Metabolic surgery and obstructive sleep apnoea: the protective effects of bariatric procedures

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ABSTRACT

The global epidemic of obesity and the worldwide prevalence of obstructive sleep apnoea (OSA) are both increasing. Epidemiological studies reveal an association between obesity, weight gain and OSA. Metabolic or bariatric operations provide sustained weight loss and resolve or improve the symptoms of OSA in the majority of morbidly obese individuals. These operations also modulate the metabolic profile to improve glycaemic control, to decrease cardiovascular risk and obesity-related mortality. The beneficial effects of metabolic operations on OSA include mechanical weight-dependent and metabolic weight-independent effects that are achieved through the BRAVE effects: (**B**ile flow alteration; **R**eduction of gastric size; **A**natomical gut rearrangement and altered flow of nutrients; **V**agal manipulation; and **E**nteric gut hormone modulation). These result in an improvement in insulin resistance, adipokines, cytokines and systemic inflammation. A literature analysis was performed with statistical pooling of available surgical and medical studies to determine whether the weighted mean decrease in body mass index and sleep apnoea severity (measured by the apnoea-hypopnoea index) are larger in metabolic surgical studies than in non-surgical weight loss studies (diet, exercise and medication). However, heterogeneity across available trials, poor follow-up measures and a deficiency in comparative studies between surgical and non-surgical therapy precludes definitive statements regarding the relative benefits of surgical therapy. Further research is required to quantify robustly the effects and mechanisms of sleep apnoea resolution by metabolic surgery, which may reveal novel non-surgical treatments or enhanced surgical strategies in the management of this multisystem sleep disorder.

INTRODUCTION

The global epidemic of obesity and the worldwide prevalence of sleep apnoea are both increasing. According to the WHO there are at least 300 million obese adults[1] and an estimated 100 million individuals who suffer from sleep apnoea.[2] Both conditions contribute to increased worldwide mortality and healthcare costs, and sleep apnoea is now considered as one of the most common organic sleep disorders. Obstructive sleep apnoea (OSA) syndrome is characterised by frequent episodes of apnoea and hypopnoea due to periods of upper airway collapse which can result in hypertension, increased cardiovascular mortality, stroke, decreased quality of life, sleepiness and morbidity associated with disordered sleep.[3]

The epidemiological association between obesity rates and sleep-disordered breathing has been progressively studied to identify obesity as a significant risk factor for the development of OSA.[3] There are several other risk factors for sleep apnoea including sex, family history, race/ethnicity, craniofacial abnormalities, type 2 diabetes mellitus, menopause and behaviours including smoking and alcohol consumption. Several methods have been applied to reduce the burden of obesity, including disease prevention, lifestyle change, behavioural modification and pharmacotherapy. Patients have found the weight loss offered by these treatments difficult to maintain in the long term. Surgical modalities do, however, achieve longstanding weight loss in the severely obese population. The operations, initially called 'bariatric' procedures, have demonstrated a maintenance of weight loss for over 15 years[4 5] while also providing beneficial metabolic effects that include improved glycaemic control in the majority of morbidly obese patients.[6–9] In view of their significant metabolic effects, these procedures are now known as 'metabolic' operations.

Longitudinal studies on metabolic surgery have revealed that successful weight loss also results in lower sleep apnoea rates. In this review we describe the effects and potential mechanisms of sleep apnoea resolution by metabolic surgery.

EPIDEMIOLOGY OF OBESITY AND OSA

OSA is present in 4—9% of adult men and 1—2% of adult women in the general population when assessed by polysomnographic criteria (apnoea-hypopnoea index (AHI) >5/h) and the presence of sleepiness.[10] Its prevalence is highest in men aged 40—65 years although it is increasingly diagnosed in all age groups of both sexes. Based on polysomnography alone, the prevalence can be as high as 17—24% in men and 5—9% in women. The data from these studies were collected in the late 1980s and early 1990s when obesity was significantly less prevalent, rendering these values as a likely underestimation of the actual prevalence of OSA in the current era.[10—18]

The association of obesity with sleep apnoea was first described in the Ancient Ptolemaic dynasty (305—30 BC) and was regarded in the late 19th century as the Pickwickian syndrome.[19 20] Approximately 70% of patients with sleep apnoea present with obesity,[21] and 40% of patients with obesity suffer from sleep apnoea. The 'Sleep in America' survey of the National Sleep Foundation[22] revealed that 57% of obese individuals are at high risk of OSA, and its incidence in morbidly obese patients can be 12—30 times higher than the incidence in the general population.[23] The prevalence

of OSA in metabolic surgical candidates with a body mass index (BMI) of ≥35 kg/m^2 may range from 60% to 83%.[23–35]

The Wisconsin Sleep Cohort Study prospectively demonstrated in 690 randomly selected individuals that a 10% increase in body weight was associated with a sixfold increase in the risk of developing sleep apnoea over a 4-year period and also raised the AHI by 32%. Conversely, it showed that a 10% weight loss was associated with a 26% decrease in AHI. In this study, an increase of 1 SD in any measure of obesity body habitus was related to a threefold increase in the risk of an apnoea-hypopnoea score of ≥5.[10] The Sleep Heart Health Study reported an OR of 2.4 for an AHI of ≥15 with a BMI difference of 10 kg/m^2. It also revealed that, of the three measures of body habitus assessed, the effect size for an AHI of ≥15 was greatest for BMI and was negligible for waist-to-hip ratio.[36]

The Cleveland Family Study reported that the 5-year incidence of sleep apnoea is approximately 7.5% where both BMI and waist-to-hip ratio are independent predictors of disease. They demonstrated that the predominance for men suffering from sleep apnoea diminished with increasing age so that, by the age of 50, the incidence between men and women was equal.[37] Furthermore, the study showed that the contribution of BMI to sleep-disordered breathing was negligible after 60 years of age.[37]

Although the incidence of OSA is highest for middle-aged men in the general population, one prospective survey has revealed an increased female prevalence of sleep apnoea in morbidly obese surgical candidates (78% women, 22% men).[38] One study which specifically studied women undergoing bariatric surgery found the prevalence of OSA to be as high as 92.5% in this subgroup of patients.[39] These changes may reflect the role of sex steroids on respiratory control and the pathogenesis of sleep apnoea. Decreased hormone levels in the menopause are associated with the development of sleep apnoea, and hormone therapy with oestrogen and progesterone replacement provides a therapeutic effect.[40–42]

Several anthropometric measures of body fat have been associated with the severity of sleep apnoea symptoms and polysomnographic findings. These include BMI, percentage of body fat, percentage predicted body weight, neck and abdominal circumferences, skin folds, subcutaneous fat of the neck region, parapharyngeal fat pads, subcutaneous and intra-abdominal fat. Of these, BMI has been the most widely applied measure of body fat in OSA due to its practicality and consistency of calculation in obese patients. Patients in their sixth decade and onward have a decreasing association between sleep apnoea and BMI.[43] It is also recognised that obese subjects can suffer from sleepiness which is related to the systemic effects of obesity and not necessarily related to sleep apnoea.

It is now increasingly recognised that the symptoms of sleep apnoea can improve with surgical-induced weight loss. Dixon *et al* demonstrated independent predictors of AHI based on multivariate analysis of an OSA structured interview known by the BASHIM acronym. These included (1) BMI ≥45 kg/m^2; (2) age; (3) sleep apnoea (observed); (4) glycosylated haemoglobin (HbA1c) ≥6%; (5) insulin ≥28 μmol/l (fasting plasma levels); and (6) male sex. The authors proposed a simple scoring system to predict moderate or severe OSA. A score of ≥3 points with an AHI ≥15 had 89% sensitivity and 81% specificity whereas a score of ≥3 points with an AHI ≥30 had 96% sensitivity and 71% specificity.[44]

METABOLIC SURGERY AND REDUCTION IN OBESITY-RELATED MORTALITY
Metabolic operations are increasingly performed worldwide, accounting for over 344 000 cases each year.[45] There are numerous types of operations (gastric banding, sleeve gastrectomy, biliopancreatic diversion, biliopancreatic diversion/duodenal switch and gastric bypass) and the mechanisms by which they work are still unclear. The gastric bypass procedures consist of a number of physiological steps, the so-called BRAVE effects[46]: (1) **B**ile flow alteration; (2) **R**eduction of gastric size; (3) **A**natomical gut rearrangement and altered flow of nutrients; (4) **V**agal manipulation; and (5) **E**nteric gut hormone modulation (figure 1).

Most operations are now performed minimally invasively (using laparoscopic techniques) and a recent multicentre prospective observational study revealed an overall operative 30-day mortality of 0.3% with a 30-day morbidity of 4.3%.[47] These procedures provide sustained long-term weight loss, improved glycaemic control and long-term cost-effectiveness.[48] Traditionally they have been applied only to patients with BMI >35 kg/m^2 and obesity comorbidities (suggested by the National Institutes of Health (NIH) in the USA and the National Institute for Health and Clinical Excellence (NICE) in the UK). In view of their favourable metabolic effects, however, these procedures have been increasingly performed within study protocols in patients with BMI <35 kg/m^2.

Metabolic surgery has never been subjected to a randomised controlled study for mortality benefit but, within cohort studies, an overall all-cause mortality benefit has been demonstrated when compared with non-surgical obese matched controls.[5 49]

METABOLIC SURGERY AND OSA REDUCTION
Metabolic surgery can significantly improve or resolve sleep apnoea in morbidly obese individuals. One large meta-analysis[6] of 136 metabolic surgical studies with a total of 22 094 patients reported that 19.6% of surgical candidates reporting sleep-disordered breathing. The studies that considered OSA reported on a total of 1195 patients where sleep apnoea was resolved in 85.7% (95% CI 79.2% to 92.2%), improved or resolved in 83.6% (95% CI, 71.8% to 95.4%) and corresponded to a decrease in apnoeas or hypopneas by 33.9/h (95% CI 17.5 to 50.2). It is unclear why the proportion of patients with disease resolution is higher than the proportion of patients with resolution or improvement after surgery. This could be a result of the heterogeneity in study outcomes, diagnosis criteria and selection for this analysis. The Swedish Obese Subjects (SOS) study commenced in 1987 and is ongoing. It is a prospective non-randomised controlled study of 4047 matched individuals
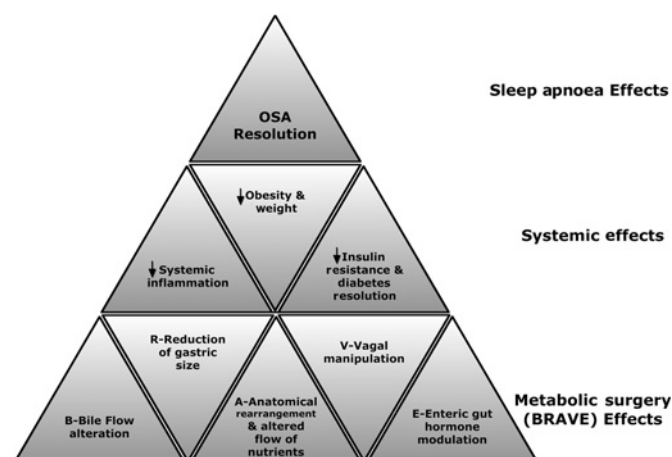

Figure 1 Mechanisms of the resolution of obstructive sleep apnoea (OSA) after metabolic surgery.

approximately divided into two equally-sized arms: surgically treated patients and a conventional obesity treatment group.[4 5] In their cohort, the study group identified 1592 individuals who completed 2-year follow-up sleep apnoea questionnaires used in the study. They demonstrated that, compared with a control group, postoperative patients had significantly lower symptoms of sleep apnoea and reported a significant reduction in the persistence of apnoea episodes (27.9% vs 71.3%) and snoring (21.6% vs 65.5%).[50]

A recent meta-analysis[51] assessing the effects of surgical weight loss on measures of OSA identified 12 studies with 342 patients in whom the pooled AHI was reduced by 38.2 events/h (95% CI 31.9 to 44.4) to a final value of 15.8 events/h (95% CI 12.6 to 19.0) based on a random effects model. The pooled BMI was reduced by 17.9 kg/m^2 (95% CI 16.5 to 19.3) to 37.7 kg/m^2 (95% CI 36.6 to 38.9). The inclusion criteria for this study required the reporting of both preoperative and postoperative measures of polysomnography performed in accordance with recommendations of the American Academy of Sleep Medicine. As a result, the pooled outcomes for the change in BMI and AHI were not derived from matching studies and the analysis for

each parameter did not include all 12 studies listed, despite an unavoidable heterogeneity between them.

We calculated (table 1) the weighted mean change (random effects model) of BMI and AHI of all metabolic surgical studies to date using the databases Medline, PubMed, EMBASE and the Cochrane Library (from inception to June 2011) reporting on both these parameters (inclusion criteria for analysis). The results show that, in 359 subjects with a mean BMI of 55 kg/m^2, surgery offers a weighted decrease of BMI by 16 kg/m^2 (16.09, 95% CI 13.27 to 18.92) and a weighted decrease of AHI by 34/h (34.22, 95% CI 25.27 to 43.18) (RevMan Computer program Version 5.0, Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2008). This statistical pooling analysis was only possible for a limited number of studies because data were lacking. Although there are no randomised controlled studies comparing lifestyle and surgical weight loss therapies that focus on robust sleep apnoea endpoints, both the weight loss effects of surgery (based on BMI) and the changes in AHI are greater in surgical studies (tables 1 and 2).

The limitation of the surgical studies is related to their design. The majority are non-comparative retrospective studies with

Table 1 Metabolic surgical studies reporting on weight loss and indices of sleep apnoea before and after surgery

Author	Metabolic operation	No of subjects	Follow-up (months)	BMI (kg/m^2) Preop	BMI (kg/m^2) Postop	AHI (/h) Preop	AHI (/h) Postop
Harman et al, 1982[29]	Jejuno-ileal bypass	4	24	NS	NS	78	1.4
Peiser et al, 1984[23]	RYGB	15	2—4	NS	NS	81.9	15.0
Peiser et al, 1984[23]	RYGB	6	4—8	NS	NS	81.9	5.5
Charuzi et al, 1985[26]	RYGB	13	6	NS	NS	88.8	8.0
Charuzi et al, 1987[24]	RYGB, VBG	46	6	NS	NS	58.8	36.1
Rubinstein et al, 1988[16]	VBG or diet (unknown split)	12	NS	41	32	57	14
Summers et al, 1990[52]	VBG	1	4	54	37	40	<5
Rajala et al, 1991* [15]	VBG	3	NS	52.2	34.23	44.67	5.33
Charuzi et al, 1992[25]	RYGB, VBG	47	10.65	NS	NS	60.8	8.0
Charuzi et al, 1992[25]	RYGB, VBG	6	12	NS	NS	60.3	12.4
Charuzi et al, 1992[25]	RYGB, VBG	6	84	NS	NS	60.3	34.5
Sugerman et al, 1992* [34]	RYGB, VBG, HG	40	54	58	39	64	26
Pillar et al, 1994[32]	RYGB, VBG	14	4.5	45	33	40	11
Pillar et al, 1994* [32]	RYGB, VBG	14	90	45	35	40	24
Noseda et al, 1996[53]	VBG + CPAP Diet + CPAP	39 (3 VBG, 36 diet)	12	NS	NS	66.5	50.3
Scheuller and Weider, 2001[54]	BPD, VBG	15	12—144	NS	NS	96.9	11.3
Rasheid et al, 2003* [55]	RYGB	11	3—21	62	40	56	23
Guardiano et al, 2003* [56]	RYGB	8	28	49	34	55	14
Valencia-Flores et al, 2004* [35]	RYGB, VBG	29	13.7	56.5	39.2	53.7	13.7
Busetto et al, 2005* [57]	Intragastric balloon	17	6	55.8	48.6	59.3	14
Dixon et al, 2005* [27]	Gastric banding	25	17.7	52.7	37.2	61.6	13.4
Lankford et al, 2005[58]	RYGB	15	12	48	32	40 (CPAP:11 cm H$_2$O)	NA (CPAP:9 cm H$_2$O)
Kalra et al, 2005[59]	RYGB	10	5.1	60.8	41.6	9.1 (median)	0.65 (median)
Poitou et al, 2006* [60]	RYGB, gastric banding	35	12	51.3	39.9	24.5	9.7
Haines et al, 2007* [28]	RYGB	101	6—42	56	38	51	15
Grunstein et al, 2007[50] (SOS Study)	RYGB, VBG, gastric banding	1592	24	42.2	32.5	24 (frequency apnoeas)	8.3 (frequency apnoeas)
Fritscher et al, 2007[61]	RYGB	12	24.2	55.5	34.1	46.5 median (range 33—140)	16.0 median (range 0.9—87)
Martí-Valeri et al, 2007* [31]	RYGB	30	12	56.53	32.12	63.59	17.45
Valera et al, 2007[62]	RYGB	56	12	49	NS	35	NS
Kuzniar et al, 2008[63]	NS	1	7	44.5	29.4	44 (CPAP:16 cm H$_2$O)	NS (CPAP:8 cm H$_2$O)
Lettieri et al, 2008* [30]	Gastric banding	24	12	51	32.1	47.9	24.5
Rao et al, 2009[33]	Gastric banding	46	12.6±20	45.2	30	38.11	13.18
Pallayova et al, 2011* [64]	RYGB, SG, BPD-DS	23	12	52.3	35.7	45.6	10.1
Weighted mean (random effects) postoperative change					↓**16.09**		↓**34.22**

*Studies reporting the postoperative changes of both BMI and AHI which were subsequently included in the analysis to derive the weighted mean change of BMI and AHI.
AHI, apnoea-hypopnoea index; BMI, body mass index; BPD, biliopancreatic diversion; CPAP, continuous positive airway pressure; DS, duodenal switch; HG, horizontal gastroplasty; NS, not specified; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VBG, vertical banded gastroplasty.

Table 2 Non-surgical studies of weight loss and indices of sleep apnoea before and after weight loss intervention

Author	Lifestyle intervention	Number of subjects	Follow-up (months)	BMI (kg/m^2) Preop	Postop	AHI (/h) Preop	Postop
Smith et al, 1985[65]	Weight loss advice	15	5.3	NS	NS	55	29.2
Rubinstein et al, 1988*[16]	Diet or surgery	12 (study proportion unknown)	NA	41	32	57	14
Pasquali et al, 1990*[14]	Diet	23	3—14	37.5	30.9	66.5	33
Rajala et al, 1991*[15]	Diet	8	NS	50.7	44.1	45.75	31.63
Schwartz et al, 1991*[66]	Diet	13	NS	42.0	34.7	83.3	32.5
Suratt et al, 1987[67] and 1992*[68]	Diet	8	1 month<24	54	46	90	62
Kiselak et al, 1993[69]	Diet	14	4.5—5	54.88	NS	17.63	1.03
Nahmias et al, 1993[70]	Diet	24	5—19	NS	NS	56.5	17.5
Noseda et al, 1996[53]	Diet+CPAP or surgery+CPAP	39 (36 diet, 3 surgery)	12	NS	NS	66.5	50.3
Kansanen et al, 1998*	Diet	15	3	38.1	35.1	29	18
Sampol et al, 1998[17]	Diet	67	NS	31.5	25.9	52.3	44.2
Sampol et al, 1998[17] (cured patients)	Diet+exercise	24	11.5	32.8	27.2	44.3	3
Sampol et al, 1998[17] (cured patients)*	Diet+exercise	24	94.3	32.8	30.8	44.3	26.4
Martinez and Basile, 2005[13]	Sibutramine	10	1	25—35	NS	28	27
Yee et al, 2007*[18]	Sibutramine+diet	87	6	34.2	31.0	46	29.6
Verhulst et al, 2009[71] (teenagers)	Diet	21	5	NS	NS	3.8	1.9
Barnes et al, 2009*[72]	Diet+exercise	10	4	36.1	30.1	24.6	18.3
Phillips et al, 2009*[73]	Sibutramine+diet+exercise	93	6	34.1	31.6	45.9	30.2
Ferland et al, 2009[74]	Sibutramine+diet+exercise	22	12	36.8	35.0	39.8	37.0
Foster et al, 2009*[11]	Weight loss advice	139	12	36.5	36.3	23.5	27.7
Foster et al, 2009*[11]	Diet+exercise	125	12	36.8	33.0	22.9	17.5
Nerfeldt et al, 2010*[75]	Diet+behavioural support	22	24	40.0	35.0	43.0	28.0
Tuomilehto et al, 2010*[76]	Diet	35	24	33.4	30.9	10	5.4
Johansson et al, 2011[77][78]	Diet+behavioural support+exercise+sibutramine/orlistat	49	12	34.8	31.1	36	19
Weighted mean (random effects) post-intervention change					↓3.27		↓13.73

*Studies reporting the post-intervention changes of both BMI and AHI which were subsequently included in the analysis to derive the weighted mean change of BMI and AHI.
AHI, apnoea-hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; NS, not specified.

variable follow-up times, variable operative procedures and an inconsistency in measuring surgical outcomes. These studies were not intentionally designed to identify sleep apnoea outcomes prospectively and do not fulfil all the criteria for the causal association between metabolic surgery and its effects on sleep apnoea resolution, progression or prevention. Much of the data used may be influenced by the bias of measuring BMI (as patient selection based only on BMI may not reveal the full effect of surgery on OSA), ascertainment bias (sampling from non-random cohorts), treatment biases (such as those for continuous positive airway pressures), intervention bias (such as otolaryngology intervention) and differential follow-up bias (comparing results from patients with variable follow-up times).

Nevertheless, these studies suggest an association between metabolic operations, improved polysomnography results and decreased sleep apnoea symptoms. This may occur through a variety of mechanisms including weight-dependent and weight-independent metabolic pathways.

MECHANISMS OF OSA RESOLUTION AFTER METABOLIC SURGERY
Metabolic surgery offers a number of protective mechanisms that may lead to decreased symptoms of OSA. Metabolic surgical actions (BRAVE effects) modulate the systemic metabolism to achieve metabolic enhancements and mechanical improvements in disease resolution (figure 1).

Decreased sleep apnoea and weight loss
Decreased obesity achieved through surgical weight loss may contribute to a reduction or resolution of OSA. The prospective non-randomised controlled SOS study revealed that 10-year

surgical weight loss was as high as 25% for 58 patients who underwent gastric bypass compared with no weight loss (actually a mild weight increase) in the 886 medically-treated patients.[5] Dixon et al[79] demonstrated that, at 2 years, laparoscopic adjustable gastric banding surgery achieved 20.7% weight loss compared with 1.7% in medically-treated patients in a randomised controlled trial of patients with recently diagnosed type 2 diabetes with a BMI of 30—40 kg/m^2.

The mechanisms for weight loss after metabolic surgery are multifactorial and include alterations in hunger, satiety, food preferences, alterations in metabolic rate, metabolic modulation, the gut microbiome and increased exercise capacity. As a result, the effects of surgery on weight are much broader than the unverified extent of nutrient malabsorption or the mechanical occlusive effect of stomach restriction.

Surgically-induced weight loss may reduce the severity of sleep apnoea through the mechanical decrease of adiposity (both visceral and subcutaneous). As a result, this can alleviate the physical pressure on the neck, upper airway and the breathing apparatus (including the diaphragm which may also receive excess pressure from visceral fat)[80] in addition to beneficial anatomical changes (airway size, collapsibility, changes in functional residual capacity).

There is also some evidence associating obesity with poor or short sleep,[81][82] which might reveal further potential benefits of surgery by reversing this harmful association and improving sleep quality and length. A randomised trial in patients of normal weight showed that short sleep duration (4 h) resulted in a decrease in the satiety hormone leptin by 18%, an increase in the appetite stimulating hormone ghrelin by 28% and an overall increase of both appetite and hunger by 23-24% (associated with

an increased consumption of calorie-dense foods with high carbohydrate content) when compared to subjects with long sleep duration (10h).[82] This finding has been supported by several large epidemiological studies associating sleep duration with BMI.[81] [83] The literature, however, is still unclear in differentiating between the metabolic effects of general sleep restriction and the sleep fragmentation of sleep apnoea. As a result, the metabolic contribution of surgery in this context requires further robust evidence.

Comparing the effects of surgical and non-surgical weight loss on sleep apnoea severity can help identify the relative contribution of surgical weight loss on disease resolution. We calculated the weighted mean change (random effects model) of BMI and AHI of all lifestyle intervention and medical studies (diet, exercise, behaviour and drugs including sibutramine) to date using the databases Medline, PubMed, EMBASE and the Cochrane Library (from inception to June 2011) reporting on both BMI and AHI (inclusion criteria for analysis). We found that, in 685 subjects with a mean BMI of 36 kg/m^2, non-surgical weight loss therapies resulted in a weighted decrease in BMI of 3.27 kg/m^2 (3.27, 95% CI 2.41 to 4.14) and a weighted decrease in AHI by 13.73/h (13.73, 95% CI 8.60 to 18.86) (RevMan Computer program Version 5.0. Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2008). This statistical pooling analysis was only possible for a limited number of studies because data were lacking.

Weight loss by any means has a beneficial effect on sleep apnoea and AHI (tables 1 and 2), although few studies have directly compared these treatments for robust sleep apnoea endpoints. The finding that some non-surgical weight loss therapies offer significant improvements in AHI with much more modest weight loss than in the surgical studies emphasises the likely contribution of anatomical factors that can modify the severity of sleep apnoea further to the metabolic and weight loss changes noted after surgery. Currently, there are limited choices for weight loss medications and many of the dietary therapies that have a beneficial effect on sleep apnoea are based on a low calorie diet which many individuals cannot tolerate in the long term. Metabolic surgery, however, can provide a long-standing and well-tolerated decrease in caloric intake, although it is associated with the risk of surgical mortality and morbidity in the early postoperative period.

Cytokine and anti-inflammatory effects

Patients with excessive daytime sleepiness (EDS) and sleep apnoea have increased levels of the proinflammatory cytokines interleukin (IL)-6 and tumour necrosis factor α (TNFα).[84] Although the plasma levels of these cytokines are also positively associated with BMI, IL-6, TNF, leptin and insulin are elevated in patients with sleep apnoea independent of obesity. The inflammatory biomarker C-reactive protein (CRP) is also elevated in sleep apnoea, and serum CRP levels correlate with polysomnography scores independent of adiposity.[85]

Surgical and non-surgical weight loss can result in a decrease of IL-6 and several other oxidative stress and systemic inflammatory markers including CRP, sialic acid, plasminogen activator inhibitor-1, malondialdehyde and von Willebrand factor; conversely, IL-8 levels can be increased.[8] [65] IL-6 is reported to decrease in two-thirds of studies of this cytokine after metabolic surgery, with levels falling by 9—59%. Analysis by multiple regression has shown that the reduction in postoperative insulin resistance after surgery is independently associated with a decrease in IL-6 concentrations.[86] TNFα was reduced in one study of patients undergoing liposuction[87] (which does not offer long-term metabolic or weight loss effects) and was not modulated in patients undergoing metabolic surgery,[61] although the levels of the soluble TNF-α receptor 2 (sTNFαR2) were decreased after bariatric surgery (independent of weight loss and other covariates).[65] The cytokine effects of metabolic procedures—specifically those on IL-6 (and the TNF-α/IL-6 ratio)—may contribute to disease resolution after surgery, although it is difficult to differentiate between the direct mechanistic contribution of surgical weight loss and cytokine modulation to sleep apnoea.

Type 2 diabetes mellitus and insulin resistance

There is increasing epidemiological and clinical evidence associating type 2 diabetes mellitus and insulin resistance with OSA. The prevalence of OSA in diabetic men is approximately 23% compared with 6% in a community-based cohort.[88] Furthermore, the prevalence of OSA in obese patients with type 2 diabetes can be as high as 86% based on polysomnographic criteria.

Several population-based studies have shown that OSA has metabolic features and complications in addition to its mechanical sequelae. This condition is a risk factor for insulin resistance independent of age, gender, BMI and waist circumference. Clinically, patients have higher fasting blood glucose levels and insulin levels compared with age- and BMI-matched controls. Even mild sleep apnoea can result in glucose intolerance[89] and, furthermore, non-obese subjects with sleep apnoea can develop insulin resistance.[90] Although some studies have not shown a consistent association between sleep apnoea and insulin resistance, this may be affected by the diagnostic accuracy of sleep apnoea and insulin resistance measurements in these cohorts. Possible mechanisms associating sleep apnoea and insulin resistance include the direct effects of obesity and the modulation of the autonomic nervous system on sympathetic drive.[91] Early reports show that improvements in OSA by continuous positive airway pressure (CPAP) therapy might improve glycaemic control,[92] but this has not been universally demonstrated[93] and there is currently no clear evidence that the successful treatment of insulin resistance and diabetes results in improved sleep apnoea symptoms. As a result, the proposed causation between impaired glucose metabolism and OSA still needs to be proven.

Among the most pronounced effects of metabolic surgery is the improvement in glycaemic control and decreased cardiovascular risk (including a reduction in OSA-associated atrial fibrillation).[8] [9] A recent systematic review and meta-analysis of the effects of metabolic surgery on diabetes incorporating 621 studies with 888 treatment arms and 135 246 patients reported that 78.1% of diabetic patients had a fasting glucose level <7 mmol/l and glycaemic control was improved in 86.6% of patients.[7]

Mechanisms of improved glycaemic control in patients undergoing metabolic surgery include the long-term effects of surgical weight loss in addition to several mechanisms independent of weight loss such as the modulation of the gut hormone glucagon-like peptide-1 which together improve insulin resistance and improve insulin secretion after surgery. These include the rearrangement of the gastrointestinal anatomy through foregut, midgut and hindgut hypotheses.[9] [46] [94] [95] Metabolic procedures also offer the beneficial modulation of the autonomic nervous system which may contribute to the resolution of diabetes, sleep apnoea and even obesity-associated heart rate dysrhythmias in morbidly obese subjects.[8] [96] [97] The improvement in insulin resistance resulting from these metabolic surgical

procedures may therefore contribute to the improvements and resolution of OSA observed in these operations.

Adipokines

Leptin is a 16 kDa product of the adipose obese (ob) gene, mainly synthesised by fat cells. It acts on the hypothalamus to increase energy expenditure and decrease food intake. In non-obese individuals, raised leptin levels result in the expected rise in energy expenditure and decreased food intake. In obese individuals, however, circulating levels are chronically high without a significant decrease on food intake or increased energy expenditure, which suggests that there is leptin insensitivity in the obese state. Hyperleptinaemia is associated with obesity hypoventilation and sleep apnoea and metabolic procedures decrease serum leptin levels in proportion to postoperative weight loss.[98]

Gut hormones and sex steroids

Obese patients with sleep apnoea have increased levels of the orexigenic (appetite stimulating) hormone ghrelin, the levels being positively correlated with the number of sleep-disordered breathing events.[99 100] Both adenotonsillectomy in children with sleep-disordered breathing and nasal CPAP in adults can decrease ghrelin levels.[100 101] The effects of metabolic surgery on the modulation of ghrelin is controversial in view of the large variation in ghrelin levels reported postoperatively.[94] As a result, it has been difficult to determine whether the surgical modulation of ghrelin results from weight-independent surgical effects (as is the case for glucagon-like peptide-1 or peptide YY) or those secondary to surgical weight loss. Further investigation to clarify the role of metabolic surgery on gut hormones and sleep apnoea may offer novel treatments and an increased understanding of the disease mechanism.

The current evidence associating sleep apnoea and sex steroids identifies the role of a decrease in menopausal hormone in sleep apnoea and the possible therapeutic role of oestrogen and progesterone replacement therapy.[40–42] The studies to date have not, however, identified the role of these sex hormones on sleep apnoea in the context of obesity. Metabolic surgery is known to have beneficial effects on sex steroid-related physiology including improved fertility, polycystic ovary syndrome and libido, mainly attributed to weight loss effects.[102] The surgical modulation of sex steroids may contribute to the observed postoperative decrease in obesity-related female cancers[103] and are considered to occur predominantly through weight loss effects. These procedures decrease the levels of oestradiol and sex hormone-binding globulin, although the effect of these changes requires formal study in the context of sleep apnoea.

CONCLUSIONS

Metabolic surgery is increasingly being performed worldwide as the obesity epidemic advances. As these procedures induce significant metabolic changes, they are no longer applied with the sole purpose of weight loss but are progressively being used to improve patient health and are now considered to produce 'bionic' effects.[104] Metabolic surgery offers a significant reduction of the symptoms and measures of OSA. The beneficial effects of metabolic surgery on OSA may include both weight-dependent and weight-independent mechanisms. These include adipokine effects, cytokine actions, altered gut hormonal release and the improvement of insulin resistance. Identifying the precise mechanisms through which metabolic surgery improves or resolves OSA will increase our understanding of how obesity and metabolic dysfunction contribute to this multisystem sleep disorder. Currently, the heterogeneity across the available trials

and a deficiency in comparative studies between surgical and non-surgical therapy precludes definitive statements regarding the relative benefits of surgical therapy.

The future of this field requires further research to outline robustly the mechanisms and translational clinical effects of sleep apnoea resolution after metabolic surgery. This includes the quantification of weight-dependent and weight-independent effects on disease resolution and will require further randomised control trials of both in vitro and in vivo (animal) models of metabolic surgery and sleep-disordered breathing. Furthermore, mechanistic studies can employ genomic, transcriptomic and metabolic profiles using a systems biology approach.[105] This may ultimately offer a refinement of metabolic procedures to maximise their effects on OSA. It may also offer novel treatment strategies in the management of sleep-disordered breathing.

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