperative sleep study.

Data collection:

Subjects were evaluated before and after BS. Both evaluations included a clinical assessment by a sleep specialist and an overnight attended polysomnography (PSG) (Siesta, Compumedics, Melbourne, Australia) or respiratory polygraphy (RP) (P-series, Compumedics, Melbourne, Australia).

In the clinical evaluation, anthropometric data (body mass index), comorbidities and tobacco and alcohol habits were collected. The excessive daytime sleepiness was defined by an Epworth Sleepiness Scale (ESS) >10 [16]. Spirometry and arterial blood analysis were also performed at the preoperative evaluation.

Polysomnography (PSG) included two electroencephalogram channels (EEG), two electrooculography channels, chin electromyography, oronasal flow measured by a thermistor and nasal canula, thoracic and abdominal excursion bands, oxygen saturation recorded with a digital pulse oximeter ($Sp0_2$), electrocardiogram, anterior tibial electromyogram, sound

recording for snoring and a body position sensor. The studies were scored in 30-second epochs following standard criteria for sleep staging [17]. Respiratory polygraphy (RP) included oronasal flow by thermistor and nasal canula, thoracic and abdominal excursion, $Sp0_2$ recorded by a digital pulse oximeter, body position and snoring recorded by microphone. The AHI was defined by the number of apneas and hypopneas occurring per hour of sleep (PSG) or per hour of recording (RP). An obstructive apnea was defined as no airflow for ≥10 seconds, despite ongoing respiratory effort. A hypopnea was defined as a decrease in airflow associated with a reduction of ≥3% in $Sp0_2$ or EEG arousal [18]. The percentage of sleep time (PSG) or recording time (RP) with a $Sp0_2$ below 90% (CT90%) was also quantified. OSA severity was classified as follows: mild 5 <AHI≤ 15 events/hour; moderate 15 <AHI ≤ 30 events/hour; severe 30 <AHI ≤ 50 events/hour and very severe AHI > 50 events/hour.

Pre-operative continuous positive airway pressure (CPAP) or bilevel ventilatory support (BVS) was indicated in all patients suffering from severe or very severe OSA. In moderate cases, the indication was individualized according to symptoms and cardiovascular comorbidity. The optimal pressure was determined when indicated, by manual titration [19] or by automatic titration with autoCPAP (Autoset Clinical System, Resmed, North Ryde, Australia) [20]. Bilevel ventilatory support (BVS) was indicated when sustained diurnal hypercapnia and/or nocturnal oxygen desaturation persisted even when CPAP could resolve the obstructive events.

Endpoints

The main endpoints were OSA resolution defined by an AHI post-BS < 5 events/hour and OSA improvement defined as a reduction in AHI greater than 50% (AHI pre-BS – AHI post-BS) / AHI pre-BS ≥ 0.5).

Statistical Analysis

Statistical analyses were performed using computerized software (SPSS version 17.0). All tests were 2-tailed, and p values <0.05 were assumed to represent statistical significance. Data was presented as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Kolmogorov-Smimov test was used to test the normality distribution of continuous variables. For categorical variables, the bivariate comparisons were made using the Chi-squared test or Fisher's test, if the expected counts < 5. For continuous variables, in unpaired data comparisons were made using unpaired t-test (parametric) or Mann-Whitney test (non-parametric) and in paired data comparisons between the variables "difference preBS - postBS" were tested using paired t-test (parametric) or Wilcoxon test (non-parametric). Logistic binary regression was used to identify independent predictors of OSA improvement. The association results were summarized using unadjusted and adjusted β coefficients with their 95% confidence intervals (95% CI).

RESULTS

A total of 70 patients completed the preoperative sleep study. Nine subjects had an AHI pre-BS <15 events/hour. Of the

remaining 61, 2 patients refused to participate in the postoperative study. Thus, 59 patients underwent both sleep studies. The flowchart is shown in Figure 1.

Table 1 illustrates the baseline characteristics in patients with paired data (n=59). Overall, 80% were women with a mean age of 47 ± 10 years and a mean BMI of 52 ± 7 Kg/m^2 (range 36-73 Kg/m^2). The most prevalent concomitant conditions were hypertension (49%) and diabetes (39%). No patient had severe diurnal hypoxemia ($Pa0_2$ < 60mmHg). Ten patients (17%) presented mild diurnal hypercapnia ($PaC0_2$ > 45mmHg, mean value of 48 ± 2 mmHg and range 46-53).

Table 2 shows the pre-operative sleep data in the paired sample. The mean AHI was 56 ± 33 events/hour and the majority did not report hypersomnia (70% reporting ESS ≤ 10, mean: 9 ± 6). As regards OSA severity: 31% had moderate OSA, 22% severe OSA and 48% had very severe OSA. CPAP treatment was indicated in 80% (47 out of 59 patients) with a mean pressure of 11 ± 2 (range 6-14 mmH_20) and one patient required BVS (inspiratory and expiratory pressure parameters were: 20 cmH_20 and $10cmH_20$, respectively).

The mean period between BS and postoperative assessment was 15 ± 6 months (range 6-33 months). Table 3 shows the absolute changes AHI, BMI, ESS and CT90. AHI decreased from 56 ± 33 to 15 ± 14 events/hour ($p < 0.001$) and CT90 lowered from 26 ± 25 to 5 ± 10% ($p < 0.0001$). Both ESS and BMI decreased from 9 ± 6 to 5 ± 4 ($p < 0.0001$) and from 52 ± 7 to 33 ± 5 Kg/m^2 ($p < 0.0001$).

Most patients also experienced a significant weight reduction, although only 3% achieved normal weight (BMI 18.5-24.9 Kg/m^2) and 65% still presented moderate obesity (BMI 30-39.9 Kg/m^2) (Fig 2). The individual changes in BMI and AHI after surgery are shown in Figure 3 and Figure 4, illustrating how AHI improvement was not always related to lowering of the BMI. Figure 5 shows OSA categories before and after BS. After BS, nearly all the patients experienced a significant AHI reduction, with noticeable reductions in very severe and severe cases: the percentage of patients with an AHI >=30/h was reduced from 70% to 12%, leading to a CPAP withdrawal rate of 96% (46 of 48 patients with CPAP pre-BS) and the patient requiring BVS could do without it after BS. Furthermore, 42% of the patients reduced their OSA to mild forms (AHI 5-15/h) and 19% experienced complete resolution (AHI <5/h). In contrast, moderate OSA (AHI 15-30/h) was still present in 27% of the patients.

Considering OSA improvement as a reduction in AHI greater than 50%, the patients who improved (46/59) were younger and had more severe OSA at the preoperative assessment than those patients who did not improve (Table 4). However, they did not differ in terms of gender, comorbidities, BMI changes, subjective hypersomnia or baseline blood gases. Moreover, according to the univariate logistic regression analysis, younger age and higher AHI pre-BS were the only independent variables associated with OSA improvement, with unadjusted β coefficients (95% CI, p-value) as follows: 0.921 (0.851 – 0.998, p 0.043) and 1.027 (1.001 – 1.054, p 0.039), respectively. Furthermore, in the multiple logistic regression

model only higher AHI pre-BS (>= 30 events/hour) remained independently associated with OSA improvement after adjusting for age, gender and BMI improvement, with the following adjusted β coefficient (95% CI and p-values): 10.937 (2.064-57.965, p 0.005).

DISCUSSION

Surgical weight loss results in a significant OSA improvement after medium term follow-up, leading to a noticeable reduction in severe cases (from 70% to 12%) and, consequently, a high CPAP withdrawal rate (96%). Most patients improved to mild OSA (42%), while many still had moderate OSA (27%) and only a few achieved complete resolution (19%). This improvement was related to younger age and higher AHI pre-BS but cannot be predicted by changes in BMI or ESS. Therefore, at the moment, OSA patients undergoing BS should perform an objective sleep assessment after surgery in order to check for sleep disorder resolution.

Many previous works on the impact of BS on OSA severity had several limitations. Some had a small sample size, with less than 20 patients studied [10-13], so their results should be analyzed with caution. Others lacked clear definitions of OSA diagnosis, improvement and resolution and, therefore, of success rates after BS, so it is difficult to compare studies [21]. Moreover, some published data have defined OSA without any sleep study and considered its resolution after BS on the basis of amelioration of symptoms, without confirming the improvement with an objective postoperative sleep study [22-25]. The main limitation of many

previous studies, however, was undoubtedly their follow-up bias: only 11-29% of patients studied during the preoperative period were reassessed in the post-operative period [8,13,14,21,26]. Many patients did not consider it necessary to repeat a polysomnography or respiratory polygraphy since they reported significant subjective improvement. Even some of the physicians taking care of these patients considered snoring resolution synonymous of OSA resolution, thus they did not reinforce their patients to perform a control sleep study after surgical weight loss. In the present study, the follow-up bias is insignificant as the follow-up rate is nearly 97% (59/61). Only two previous smaller series had similar follow-up rates [12, 27].

A meta-analysis published in 2009 [28] reviewed the published works that analyzed the effects of surgical weight loss on the AHI. They concluded that 12 studies were relevant; of these, only 2 were prospective and had no significant follow-up bias, despite their limited sample sizes (less than 25 patients) [12,27]. Notwithstanding these limitations as regards data heterogeneity, small sample size and follow-up bias, the final results of several of these 12 studies, examining a total of 80 patients via an objective sleep study before and after BS, did not substantially differ from our own results. In the meta-analysis, the AHI post-BS was reduced to less than 5 and less than 10 events/hour in 25% and 44% of patients, respectively, while in our series it was reduced to 19% and 46%, respectively. The mean BMI reductions were also similar: 17.9 Kg/m^2 (95% CI, 16.5-19.3) in the meta-analysis and 18.3 Kg/m^2 (95% CI, 16.9-19.7) in the present work. In the meta-analysis, the

search for predictive factors of OSA improvement after BS found only two independent factors: age (younger) and a weight loss > 100Kg (although this had a low predictive capacity as only a few of the patients experienced a surgical weight loss >100Kg). Therefore, the authors finally recommended an objective sleep study after BS as the only reliable means of verifying OSA resolution.

According to the results of the present study's regression analysis, it seems that younger and more severe OSA patients are more likely to improve their OSA status after BS. Moreover, after adjusting for age, gender and BMI improvement, suffering from severe OSA before BS (AHI preBS ≥ 30 events/hour) seems to be the only independent variable associated with significant OSA improvement after BS. However, we are aware that these variables, although significantly associated with post-BS OSA improvement, did not have sufficient power to fully identify, in all cases, those patients who would experience a significant AHI reduction after BS. This result should therefore be taken as an explicative model, rather than a predictive one. Our findings in this homogeneous and moderately broad sample (>50 patients) therefore endorse the final recommendation made by the meta-analysis published in 2009 [28]: that clinicians should have low thresholds for evaluating postsurgical patients with repeated polysomnograms, as this is the only means available for objectively reassessing OSA status, in the absence of a reliable clinical model for predicting significant OSA improvement after BS. Moreover, it is important to emphasize that improvement in subjective somnolence after BS was not a predictor of OSA improvement, thus reinforcing the need to perform an

objective sleep study during the follow-up in order to verify OSA resolution after optimal surgical weight loss.

Like many previous bariatric cohorts [4,29], ours had a clear female predominance and most patients did not report subjective sleepiness before BS, despite suffering from OSA. As expected, BS resulted in a significant mean reduction in BMI, AHI, CT90%, ESS score and CPAP requirements. The most significant improvement was seen in younger patients suffering from severe OSA. Mild-moderate OSA patients also experienced a significant reduction in the AHI after surgery, but this was less marked, even when the reduction in BMI was similar. The reasons for this discrepancy are still unclear. The substantial variability in AHI response to surgical weight loss, along with the lack of sufficient independent clinical predictors of OSA improvement after BS, may reflect a relationship between OSA and surgical weight loss that is more complex than a mere two-way correlation between AHI and BMI. Changes in the BMI may not be the best parameter for linking OSA improvement with obesity improvement after bariatric surgery. Other uncontrolled factors, apart from the final BMI, could also play a part.

Fat distribution is not homogenous in obese patients and BMI represents only the overall increase in body weight [30], adipose tissue quantification of abdominal and neck regions by nuclear MRI [31,32] or CT scanner [33], or even other simpler measurements, such as neck and waist circumferences [34], may better reflect specific fat distribution phenotypes that are probably more closely related to OSA. Even with an equal BMI decrease,

some patients may reduce these parameters more than others, leading to a higher reduction in AHI. Another possible explanation is the notion that airway narrowing depends on the balance between the amount of soft tissue surrounding the pharyngeal airway and the craniofacial bony enclosure [35]. Before BS, airway size could be reduced in both respects, but particularly in the "obesity" factor; after BS, at equal weight loss post-BS, the AHI would be reduced more in patients in whom airway reduction was primarily governed by the "obesity" factor, compared to those in whom the "anatomical" factor also participated. Moreover, as has recently been postulated [36], it is also possible that the beneficial effects of BS on OSA include not only mechanical weight-dependent but also metabolic weight-independent effects, such as adipokine effects, cytokine actions, altered gut hormonal release and insulin resistance improvement.

The present study has several weaknesses. Firstly, the sleep reassessment was performed after a medium term follow-up; some patients may not yet have achieved their optimal weight loss. It would be interesting to evaluate whether this substantial AHI reduction could be maintained over time (high age and different weight variations). Further studies could focus on the relationship between OSA recurrence and weight regain post-BS in larger cohorts with a longer follow-up. Secondly, it seems that changes in the BMI do not predict OSA improvement, and other weight parameters more closely related to OSA development were not collected. Waist and neck circumferences could easily be assessed, thereby contributing indirect information about changes in upper-

body and abdominal fat accumulation. Others factors would require more complex quantification techniques.

Conclusions

Bariatric weight loss results in significant OSA improvement in most patients after a medium-term follow-up. However, some patients could still have residual OSA and its associated cardiometabolic burden, despite achieving optimal BMI loss and significant subjective improvement. Although post-BS OSA improvement seems to be independently associated with younger age and higher AHI pre-BS, it cannot be reliably predicted by those two independent variables, or by changes in the BMI or clinical symptoms. Therefore, since research in this field has not advanced, OSA patients undergoing BS should undergo an objective sleep assessment after surgery in order to guarantee OSA resolution.

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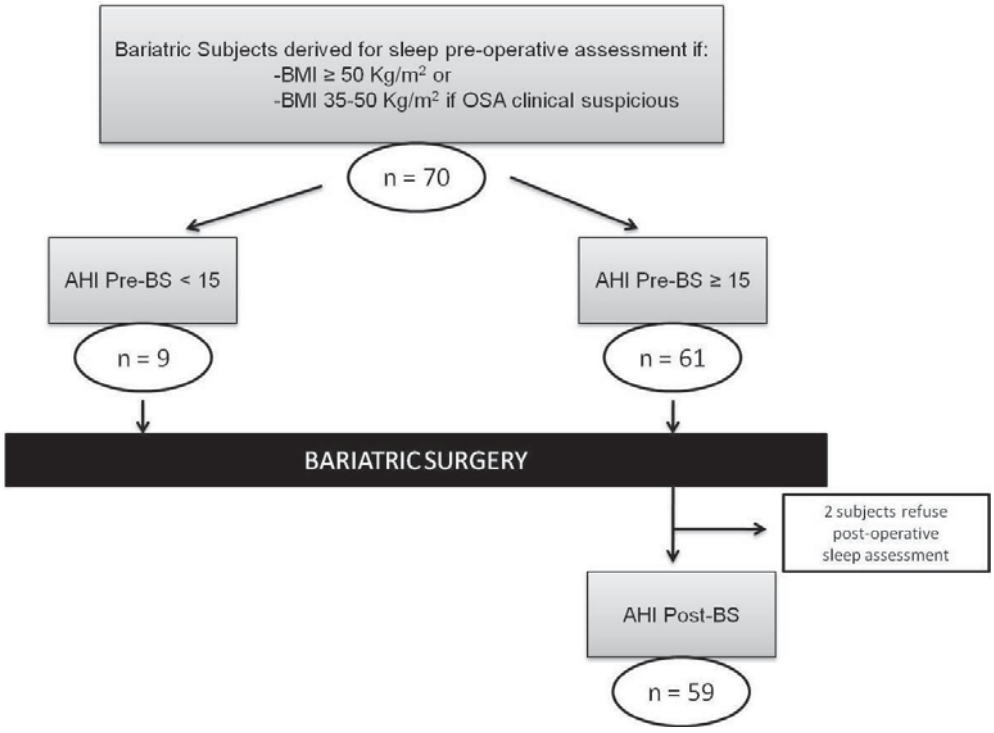
Figure 1. Patients' Flow chart



Abbreviations: BMI, body mass index; OSA, obstructive sleep apnea; AHI, apnea-hypoapnea index; BS, bariatric surgery.

Table 1. Preoperative general characteristics of the simple

Patients with paired data n = 59	
Anthropometrics and general variables	
Age, years	47.4 ± 9.7
Gender, females (%)	47 (80%)
BMI, Kg/m^2	51.7 ± 7.0
Lung functional variables	
FVC, %	93.6 ± 20.3
FEV_1, %	93.0 ± 18.5
FEV_1/FVC	81.8 ± 6.3
$Pa0_2$, mmHg	83.2 ± 9.5
$PaC0_2$, mmHg	40.9 ± 5.0
Comorbidities and habits	
Hypertension, n (%)	29 (49%)
Diabetes , n (%)	23 (39%)
COPD, n (%)	5 (9%)
Smoking, n (%)	13 (22%)
Alcohol consumption, n (%)	2 (3%)
Sedatives, n (%)	8 (14%)

Table 2. Preoperative sleep characteristics of the simple

Patients with paired data n = 59	
Sleep variables and OSA severity	
AHI, events/hour	55.6 ± 33.4
CT90%, %	25.9 ± 25.4
OSA category, n (%) no OSA: AHI <5 mild: AHI 5-15 moderate: AHI 15-30 severe: AHI 30-50 very severe: AHI >50	- - 18 (31%) 13 (22%) 28 (48%)
Preoperative indication of positive airway pressure therapy	
CPAP, n (%)	47 (80%)
BVS , n (%)	1 (1%)
Subjective sleepiness assessment	
ESS, score	9 ± 6
EDS, n (%)	17 (30%)

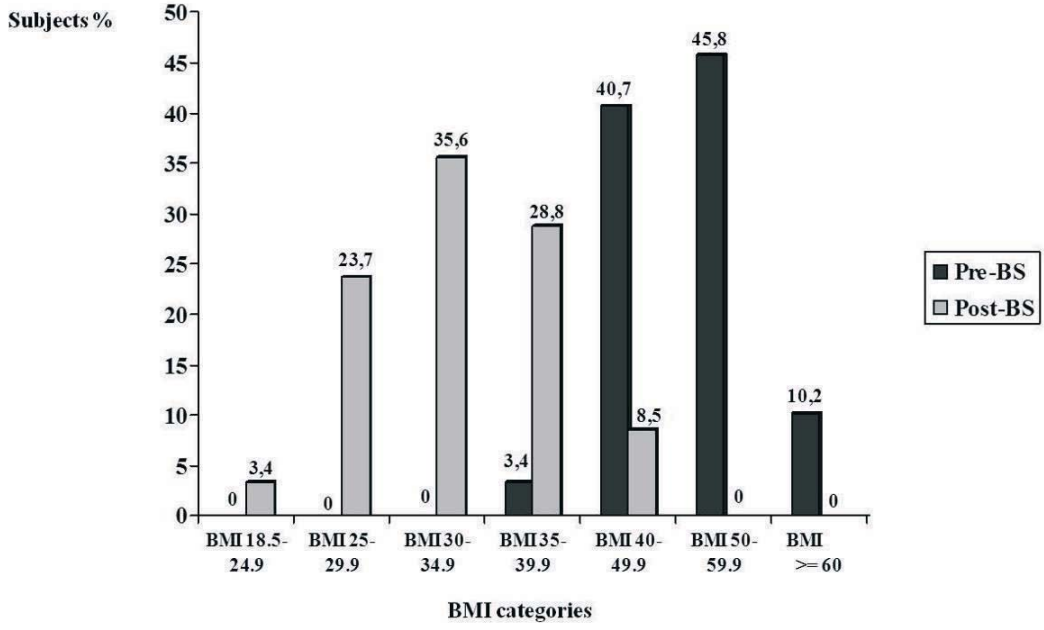
Table 3. Mean changes in the principal characteristics after surgery

	Pre-BS	Post-BS	Mean difference	95% IC	p
BMI, Kg/m	51.7 ± 7.0	33.4 ± 5.0	18.3 ± 5.4	19.7 – 16.9	< 0.001
ESS, score	9.0 ± 5.8	4.7 ± 4.1	4.3 ± 5.5	5.8 – 2.8	< 0.001
AHI, events/h	55.6 ± 33.4	15.3 ± 14.1	40.4 ± 32.1	48.7 – 32.0	< 0.001
CT90%, %	25.9 ± 25.4	5.2 ± 10.1	20.7 ± 23.4	26.8 – 14.6	< 0.001

Table 4. OSA improvement after Bariatric Surgery

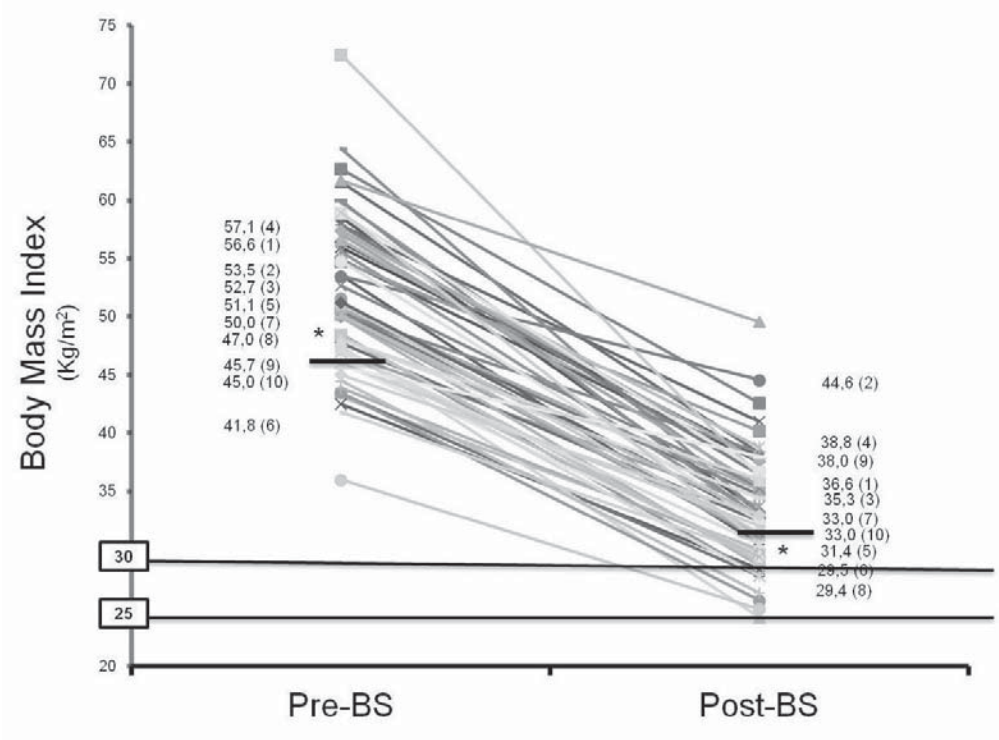
OSA IMPROVEMENT RATIO* (Ratio >= 0.5)	YES n=46	NO n=13	p
Age, years	46 ± 9	52 ± 10	**0.034**
Gender, females %	36 (78%)	11 (85%)	0.615
Hypertension, n (%)	20 (44%)	9 (69%)	0.207
Diabetes, n (%)	16 (35%)	7 (54%)	0.339
BMI pre-BS, Kg/m^2	51.9 ± 7.3	50.9 ± 5.5	0.739
ΔBMI, Kg/m^2	18.8 ± 5.2	16.5 ± 5.6	0.342
BMI Improvement ratio *	0.36 ± 0.07	0.32 ± 0.09	0.295
AHI pre-BS, events/h	60.7 ± 33.5	37.7 ± 27.1	**0.017**
CT90% pre-BS, %	25.5 ± 23.1	27.4 ± 33.5	0.947
ESS pre-BS, score	9 ± 6	8 ± 6	0.564
ΔESS, score	4.7 ± 5.4	3.1 ± 5.7	0.372
$Pa0_2$ pre-BS, mmHg	83.4 ± 9.8	82.6 ± 8.8	0.799
$PaC0_2$ pre-BS, mmHg	40.2 ± 4.7	42.7 ± 5.9	0.475
CPAP indication, n (%)	40 (87%)	9 (69%)	0.213
CPAP pressure, cmH_20	11 ± 2	12 ± 3	0.170
Post-op period, months	15.1 ± 5.9	13.6 ± 4.0	0.530

Figure 2. Changes in Body Mass Index (Kg/m^2) categories after surgery



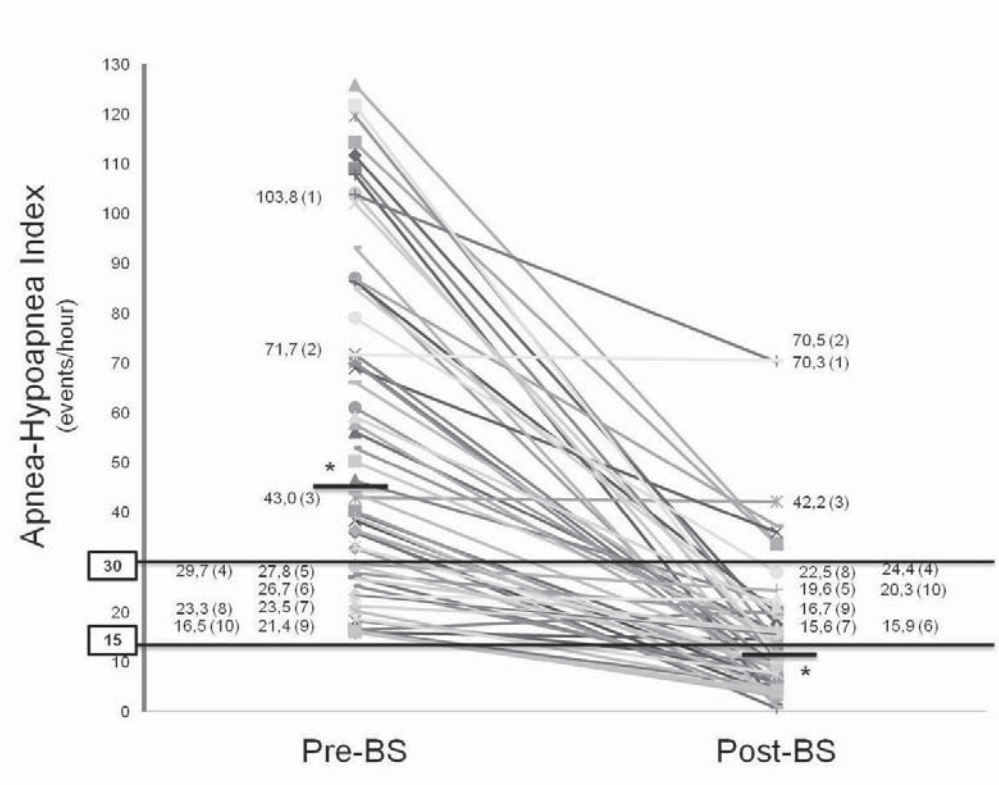
Abbreviations: BMI, body mass index; Pre-BS, preoperative period; Post-BS, postoperative period.

Figure 3. Individual changes in BMI after bariatric surgery



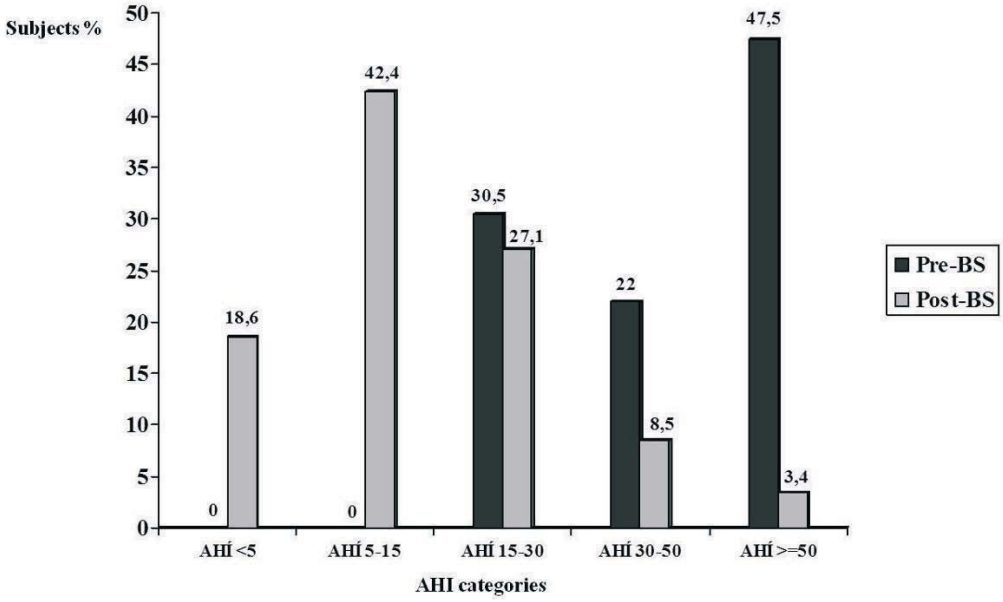
Abbreviations: BMI, body mass index; Pre-BS, preoperative period; Post-BS, postoperative period. * Patients who did not improve OSA category from pre-BS period to post-BS period are illustrated in numerical order, with their individual BMI values in brackets. * Median BMI values.

Figure 4. Individual changes in AHI after bariatric surgery



Abbreviations: AHI, apnea-hypoapnea index; pre-BS, preoperative period; post-BS, postoperative period. * Patients that did not improve OSA category from pre-BS period to post-BS period are illustrated in numerical order showing their individual AHI values in brackets. * Median AHI values.

Figure 5. Changes in Apnea-hypoapnea Index (events/hour) categories after surgery



Abbreviations: AHI, apnea-hypoapnea index; Pre-BS, preoperative period; Post-BS, postoperative period.

RESULTATS PRINCIPALS

Gasa M, Salord N, Fortuna AM, Mayos M, Vilarrasa N, Dorca J, Montserrat JM, Bonsignore MR, Monasterio C. Obstructive sleep apnoea and metabolic impairment in severe obesity. Eur Respir J. 2011 Nov;38(5):1089-97. Epub 2011 May 26.

- La SAOS és molt prevalent en la població estudiada: prevalença del 98% (IAH ≥5 events/h) i del 70% (IAH ≥15 events/hora).
- Els pacients amb SAOS presenten més MetS que els pacients sense SAOS (70% vs 36%, p 0.001).
- A mesura que augmenta la gravetat de la SAOS, el perfil metabòlic progressivament empitjora, inclús en els pacients sense diabetes mellitus tipus 2 (DM2) establerta a l'inici de l'estudi.
- Després d'ajustar per edat, sexe i paràmetres d'adipositat (índex de massa corporal (IMC) i diàmetre cintura), l'índex d'apnea-hipoapnea (IAH) s'associa de manera independent amb les xifres de pressió arterial sistòlica i diastòlica, els nivells plasmàtics de triglicèrids i el percentatge de hemoglobina glicosilada (HbA1c).
- En pacients sense DM2 establerta, dita associació es manté independent entre l'IAH i les xifres de pressió arterial sistòlica, el HbA1c i els nivells de c-HDL.

- La presència de SAOS quasi triplica la odds ratio de presentar MetS (2.8, 95% CI 1.3–6.2; p0.009) després d'ajustar per edat, sexe i IMC entre d'altres.
- A mesura que la gravetat de la SAOS augmenta, s'observa un increment progressiu del valor del risc cardíac calculat mitjançant l'escala de Framingham.

Gasa M, Salord N, Fortuna AM, Mayos M, Embid C, Vilarrasa N, Montserrat JM, Monasterio C. Optimizing screening of severe obstructive sleep apnea in patients undergoing bariatric surgery. Surg Obes Relat Dis. 2012 Feb 9. [Epub ahead of print].

- Hem construït un model predictiu senzill, fiable i segur per detectar els pacients candidats a cirurgia bariàtrica que presenten una alta probabilitat de patir SAOS greu.

- L'aplicació d'aquest model descarta el 45% (61/136) dels pacients de forma ràpida i segura sense necessitat de realitzar estudis de son complexos: el 15% únicament amb paràmetres clínics (edat, diàmetre de la cintura, pressió arterial sistòlica i apnees nocturnes objectivades) i el 30% restant afegint les dades d'una pulsioximetria com a estudi de son simplificat (l'índex de desaturació d'oxígen del 3%).

- El model proposat presenta uns valors predictius òptims: Sensibilitat 91%, Especificitat 90%, Valor predictiu positiu 92%, Valor predictiu negatiu 89%, Precisió global 0.90 (95% CI 0.84 - 0.94) i un percentatge de falsos negatius i falsos positius del 9% i del 10%, respectivament.

Gasa M, Salord N, Vilarrasa N, García Ruiz de Gordejuela A, Dorca J, Montserrat JM, Monasterio C. Impact of bariatric surgery on obstructive sleep apnea severity. [Submitted].

- La pèrdua ponderal un any després de la cirurgia bariàtrica es relaciona amb una milloria significativa en la gravetat de la SAOS en la majoria dels pacients (88% presenten un IAH postquirúrgic (postCB) <30 events/hora) permetent una alta tasa de retirada de la teràpia amb CPAP (96%); no obstant, la presencia de SAOS moderada (IAH postCB 30-15 events/hora) es manté en un 27% dels pacients i la resolució completa de la SAOS és menor (19% dels pacients amb un IAH postCB <5 events/hora).

- La reducció significativa en l'IMC postquirúrgica no reflecteix necessariament una reducció significativa en l'IAH post-quirúrgic en tots els casos.

- La presencia d'una SAOS greu preCB definida com un IAH prequirúrgic (preCB) ≥ 30 events/hora és l'únic paràmetre d'associació independent amb la milloria de la SAOS postCB aplicant la regressió logística múltiple (cofactors: edat, sexe i milloria de l'IMC postCB).

DISCUSSIO CONJUNTA

En base al primer treball, els resultats obtinguts recolzen la hipòtesis inicial plantejada: la síndrome metabòlica és més prevalent i el perfil metabòlic està més deteriorat en els pacients amb obesitat mòrbida i SAOS que en els pacients amb obesitat mòrbida però sense SAOS. A més, el perfil metabòlic està més deteriorat a mesura que augmenta la gravetat de la SAOS i aquest empitjorament és independent del sexe i persisteix inclús després d'excloure de l'anàlisi els pacients amb DM2 establerta a l'inici de l'estudi. Per això, en una població amb una alta prevalença de MetS com son els pacients obesos mòrbids candidats a cirurgia bariàtrica, la SAOS s'associa a un pitjor perfil metabòlic suggerint que podria conferir un risc cardiovascular addicional i/o incrementar el risc atribuït a l'obesitat "per se".

L'associació entre la SAOS i la disfunció metabòlica ha estat investigada àmpliament en cohorts de pacients amb obesitat moderada estudiats en les Unitats de Son per sospita clínica de SAOS [16, 55, 56-58], i més recentment també en cohorts de pacients amb conegut risc cardiovascular: pacients hipertensos [59], amb MetS [14, 15, 60], o amb una malaltia cardiovascular establerta [61]. Les dades obtingudes d'aquests estudis confirmen que la SAOS és molt prevalent en pacients de mitjana edat amb obesitat moderada i que s'associa a la MetS o a alguns

dels seus components individuals independentment de l'IMC. En aquesta tesi, hem analitzat dita associació des d'un a perspectiva nova escollint com a població d'estudi pacients amb obesitat mòrbida candidats a cirurgia bariàtrica donat que aquesta subpoblació representa un model extrem d'associació entre la SAOS, la MetS i l'obesitat greu. De fet, en el moment del disseny de l'estudi, només existia una petita sèrie publicada que assenyalava l'alta prevalença d'ambdós trastorns, SAOS i MetS, en pacients candidats a cirurgia bariàtrica [54].

Els resultats exposats del primer treball revelen que la prevalença de MetS és el doble en els pacients amb SAOS que en els pacients sense SAOS (70% versus 36%, p 0.001) i que existeix un empitjorament progressiu del perfil metabòlic a mesura que s'incrementa la gravetat de la SAOS. Per això, aquests resultats no avalen la hipòtesi defensada prèviament per altres autors suggerint que la presencia de l'obesitat mòrbida "per se" emmascara la contribució potencial que la SAOS podria exercir sobre la disfunció metabòlica global. Més encara, hem demostrat que la presencia de SAOS inclús podia triplicar la odds ratio de presentar la MetS independentment de l'IMC i del sexe. Aquest últim ajust és una nova contribució donat que en el moment de la publicació del primer treball no hi havia a la literatura cap treball que investigues la contribució metabòlica de la SAOS en dones amb obesitat mòrbida. En aquest

anàlisis, hem pogut observar que a diferencia dels homes, les dones sembla que requereixen més quantitat de greix corporal total per tal d'augmentar el greix central, considerat el greix metabòlicament més actiu. També hem apreciat que hi ha més dones post-menopàusiques amb SAOS que sense SAOS en consonància amb els resultats obtinguts en estudis previs de cohorts amplies poblacionals [62-64]; en canvi, l'estat post-menopàusic i el percentatge de greix corporal analitzat mitjançant bioimpedància elèctrica no semblen interferir en l'associació independent entre la SAOS i la MetS en el subgrup de dones obeses mòrbides. Tot l'anterior exposat fa pensar que en els pacients amb obesitat mòrbida, la disfunció metabòlica podria ser deguda no exclusivament a l'obesitat "per se" sinó també a la SAOS, i que aquesta condició concomitant no sembla estar regida per un predomini específic de gènere.

Encara manca per definir si la SAOS s'associa a un perfil metabòlic deteriorat característic tant en subjectes no obesos com en subjectes amb diferents graus d'obesitat. En diferents cohorts de pacients sense obesitat mòrbida, la SAOS s'associa a trastorns metabòlics diversos i és possible que dita divergència en els resultats sigui deguda en part a la gran heterogeneïtat dels estudis publicats [55, 56-58, 65, 66]. En el primer treball, hem trobat una clara associació lineal independent entre l'índex d'apnea-hipoapnea (IAH) i les xifres de pressió arterial sistòlica i

diastòlica, els nivells de triglicèrids i el HbA1c un cop ajustada dita associació per paràmetres d'adipositat com l'IMC i el diàmetre de la cintura. Inclús, aquesta associació entre l'IAH i les xifres de pressió arterial sistòlica, nivells de c-HDL i el HbA1c ha romangut després d'excloure els pacients amb una DM2 establerta al inici de l'estudi. Aquests resultats demostren que en pacients amb obesitat mòrbida, l'increment en la gravetat de la SAOS s'associa a un empitjorament metabòlic causat fonamentalment per la presència d'hipertensió arterial sistèmica (majors xifres de pressió arterial sistòlica, fonamentalment), de disfunció lipídica (nivells de triglicèrids elevats i de c-HDL disminuïts) i d'un pitjor control glucídic (nivells de HbA1c més elevats). I aquest empitjorament és independent de paràmetres d'adipositat central i d'altres factors de confusió com és la presencia d'una DM2 preestablerta. Per altra banda, malgrat ser conscients que l'aplicació de l'escala de Framingham en pacients obesos mòrbids és una generalització no validada per aquesta cohort concreta, els resultats obtinguts suggereixen que la SAOS podria aportar una carrega addicional sobre la morbiditat i mortalitat cardiovascular en aquesta cohort. Si és així, la presència d'una SAOS concomitant caldria ser sempre tinguda en compte i controlada en qualsevol estudi futur que tingui com a objectiu avaluar les conseqüències metabòliques del pacient obès mòrbid.

Estudis experimentals tant en animals com en humans han demostrat que l' hipòxia intermitent és un dels principals causants de la disfunció metabòlica atribuïda a la SAOS [17, 80]. En la nostra cohort, els pacients amb SAOS presenten un major grau d'hipòxia nocturna intermitent que els pacients sense SAOS en base a un major IAH, CT90% i índex de micro-despertars però en canvi no existeixen diferencies significatives en el grau de somnolència diürna subjectiva o en el percentatge de cadascuna de les fases del son. A més, l'IAH s'associa de manera independent a la majoria dels paràmetres metabòlics individuals en base als resultats obtinguts de l'anàlisi de regressió lineal; en canvi, el CT90% únicament s'associa amb el HbA1c. Aquesta diferencia podria suggerir que també en el pacient obès mòrbid, la SAOS contribueix a la disfunció metabòlica atribuïda a l'obesitat mitjançant fonamentalment la hipòxia crònica intermitent. Per altra banda, segons els resultats obtinguts en l'anàlisi de regressió logística, també hem observat que la disfunció metabòlica era superior quan es combinava un IAH basal elevat i un major grau d'hipòxia nocturna (nivells superiors del CT90%) que quan només existeix un IAH basal elevat. Aquestes observacions van en la línia amb el treball publicat per Polotsky et al. [81], que defensa la hipòtesi del "model de la doble noxa" per explicar el paper que jugaria la SAOS en el desenvolupament de la esteatohepatitis i la resistència a l'insulina en el malalt obès mòrbid. L'obesitat greu central actuaria com a la primera noxa

iniciant la disfunció metabòlica i la SAOS greu a través de l' hipòxia crònica intermitent actuaria com a segona noxa perpetuant i empitjorant dit trastorn metabòlic. Ara bé, malgrat els estudis experimentals mostren una clara evidencia de la contribució fisiopatològica de l' hipòxia crònica intermitent sobre el metabolisme [17], el paper causal definitiu que pot jugar la SAOS sobre la disfunció metabòlica en humans encara està per establir de manera rotunda. En estudis d'intervenció, la teràpia amb CPAP ha demostrat reduir les xifres de pressió arterial [82], però les dades actualment existents en relació al control glucídic i lipídic encara no son prou contundents: alguns estudis mostren resultats positius metabòlica [83-85] i altres mostren resultats negatius [86, 87] en quant a l'efecte beneficiós de la CPAP sobre la disfunció metabòlica. Per tant, és obvi que cal dur a terme més estudis d'intervenció amb CPAP, a poder ser assaigs randomitzats controlats, en mostres amplies ben seleccionades, també en obesos mòrbids, per tal de definir amb claredat la direcció de casualitat entre la SAOS i la disfunció metabòlica.

El teixit adipós a part d'esser l'òrgan principal d'emmagatzematge d'energia també és un teixit molt actiu involucrat en la regulació integral del metabolisme [88]. El greix ectòpic, particularment el localitzat a nivell visceral, és el greix que actua nocivament sobre el metabolisme, disminuint la sensibilitat perifèrica a l'insulina a través del seu efecte

paracrí i mitjançant la alliberació d'adipocines al torrent sanguini que promouen un estat pro-inflamatori latent [89]. S'ha postulat que la SAOS podria agreujar aquest estat pro-inflamatori latent [90] contribuint a augmentar el risc cardiometabòlic. En el primer treball exposat, el diàmetre de la cintura s'ha emprat com un marcador indirecte reconegut d'adipositat visceral [91]. Així, els pacients amb SAOS tenen majors diàmetres de cintura i de coll en comparació amb els pacients sense SAOS però en canvi, l'IMC i el percentatge de massa grassa és similar en ambdós grups. Aquestes troballes suggereixen que probablement la SAOS està més relacionada amb l'adipositat visceral que no pas amb l'obesitat global. A més, l'associació entre la SAOS i els diferents paràmetres metabòlics es manté independent del diàmetre de la cintura i del sexe, aquests resultats recolzen el fet que la SAOS podria jugar un paper addicional a l'obesitat visceral en la presencia de les alteracions metabòliques, inclús en aquesta població amb obesitat molt greu. Malauradament, la quantificació directa del greix visceral mitjançant tècniques d'imatge o anàlisi histològiques no es van dur a terme en aquest estudi i per tant els resultats obtinguts son aproximats. Ara bé, tenint en compte dita limitació, els resultats exposats van en línia amb el concepte de "cicle viciós" proposat prèviament per Vgontzas et al [92]: el greix visceral pot empitjorar progressivament les manifestacions metabòliques i també pot afavorir el desenvolupament de la SAOS però a la vegada, la

pròpia SAOS també pot agreujar a través d'un increment en l'activitat simpàtica, l' inflamació i la resistència insulínica la disfunció metabòlica global.

En la nostra cohort de 159 pacients candidats a CB, la prevalença de SAOS ha estat molt alta: 72% dels pacients tenen un IAH ≥ 15 events/hora i tant sols el 2% presenten un IAH <5 events/hora. En canvi, la majoria de pacients (72%) no refereixen somnolència diürna excessiva segons la puntuació en l'escala de somnolència d'Epworth (ESS) >10 malgrat que presenten una SAOS greu. Series prèvies que han analitzat la somnolència diürna a través de mesures objectives (test de latència múltiple i d'altres) han trobat que els pacients obesos presenten clarament una somnolència excessiva diürna en comparació amb subjectes sans no obesos independentment de la presència d'una SAOS concomitant [93, 94]. En canvi, els nostres resultats son concordants amb altres series que avaluen específicament pacients amb obesitat mòrbida i tampoc han trobat majoritàriament hipersomnolència. Podria ser que la l'ESS en els pacients obesos mòrbids com a mesura subjectiva del grau de somnolència, fos limitada; De fet, molt possiblement aquesta escala no es capaç de detectar altres factors que poden contribuir a la somnolència real en aquests pacients [95, 96]. El fet de no trobar un cert grau de somnolència subjectiva excessiva en aquesta població malgrat l'alta prevalença de

SAOS present té implicacions clíniques importants i emfatitza la necessitat de realitzar estudis de son en aquests pacients independentment dels símptomes referits.

Cal assenyalar certes limitacions d'aquest primer treball exposat. El disseny transversal del estudi no permet proporcionar una evidencia causa-efecte de la relació entre la SAOS i la MetS en el pacient obès mòrbid ara bé, en base a l'anàlisi de regressió si podem establir una clara associació independent entre diferents marcadors de la SAOS i la majoria dels paràmetres individuals de disfunció metabòlica estudiats. Per altra banda, hagués estat interessant avaluar la quantitat de greix visceral de forma directa mitjançant tècniques d'imatge com son la tomografia computeritzada axial o la ressonància magnètica nuclear a nivell abdominal; ara bé, existia una limitació tècnica per realitzar dites proves amb els aparells convencionals dels centres on es va dur a terme l'estudi ja que el pes corporal de la majoria de subjectes excedia el pes màxim permès per realitzar aquestes proves. I per últim, com hem discutit prèviament, el grau de somnolència diürna objectiva no va ser avaluada en el present treball.

Com hem pogut observar de les dades del primer treball, en l'àmbit de la CB, els pacients no acostumen a referir símptomes de somnolència diürna excessiva però en canvi, tenen una alta probabilitat de

patir una SAOS. Donat que els símptomes sols no serveixen per predir la presència de la malaltia, hem construït un model predictiu basant-nos en variables clíniques fàcils de recollir en una primera visita médica: l'edat, el diàmetre de la cintura, la pressió arterial sistòlica i la presència d'apnees nocturnes objectivades. D'aquesta manera, hem pogut descartar fins el 15% dels pacients en una primera valoració. Posteriorment, incluint els valors de la pulsioximetria (l'índex de desaturació del 3%) a la resta dels pacients, hem pogut descartar un 30% més dels pacients. En global, l'aplicació d'aquest model pas a pas permetria agilitzar el maneig respiratori només d'aquells pacients amb alta probabilitat de presentar una SAOS greu abans de la cirurgia donat que el 45% dels pacients inicialment avaluats podríen ser descartats de forma fàcil i segura. Per altra banda, el model ens permetria optimitzar l'ús de la PSG. En el nostre estudi, el nombre de estudis de son més complexos s'han reduït de 136 a 75 (una reducció global del 45%) amb un percentatge prou acceptable d'errors diagnòstics: percentatge de falsos negatius del 9% i percentatge de falsos positius del 10% del total de la mostra. Així, aquest model podria ser considerat com una primera eina de cribatge per tal d'optimitzar els recursos existents en les Unitats de Son a l'hora que no comprometria la seguretat peri-operatòria dels pacients. De fet, creiem fermament que donada l'alta prevalença de SAOS en els pacients bariàtrics, les mesures generals recomanades pel maneig peri-quirúrgic del

pacient amb SAOS s'haurien d'implementar en tot pacient que es sotmetés a dit procediment quirúrgic. Algunes d'aquestes mesures serien l'ús de la posició inversa de Tredelenburg durant el maneig intraoperatori, l'anticipació d'una intubació difícil, l'ús de anestèsics de curta acció, evitar derivats opiacis pel control del dolor i la extubació en posició no-supina i amb el pacient completament despert [101]. Ara bé, durant la detecció pre-operatòria de la SAOS, caldria dirigir els màxims esforços a aquells pacients amb més risc de patir una SAOS greu que son probablement el grup de pacients que més es beneficiaria de l'aplicació de la CPAP abans de la cirurgia. Òbviament, existeixen altres mesures que es podrien investigar per agilitzar encara més el maneig d'aquests pacients. Una d'aquestes mesures, per exemple, seria avaluar l'ús d'aparells de CPAP automàtica per a la titulació de la pressió optima de la CPAP abans de la cirurgia i durant el seguiment postCB.

Els resultats del segon treball avalen els resultats publicats prèviament per altres autors [22, 39, 44, 97-102] en relació a la moderada ajuda que aporten els símptomes clàssics de SAOS referits pels pacients, com serien els roncs habituals i/o la excessiva somnolència diürna mesurada per l'escala d'Epworth, a l'hora de predir la presencia de SAOS. Això podria explicar en part la limitada utilitat que han demostrat els anteriors models publicats. A diferencia d'alguns models previs [22, 43,

52], cal destacar que el model actual no ha identificat el sexe masculí com a factor predictiu de SAOS greu. Aquesta divergència podria ser explicada pel fet que en els treballs previs, les dones presentaven una SAOS significativament menys greu que els homes (Sareli et al. [22]: IAH mitjà (events/hora): 20 en dones i 46 en homes; Kolotkin et al. [43]: presencia de SAOS greu definida com IAH≥30 events/h: 16% de les dones i 63% dels homes); en canvi, en el nostre segon treball, les dones malgrat patir una SAOS més lleu que els homes, la diferencia no és tant marcada (IAH mitjà: 36 en dones i 60 en homes; IAH≥30 events/hora: 51% en dones i 68% en homes). A més, el model actual proposa noves variables clíniques no testades prèviament, com son el diàmetre de la cintura i les xifres de pressió arterial sistòlica que possiblement tinguin un major poder discriminador a l'hora de predir una SAOS greu en comparació amb variables clàssiques com son l'edat, el sexe o les apnees nocturnes objectivades. Però, inclús malgrat la incorporació d'aquestes noves variables, igual que els models previs, la precisió global del nostre model clínic ha estat insuficient per predir la presencia d'una SAOS greu requerint afegir un segon pas amb dades obtingudes de la pulsioximetria (ODI3%) per tal d'incrementar la Sp del model global.

En relació als estudis previs publicats, és molt interessant destacar el treball publicat per Sareli et al. [22] on es va intentar predir la presencia

de SAOS (IAH ≥5 events/hora) i de SAOS greu (IAH ≥30 events/hora) confirmada per PSG completa en 342 pacients bariàtrics consecutius mitjançant un model predictiu que es basava en paràmetres clínics senzills: IMC, edat, sexe i símptomes relacionats amb la SAOS. Aquests autors van concloure que el seu model no podia predir amb prou certesa la presencia de SAOS inclús després d'utilitzar els punts de tall més estrictes. Però també, suggerien, en línia amb els nostres resultats, que el seu model podia predir amb relativa alta seguretat la presencia de SAOS greu. Ara bé, el model de Sareli et al. requereix que cada pacient ompli un qüestionari complet amb multi-resposta sobre simtpomes de la SAOS; en canvi, el nostre model només formula una única pregunta binària: presencia o absencia de apnees objecctivades. Dixon et al.[39] també van construir un model amb paràmetres clínics i analítics per tal de predir la presencia de SAOS en 99 pacients bariàtrics simptomàtics basat en les següents variables: apnees nocturnes objectivades, sexe masculí, IMC elevat, insulina basal i percentatge de hemoglobina glicosilada (HbA1c) obtenint una Se elevada (96%) però amb una Sp massa baixa (71%) per detectar una SAOS greu (IAH ≥ 30 events/hora). A més, l' inclusió dels pacients no es va fer de forma consecutiva com en el nostre treball sinó en base a si referien símptomes suggestius de SAOS. Recentment, Kokotkin RL et al. [43] han avaluat el model proposat per Dixon et al. i també han proposat un nou model alternatiu basat en 10 variables clíniques

predictives en 310 pacients bariàtrics inclosos de manera consecutiva. També la Se i la Sp obtingudes van ser inferior al 80% en ambdós models. Per tant, cap d'aquests treballs previs han pogut trobar factors predictius prou fiables per detectar la presencia de SAOS en diferents poblacions de pacients bariàtrics abans de dur a terme la cirurgia.

Cal destacar 2 principals limitacions del segon treball d'aquesta tesis. Per una banda, l'absència d'un grup independent per dur a terme la validació externa del model proposat. Ara bé, hem utilitzat el mètode de validació creuada que és un mètode estadístic consensuat per tal de descartar un excés d'ajust de les dades obtenint uns valors predictius del model prou fiables i similars als obtinguts durant la construcció del model. Per altra banda, la variable "ODI3%" s'ha extret de l'oximetria de la polisomnografia intra-hospitalària, no d'una oximetria domiciliaria. Tot plegat, fa que sigui imprescindible en futurs treballs validar el model proposat en una nova cohort de pacients consecutius candidats a cirurgia bariàtrica realitzant ambdues oximetries: una obtinguda de la polisomnografia intra-hospitalària i l'altra d'àmbit ambulatori.

En relació als resultats obtinguts en el tercer treball, s'observa que la pèrdua ponderal postquirúrgica suposa una disminució significativa en la gravetat de la SAOS a mitjà termini en gran part dels pacients. Els casos greus (IAH $\geq$ 30 events/hora) es redueixen marcadament del 70% al

12% permetent una alta tasa de retirada de la teràpia amb CPAP: 96% dels pacients amb indicació de CPAP pre-quirúrgica. Molts pacients aconsegueixen reduir la gravetat de la SAOS fins ser de caràcter lleu (42%), alguns continuen presentant SAOS moderada (27%) i només uns pocs aconsegueixen la resolució completa del trastorn respiratori nocturn (19%). Els pacients que experimenten una milloria més significativa en la gravetat de la SAOS post-quirúrgica podrien ser els pacients més joves en el moment de la cirurgia i amb una SAOS més greu durant l'avaluació pre-quirúrgica (un IAH preCB superior). Ara bé, en cap cas dita milloria sembla estar relacionada amb l'IMC pre-quirúrgic ni amb el grau de somnolència diürna referit pels pacients abans ni després del procediment quirúrgic.

Molts dels treballs previs publicats que analitzen l'impacte de la CB sobre la gravetat de la SAOS presenten limitacions importants. Alguns tenen una grandària mostral reduïda (<20 subjectes estudiats) [47-49], per això els resultats cal interpretar-los amb cautela no sent àmpliament extrapolables. En altres series manquen definicions clares en quan a la presencia de SAOS i la tasa d'èxit/milloria post-CB [105, 106], motiu que dificulta la comparació dels resultats entre diferents estudis. Altres mostren dades de milloria de la SAOS postCB sense cap prova de son reglada objectiva de control basant-se únicament en la milloria subjectiva

expressada pels pacients[107-110]. Però, sense dubte, la màxima limitació que presenten molts dels treballs previs és un biaix de seguiment considerable: només el 11-29% dels pacients avaluats amb una prova de son reglada abans de la cirurgia son revaluats d'igual forma en el període post-quirúrgic [45, 50, 51, 106]. Molts pacients no consideren necessari repetir una polisomnografia o poligrafia respiratòria després de la cirurgia donat que ja han experimentat una milloria subjectiva clara. Inclús, alguns professionals que s'encarreguen del maneig post-operatori d'aquests pacients consideren que la resolució del ronc és sinònim de la resolució de la SAOS, per això tampoc motiven als seus pacients perquè es facin la prova de son de control després d'assolir una pèrdua de pes significativa. En el tercer treball d'aquesta tesis, el biaix de seguiment és insignificant ja que la tasa de seguiment és al voltant de 97% (59 de 61 pacients). Dels treballs publicats amb anterioritat, únicament dos [49, 111] tenen tases de seguiment similar al nostre però ambos estudis tenen una grandària mostral limitada (<25 pacients per estudi).

Cal assenyalar un metanàlisis publicat l'any 2009 [53] que revisa tots els treballs publicats fins aquell moment que analitzen els efectes de la pèrdua ponderal post-quirúrgica sobre l'IAH. El metanàlisis conclou que només 12 estudis son rellevants i d'aquests, únicament 2 estudis [49, 111] tenen un disseny prospectiu sense biaix de seguiment però amb

grandària mostral limitada. Malgrat això, tenint en compte les limitacions d'aquests 12 treballs degut bàsicament a la heterogeneïtat en les dades mostrades, la grandària mostral limitada i el biaix de seguiment, els resultats globals d'aquest metanàlisis en 80 pacients que tenen una prova de son objectiva abans i després de la CB no difereixen substancialment dels resultats expressats en el nostre tercer treball; el percentatge de pacients amb un IAH postCB <5 events/hora i <10 events/hora fou del 25% i del 44% en el metanàlisis i del 19% i del 46%, respectivament, en la nostra sèrie. A més, amb una reducció mitjana entre l'IMC preCB i l'IMC postCB similar: 17.9 Kg/m^2 (CI 95%, 16.5-19.3) en el metanàlisis i 18.3 Kg/m^2 (CI 95%, 16.9-19.7) en la nostra sèrie.

En un intent d'investigar factors predictius de milloria de la SAOS postCB, en base als resultats obtinguts de l'anàlisi de regressió logística del tercer treball, sembla ser que els pacients més joves amb una SAOS més greu preCB tenen més probabilitat de millorar la gravetat de la SAOS postCB. Ara bé, aquestes dos variables (menor edat i major IAH pre-CB) malgrat associar-se de manera independent a la milloria en la gravetat de la SAOS postCB, no tenen prou poder predictiu per identificar amb fiabilitat en tots els casos aquells pacients que experimentaran un descens significatiu de l'IAH post-CB. Per tant, aquestes dos variables no es poden emprar dins un model predictiu fiable sinó cal interpretar-les dins

un model explicatiu de milloria de la SAOS postCB. De manera similar, en el metanalisis del 2009 es van detectar 2 factors potencialment independents: l'edat (més jove) i la pèrdua ponderal post-quirúrgica >100Kg però igualment van obtenir una capacitat predictiva baixa ja que només una minoria de pacients experimentaven una pèrdua ponderal tan significativa. Per tant, els nostres resultats en una mostra moderadament gran (>50 subjectes) i homogènia de pacients sotmesos a CB confirmen la recomanació establerta en el metanàlisis on s'aconsellava repetir estudis de son reglats ja que de moment és la única manera objectiva de revaluar la presencia de la SAOS postCB donat que encara ens manca un model clínic fiable de predicció. També és important emfatitzar que la milloria subjectiva en el grau de somnolència referida pels pacients i inclús la milloria objectiva ponderal en base a l'IMC no prediu la milloria real de la SAOS; això també recolza la necessitat de realitzar una prova de son objectiva de control per garantir la resolució de la SAOS i/o la milloria suficient per poder retirar la teràpia amb CPAP.

L'amplia variabilitat en el canvi de l'IAH postCB a igual descens en l'IMC juntament amb la mancança de factors predictius clínics fiables que detectin una clara milloria de la SAOS postCB reflexa probablement que la relació entre la SAOS i la pèrdua ponderal post-CB és molt més complexa que únicament bidireccional entre els canvis en l'IAH i l'IMC.

De fet, en la nostra sèrie no s'ha demostrat que el canvi en l'IMC postCB s'associi a una milloria de la SAOS després de la CB. Altres factors a part del canvi en l'IMC, no tinguts en compte en aquest tercer treball i en els treballs publicats anteriorment, podrien interaccionar en dita relació. La distribució del greix corporal no és homogènia en tots els subjectes obesos i l'IMC únicament representa un augment global del pes corporal [91]; la quantificació del teixit adipós a nivell abdominal o cervical mitjançant tècniques d'imatge com la ressonància magnètica [112, 113] o la tomografia computeritzada axial [114], o inclús mesures antropomètriques senzilles regionals com el perímetre de la cintura o el perímetre del coll [115] son paràmetres que molt probablement reflecteixen millor els diferents fenotips de distribució del greix corporal en els pacients obesos. És possible que la variabilitat en la milloria d'alguns d'aquests fenotips específics de distribució del greix corporal després de la cirurgia bariàtrica siguin els responsables de la variabilitat observada en la milloria de la SAOS postCB. De manera que, a igual reducció en l'IMC, alguns pacients experimenten una major reducció en l'IAH que altres. Una altra possible explicació és suposar que la reducció de la via aèria superior depèn de l'equilibri existent entre la quantitat de teixit tou i les dimensions de l'estructura òssia cranio-facial que embolcalla la via aèria faríngia [24]. De manera que, abans de la CB la via aèria superior està reduïda pels dos factors: "obesitat" (major quantitat de teixits tous circumdants) i

"anatomia" (estructura òssia continent) però el factor que més predomina és el factor "obesitat"; després de la CB, a igual reducció en l'IMC, la via aèria superior podria estar menys reduïda en aquells pacients on el factor "obesitat" és el màxim predominant de la reducció i per tant ha quedat resolt amb la CB però en canvi, la via aèria superior continuaria estant reduïda en aquells pacients on malgrat resoldre's el factor "obesitat", el factor "anatòmic" continua sent limitant. Una altra explicació plausible, recentment postulada per Ashrafian et al. [116] seria entendre que la cirurgia bariàtrica no només beneficia la SAOS a través d'efectes purament mecànics dependents del pes perdut sinó també a través d'efectes metabòlics independents del pes perdut que guarden relació amb els canvis post-quirúrgics que tenen lloc en el transit digestiu com seria la re-modulació en l'alliberació i acció de diferents adipocines, citocines, hormones intestinals i en la milloria en la resistència insulínica. Tot plegat podria incrementar l'eficiència energètica i per tant, metabòlica global i millorar així, també la SAOS post-CB.

Cal destacar també certes debilitats del tercer treball presentat en aquesta tesis. Per una banda, l'avaluació respiratòria postCB ha tingut lloc a mitjà termini (≈ 12 mesos després del procediment quirúrgic); alguns pacients podrien no haver assolit la màxima pèrdua ponderal post-quirúrgica. Seria interessant analitzar si la reducció observada en l'IAH es

manté en el temps (amb més edat i diferents variacions ponderals entre subjectes). En estudis futurs de llarg seguiment seria interessant estudiar potencials factors causants de la recurrència de la SAOS i del guany ponderal progressiu observats en alguns d'aquests subjectes anys després de la CB. Per altra banda, sembla ser que un canvi en l'IMC postCB no tradueix necessariament un canvi de magnitud similar en l'IAH postCB. Per això, també seria interessant aprofundir en l'estudi de dita associació recollint dades a partir d'altres paràmetres esmentats prèviament que poden reflectir millor els canvis en l'acumulació regional del greix corporal a nivell abdominal i cervical i possiblement també més relacionats amb la presencia de SAOS residual postCB.

CONCLUSIONS

1. La SAOS s'associa a un pitjor perfil metabòlic en el pacient obès mòrbid candidat a cirurgia bariàtrica independentment de l'edat, el sexe i l'adiposita central suggerint que pot jugar un paper important juntament amb l'obesitat en la patogènesi de la disfunció metabòlica del pacient obès mòrbid.

2. Els professionals encarregats de tenir cura del maneig dels pacients obesos mòrbids haurien de ser conscients que la presencia concomitant d'una SAOS, a part d'altres comorbiditats clàssiques de reconegut risc cardiovascular relacionades amb l'obesitat, pot associar-se a un pitjor perfil metabòlic global i per tant, el seu correcte reconeixement i maneig és important per tal de reduir el risc cardio-metabòlic global d'aquests subjectes.

3. El model de predicció proposat pot ser una eina inicial molt útil per la detecció precoç d'una SAOS greu en programes multidisciplinaris de cirurgia bariàtrica. La seva aplicació pot agilitzar el maneig d'aquests pacients abans de la cirurgia bariàtrica optimitzant els recursos de les Unitats de Son responsables del maneig respiratori d'aquests pacients.

4. En la majoria dels pacients sotmesos a cirurgia bariàtrica, després d'un seguiment mitjà de 1 any, la pèrdua ponderal post-quirúrgica suposa una millora significativa de la gravetat de la SAOS. Ara

bé, la majoria dels pacients continuen presentant una SAOS residual de caràcter lleu-moderada malgrat assolir una òptima pèrdua ponderal.

5. La milloria en la gravetat de la SAOS després de la cirurgia bariàtrica no es pot predir de manera fidedigna mitjançant canvis en l'índex de massa corporal o en els símptomes. De moment, la única forma de garantir la resolució completa de la SAOS en pacients sotmesos a cirurgia bariàtrica és realitzant una prova de son objectiva postoperatòria.

SUMMARY (IN ENGLISH)

INTRODUCTION

OSA (obstructive sleep apnea) is a sleep disorder characterized by the narrowing of the pharyngeal airway, resulting in repeated episodes of partial or complete airflow cessation that lead to increasing respiratory effort, intermittent oxygen desaturation and sleep disruption [1, 2]. Untreated OSA patients have worse quality of life [3] and increased risk of traffic accidents [4]. Furthermore, OSA is associated irrespective of excessive sleepiness with increased overall mortality [5] and cardiovascular diseases [6]. But, treatment with Continuous Positive Airway Pressure (CPAP) can significantly ameliorate this risk [7].

Metabolic abnormalities, whether assessed as metabolic syndrome (MetS) [8] 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 [9-12]. Central obesity seems to play a crucial role in the origin of metabolic disruption, but many other mechanisms have also been considered responsible [13]. 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 [14, 15].

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 [16]. 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 [17], but data in humans are scarce.

Obesity is the main confounding factor in the investigation of the association between OSA and metabolic dysfunction [18]. 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 [117] and OSA [22]. Therefore, investigating this association in MO should contribute to a better understanding of the relative interaction between OSA, MO and metabolic dysfunction.

By the other hand, obesity is the major risk factor for OSA development [19, 20]. In general population, the estimated prevalence is

about 24% in men and 9% in women [3] but it can reach rates of up to 30% in obese subjects (BMI >30 Kg/m^2) [21]. Even in morbidly obese subjects (BMI >40 Kg/m^2), the prevalence of OSA could reach rates higher than 90% and more than half (53 %) may present a severe form of the disease (AHI ≥ 30 events/hour) [22]. In this specific setting of morbidly obese patients, bariatric surgery (BS) has became a recommended weight loss option for patients suffering from serious co-morbidities related to obesity who have failed to lose weight with conservative approaches. BS results in sustained weight loss, which, in turn, reverses the severity of many obesity-related disorders, such as diabetes, dyslipemia and hypertension [23].

OSA subjects have special predisposition to suffer from peri-operative complications [24]. In several surgical settings, OSA patients had more peri-operative complications that those without OSA [25, 26]. In abdominal surgery, those who were treated with Continuous Positive Airway Pressure (CPAP) had fewer peri-operative complications and less rates of post-extubation respiratory failure than those who were not [27]. In fact, recent guidelines for patients scheduled for elective major surgery recommend considering a pre-operative assessment of OSA and introducing CPAP therapy if required [28].

Although the evidence is limited in the bariatric setting, this assessment could be even more important since these subjects have higher anaesthetic risk due to their extreme obesity [29] and they also tend to present concomitant OSA. Unrecognized and untreated OSA could increase the length of hospital stay [30] and the costs of post-operative care [31], while its identification, and subsequent precautionary measures during the peri-operative period may help avoiding intensive care after BS [32]. Many standard guidelines [33, 34] recommend OSA screening before BS since it is considered a highly prevalent concomitant condition related to obesity and untreated may induce perioperative complications. However, in general practice this recommendation is still not fully implemented in many bariatric centres. In fact, a systematic OSA screening in the BS setting is a major healthcare challenge, due to the frequent lack of symptoms, even in severe OSA. Full overnight Polysomnography (PSG) is the standard diagnostic test but it is costly and time-consuming. Various authors have attempted to find clinical predictors to rule out patients with a low risk of OSA and to detect those at high risk who would need further sleep management prior to BS [22, 38-40, 42-44]. However, most of these previous works were unable to find any reliable predictive factor, and finally, they strongly recommend PSG for all patients undergoing BS.

Moreover, most bariatric patients do not report OSA-related symptoms during the preoperative assessment [39, 44] and they report even fewer symptoms after surgery [45]. This may mean that the presence of OSA is overlooked in both of these periods: before and after BS. In many cases of severe OSA patients treated with continuous positive airway pressure therapy (CPAP) before surgery have this therapy withdrawn once they experience a significant weight loss after BS, without any reassessment of objective OSA improvement. However, optimal surgical weight loss may not always guarantee OSA resolution[46] and these subjects could still suffer from OSA and its cardiometabolic burden, even though they may not complain about any OSA-related symptoms.

The presence of residual OSA after BS may worsen the deleterious consequences of obesity due to the association of OSA with the metabolic syndrome. It is thus important to know the specific outcomes of bariatric surgery with respect to OSA improvement. The current literature on OSA resolution after BS is still inconclusive, for several reasons. Many published works had small sample sizes [47, 48, 118] and/or significant follow-up bias [50-52], and so their results should be interpreted with caution. Furthermore, the number of works where the patients are studied for OSA before BS and they are reassessed after

surgery via an objective sleep study, regardless of OSA symptoms is still limited. So, the results of these previous works should be interpreted with caution and the derived conclusions are still not enough conclusive.

In summary, morbidly obese patients submitted to a bariatric surgery programme can be an ideally extreme model to investigate the association between OSA and its cardio-metabolically consequences related or not to severe obesity. A systematic OSA screening before BS should be an optimal recommendation since OSA is a highly prevalent condition and untreated may induce perioperative complications; however there is still no reliable way to detect this condition without an objective sleep study. Thus, studying whether any simple formula based on clinical parameters could optimize severe OSA cases before BS should be an important topic of interest. It is also becoming a major healthcare challenge to better understand the specific BS outcomes on OSA severity and if there exists any predictive factor before BS that could help to detect patients that would experience a significant OSA improvement regardless of the amount of surgical weight loss.

MAIN HYPOTHESIS:

OSA is associated with a more impaired metabolic profile in a cohort of consecutive morbidly obese patients enrolled in a bariatric surgery programme, and consequently may contribute to a higher cardio-metabolic burden in the morbidly obese.

In a cohort of morbidly obese patients waiting for bariatric surgery, it is possible to construct a concise and easy-to-use predictor model to detect those patients with severe OSA avoiding the need of a preoperative sleep study.

In patients with OSA and morbid obesity, the surgical weight loss not always leads to OSA improvement and the complete OSA resolution is not achieved only by an optimal weight loss.

OBJECTIVES:

(1) To study whether the presence of OSA is associated with a worse metabolic profile in a cohort of consecutive morbidly obese patients enrolled in a bariatric surgery programme and if this association is independent of central obesity.

(2) To detect if there is any specific metabolic dysfunction pattern related to OSA in this cohort of morbidly obese patients.

(3) And, if the overall cardiovascular risk increases in parallel with OSA severity in this morbidly obese cohort

(4) To perform a concise and easy-to-use predictor model to detect patients with severe OSA since probably they are those being more benefited from CPAP therapy before BS.

(5) To analyze the objective impact of Bariatric surgery on OSA severity after one year of surgery reassessing objectively the entire bariatric cohort regardless of symptoms.

(6) To attempt to find preoperative clinical predictors of OSA improvement related or not to surgical weight loss.

RESULTS:

Gasa M, Salord N, Fortuna AM, Mayos M, Vilarrasa N, Dorca J, Montserrat JM, Bonsignore MR, Monasterio C. Obstructive sleep apnoea and metabolic impairment in severe obesity. Eur Respir J. 2011 Nov;38(5):1089-97. Epub 2011 May 26.

- OSA is very prevalent in this population of morbidly obese patients candidates to bariatric surgery.
- The prevalence of MetS was significantly higher in OSA patients compared to non-OSA patients (70% vs 36%, 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 blood pressure, triglycerides and the percentage of glycosylated haemoglobin (HbA1c) in the total sample, and with systolic BP, high-density lipoprotein cholesterol and HbA1c in those patients without DM2.
- OSA increased the adjusted odds ratio of having MetS by 2.8 (95% CI 1.3–6.2; p 0.009).
- As OSA severity rises according to AHI categories, the Framingham cardiac risk score also increases.

Gasa M, Salord N, Fortuna AM, Mayos M, Embid C, Vilarrasa N, Montserrat JM, Monasterio C. Optimizing screening of severe obstructive sleep apnea in patients undergoing bariatric surgery. Surg Obes Relat Dis. 2012 Feb 9. [Epub ahead of print].

- We have constructed an easy, reliable and secure predictive model to detect in a cohort of patients waiting for bariatric surgery those more prone to suffer from severe OSA.

- Using this two-step model, we ruled out 45% of the patients: 15% of the patients would be ruled out by applying the first formula based on clinical parameters (age, waist circumference, systolic blood pressure, and witnessed apnea episodes) and 30% applying the second formula adding data form the pulse-oximetry (oxygen desaturation index of ≥3%) in the remaining subjects. Furthermore, the number of more complex sleep evaluations has been reduced from 136 to 75.

- The final predictive values of the two-step model were: Sensibility 91%, Specificity 90%, Postive predictive value 92%, Negative predictive value 89% and an overall accuracy of 0.90 (95% CI from 0.84 to 0.94) with an acceptable percentage of misclassification rates: false negative of 9% and false positive of 10%.

Gasa M, Salord N, Vilarrasa N, García Ruiz de Gordejuela A, Dorca J, Montserrat JM, Monasterio C. Impact of bariatric surgery on obstructive sleep apnea severity. [Submitted].

- Surgical weight loss is related to a significant OSA improvement nearly in all patients after one year of bariatric surgery with noticeable reductions in very severe and severe cases: the percentage of patients having an AHI >=30/h is reduced from 70% to 12% bringing a CPAP withdrawal rate of 96%. But, complete OSA resolution (AHI <5/h) is observed in 19% of patients and moderate OSA (AHI 15-30/h) is still presented in 27% of the patients.

- The individual changes in BMI and AHI after surgery show that an AHI improvement is not always related to BMI lowering.

- According to the multiple logistic regression analysis, the presence of severe OSA before surgery (AHI pre-BS >= 30 events/hour) is the only independent parameter associated with OSA improvement after adjusting for age, gender and BMI improvement, with the following adjusted β coefficient (95% CI and p-values): 10.937 (2.064-57.965, p 0.005).

GLOBAL DISCUSSION

In agreement with our hypothesis in the first work, MetS is more prevalent, and the metabolic profile more impaired, in morbidly obese patients with OSA than in those without. The metabolic profile progressively worsens with increasing OSA severity, irrespective of sex. This worsening remains 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 [16, 55, 56-58], and more recently in specific high cardiovascular risk populations, such as MetS [14, 15, 60], hypertensive [59] and CV disease cohorts [61]. 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 [54].

The comparison of OSA and non-OSA patients reveals 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. 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 [62-64]; 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.

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 [55, 56-58, 65, 66]. 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.

Experimental studies in animals and humans have shown intermittent hypoxia to be a major determinant of metabolic dysfunction associated with OSA [17, 80]. In our cohort, OSA compared with non-OSA patients have a greater degree of nocturnal CIH due to higher AHI, CT90% and arousal index without higher subjective EDS or differences in sleep-stage percentages. Furthermore, AHI is independently associated with most of the individual metabolic parameters, according to the linear regression analysis, whereas CT90% is 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 CT90% 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. [81], 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 [17], a definitive causal role of OSA in metabolic impairment in humans cannot be firmly established. In interventional studies, CPAP therapy lowered BP [82], while data on glucose and/or lipid control still appear to be inconclusive [84-87]. 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 [88]. 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 proinflammatory state [89]. OSA may worsen this state [90] by acting as an additional cardiometabolic burden risk. In the present study, we used WC as an accepted surrogate of visceral

adiposity [91]. OSA patients have 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. [92]: 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 is notably high: 72% of patients have an AHI $\geq$ 15 events/hour and only 2% have an AHI <5 events/hour. Significantly, most subjects do not complain about EDS (72% of OSA patients had ESS $\leq$10), even if they have severe OSA. Although previous studies demonstrated objectively higher EDS in obese patients, compared with healthy non-obese controls, regardless of OSA status [93, 94], 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 [95, 96]. Our finding of a lack of subjective sleepiness is clinically relevant since it emphasises the need to perform sleep studies in this specific population, regardless of self-reported symptoms.

With regard to limitations of this first work, 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.

As we observe from the data of our first work, in bariatric setting the majority of patients do not refer subjective somnolence although most of them suffer from OSA. Since symptoms alone are not enough to predict OSA, we have constructed a model based on clinical parameters that can be collected easily during the first medical visit: age, waist circumference, systolic blood pressure and witnessed apnea episodes. Applying this first step, 15% of patients would be ruled out. In the remaining patients, a

pulse-oximetry would be performed and applying the second step 30% more of patients would be ruled out. Thus, nearly one half of the patients would be reasonably excluded without any complex sleep study allowing to be concentrate in the management of those that are more prone to suffer from severe OSA before BS. By the other hand, using this model we could also optimize the use of PSG resources with an acceptable percentage of misdiagnosed cases. The model could therefore become a first step toward the optimization of sleep resources in the management of bariatric patients, without compromising their peri-operative security. In fact, the general measures for OSA peri-operative management, such as use of the reverse Tredelenburg position, anticipation of a possible difficult airway, use of short-acting anesthetic agents, avoidance of opioids and extubation while awake in a non-supine position) [101] should be applied in every patient who undergoes BS, since the prevalence of OSA (AHI ≥5/h) is extremely high in bariatric populations. Thereby, the major efforts related to OSA pre-operative diagnosis should concentrated towards the detection of those suffering from severe disease that would be greatly benefited from CPAP therapy prior the surgical procedure. Obviously, many others studies could be performed to speed up even more the sleep management of these patients, such as the evaluation of the Auto-CPAP use as the first-choice treatment for OSA patients in a BS program, which would simplify the CPAP titration prior

to surgery. It would also be useful to automatically adjust the pressure changes required over time, as patients experience a progressive weight loss after surgery.

Our predictive model supports the notion reported by previous authors [22, 39, 44, 98, 99, 102] that typical OSA-related symptoms (such as snoring and daytime sleepiness assessed by ESS) do not predict OSA in bariatric cohorts. That could explain the limited usefulness of previously published models. Moreover, in contrast to earlier models, our proposal includes new, more discriminating clinical variables (such as WC and SBP), in addition to age and observed apneas. But, even so, like previous works, the overall accuracy of the present clinical model was insufficient to predict severe OSA making necessarily to increase the overall Sp by adding a second step using data (ODI3%) from a simplified sleep study.

Regarding previous studies, it is worth mentioning the work published by Sareli et al [22] attempting to predict OSA (AHI ≥ 5/h) and severe OSA (AHI ≥ 30/h) confirmed by an overnight PSG, in 342 consecutive bariatric patients by developing a model based on BMI, age, gender and OSA-related respiratory symptoms. They concluded that even with the most stringent possible cut-off value, their model could not predict OSA with sufficient certainty They also suggested, however – in line with our data – that their model could predict with relatively high

certainty severe OSA. In this model, each patient needs to fullfill a multiple choice questionnaire regarding OSA sympthoms; by contrast, our model only requires a unique binary question: witnessed apnea episodes yes/no. Dixon et al. [39] also constructed a clinical-analytical model to predict OSA in 99 symptomatic patients waiting for BS, based on observed apnoeas, male gender, higher BMI, age, fasting insulin and the percentage of haemoglobin glicosilated (HbA1c) with high Se and moderate Sp (96% and 71% for AHI $\geq$ 30/h) but, in contrast to our study of consecutive patients, these authors studied only those with clinical suspicion of OSA. Recently, Kokotkin RL et al. [43] have evaluated the model proposed by Dixon et al. as well as a new alternative model based on 10 predictive variables in 310 consecutive bariatric patients regardless of symptoms. However, the Se and Sp values observed were less than 80% in any of the two models. Therefore, all those previous works could not find any reliable predictive factor to assess OSA in bariatric population prior to BS.

Some limitations should be mentioned from this second work. First, our study did not include an external validation group, although we used the 10-fold cross-validation method to check the presence of overfitting data. Second, ODI3% data were obtained from the PSG, not from an ambulatory study with a home pulse-oximeter. Additional studies

are needed to validate this model in a new cohort of consecutive bariatric patients with both tests used: intralaboratory PSG and home pulse-oximetry.

Regarding BS outcomes on OSA severity, in most patients surgical weight loss results in a significant OSA improvement at medium term follow-up leading to a noticeable reduction of severe cases (from 70% to 12%) and, consequently a high CPAP withdrawal rate (96%). Most patients improved to mild OSA (42%), many still had moderate OSA (27%) and only few achieved complete resolution (19%). This improvement was related to younger age and higher AHI pre-BS but cannot be predicted by changes in BMI or ESS. Therefore, at the moment, OSA patients undergoing BS should perform an objective sleep assessment after surgery in order to check for sleep disorder resolution.

Many previous works concerning the impact of BS on OSA severity had several limitations. Some had small sample size with less than 20 patients studied [47-49], thereby their results should be analyzed cautiously. Others lacked clear definitions of OSA diagnosis and success rates after BS (how to define OSA improvement or resolution?), thus comparisons between studies are difficult [105, 106]. Moreover, some published data defined OSA without any sleep study and considered its resolution after BS based on the amelioration of symptoms without

confirming the improvement with an objective postoperative sleep study [107-110]. But, undoubtedly the main limitation of many previous studies was the follow-up bias: only 11-29% of patients studied during the preoperative period were reassessed in the post-operative period [45, 50, 51]. Many patients did not consider necessary to repeat a polysomnography or respiratory polygraphy since they reported significant subjective improvement. Even some physicians taking care of these patients consider that snoring resolution is synonymous of OSA resolution, thus they do not reinforce their patients to perform a control sleep study after surgical weight loss. In our study, the follow-up bias is insignificant with a follow-up rate is nearly 97% (59/61). Only two previous smaller series had similar follow-up rates [111, 118].

A meta-analysis published in 2009 [53] reviewed the published works that analyzed the effects of surgical weight loss on the AHI. They concluded that 12 studies were relevant; of these, only 2 were prospective and had no significant follow-up bias, despite their limited sample sizes (less than 25 patients) [111, 18]. Notwithstanding these limitations as regards data heterogeneity, small sample size and follow-up bias, the final results of several of these 12 studies, examining a total of 80 patients via an objective sleep study before and after BS, did not substantially differ from our own results. In the meta-analysis, the AHI post-BS was reduced

to less than 5 and less than 10 events/hour in 25% and 44% of patients, respectively, while in our series it is reduced to 19% and 46%, respectively. The mean BMI reductions are also similar: 17.9 Kg/m^2 (95% CI, 16.5-19.3) in the meta-analysis and 18.3 Kg/m^2 (95% CI, 16.9-19.7) in the present work. The search for predictive factors of OSA improvement after BS in the meta-analysis published in 2009 found only two independent factors: age (younger) and a weight loss > 100Kg (although this had a low predictive capacity as only a few of the patients experienced a surgical weight loss >100Kg). Similary, according to the results of our third study, it seems that younger and more severe OSA patients are more likely to improve their OSA status after BS. However, we are aware that these variables, although significantly associated with post-BS OSA improvement, did not have sufficient power to fully identify, in all cases, those patients who would experience a significant AHI reduction after BS. This result should therefore be taken as an explicative model, rather than a predictive one. Thus, our findings in this homogeneous and moderately broad sample (>50 patients) endorse the final recommendation made by the meta-analysis published in 2009 [53]: clinicians should have low thresholds for evaluating postsurgical patients with repeated polysomnograms, as this is the only means available for objectively reassessing OSA status, in the absence of a reliable clinical model for predicting significant OSA improvement after BS. Moreover, it

is important to emphasize that improvement in subjective somnolence after BS was not a predictor of OSA improvement, thus reinforcing the need to perform an objective sleep study during the follow-up in order to verify OSA resolution after optimal surgical weight loss.

The substantial variability in AHI response to surgical BMI decrease with the lack of sufficient independent clinical predictors to prove OSA improvement after BS may reflect that the relationship between OSA and surgical weight loss is more complex than being only bidirectional between AHI and BMI. This is still an unresolved question. BMI change could not be the best parameter to relate OSA improvement with obesity improvement after bariatric surgery. Fat distribution is not homogenous among obese patients and BMI represents only overall increase in body weight [91]; adipose tissue quantification of abdominal and neck regions by nuclear MRI [112, 113] or CT scanner [114] or even other simple measurements, such as neck and waist circumferences [115] may better reflect specific fat distribution phenotypes probably more related to OSA. At equal BMI decrease, some patients could reduce those parameters more than others leading to a higher reduction in AHI. Another possible explanation is the notion that airway narrowing depends on the balance between the amount of soft tissue surrounding the pharyngeal airway and the craniofacial bony enclosure [24]. Before BS

airway size could be reduced by both aspects but mainly by the "obesity" factor; after BS, at equal weight loss, AHI would be reduced more in those where the main responsible of airway reduction was the "obesity" factor compared to those where the "anatomical" factor also participated. Moreover, as it is recently postulated [116, 120], it is also possible that the beneficial effects of BS on OSA include not only mechanical weight-dependent but also metabolic weight-independent effects such as adipokine effects, cytokine actions, altered gut hormonal release and insulin resistance improvement.

The third study has several weaknesses. Firstly, the sleep reassessment was at medium term follow-up; some patients could still not achieve optimal weight loss. It would be interesting to analyze if this AHI reduction could be maintained over time. Further studies may be focused on the relationship between OSA recurrence and weight regain post-BS in larger cohorts with longer follow-up. Secondly, it seems that BMI change did not predict OSA improvement. Other weight parameters more related to OSA development were not collected. Waist and neck circumferences could be easily assessed bringing indirect information about changes on upper-body and abdominal fat accumulation. Others factors would require more complex techniques to be quantified.

CONCLUSIONS

1. OSA is associated with a more severe metabolic profile in morbidly obese patients, independent of age, sex, central adiposity and smoking, suggesting an important role of OSA, in addition to obesity, in the pathogenesis of metabolic dysfunction in this population.

2. Since OSA is a treatable condition, and excessive daytime sleepiness assessed by the Epworth sleepiness scale is not a good OSA marker in morbidly obese cohorts, clinicians dealing with these subjects should appropriately assess OSA in addition to other classic known obesity-related comorbidities, in order to better treat the overall metabolic dysfunction.

3. The proposed two-step predictive model could be a useful first screening tool to detect those at higher risk, as well to optimize the sleep laboratory resources and consequently, improve the management of severe OSA in bariatric cohorts.

4. Bariatric weight loss results in significant OSA improvement in most patients after one-year follow-up. However, some patients could still have residual OSA and its associated cardiometabolic

burden, despite achieving optimal BMI loss and significant subjective improvement.

5. Although post-BS OSA improvement seems to be independently associated with younger age and higher AHI pre-BS, it cannot be reliably predicted by those two independent variables, or by changes in the BMI or clinical symptoms. Therefore, OSA patients undergoing BS should undergo an objective sleep assessment after surgery in order to guarantee OSA resolution.

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