CLINICAL REVIEW

The reciprocal interaction between obesity and obstructive sleep apnoea

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SUMMARY

Obesity is a significant risk factor in the pathogenesis of obstructive sleep apnoea (OSA) altering airway anatomy and collapsibility, and respiratory control. The association between obesity and OSA has led to an increasing focus on the role of weight loss as a potential treatment for OSA. To date, most discussion of obesity and OSA assumes a one-way cause and effect relationship, with obesity contributing to the pathogenesis of OSA. However, OSA itself may contribute to the development of obesity.

OSA has a potential role in the development and reinforcement of obesity via changes to energy expenditure during sleep and wake periods, dietary habits, the neurohormonal mechanisms that control satiety and hunger, and sleep duration arising from fragmented sleep. Thus, there is emerging evidence that OSA itself feeds back into a complex mechanism that leads either to the development or reinforcement of the obese state.

Whilst current evidence does not confirm that treatment of OSA directly influences weight loss, it does suggest that the potential role OSA plays in obesity and weight loss deserves further research.

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Introduction

Obesity and obstructive sleep apnoea (OSA) are emerging public health issues. Obesity in particular, is increasing steadily as reflected by a large recent epidemiological analysis estimating that, between 1980 and 2008, worldwide mean body mass index (BMI) increased by 0.4 kg/m^2 per decade for men and 0.5 kg/m^2 for women.[1] Obesity is a well-defined risk factor for a number of cardio-metabolic disorders including OSA.

Sleep disordered breathing (SDB) is highly prevalent with 24% men and 9% women in the Wisconsin Sleep Cohort found to have an apnoea hypopnoea index (AHI) > 5 events/h.[2] With increasing obesity however, these 20 year old data are likely underestimates. In addition, OSA is an emerging chronic disease with an estimated prevalence as a disease syndrome (which includes daytime sleepiness) of 2% of women and 4% of men in the general population.[2] In the presence of obesity, the prevalence of OSA is estimated to be as high as 45%.[2,3] Among adults aged 30–69 years of age,

approximately 17% have at least mild or worse SDB and 41% of those adults have SDB which is attributable to having excess weight (BMI $\geq$ 25 kg/m^2),[3] highlighting the role of obesity in this condition. There are strong population and clinic based data demonstrating an association between OSA and cardiovascular disease,[4] in particular risks for the development of hypertension,[5] chronic heart failure[6] and insulin resistance,[7,8] where obesity, is closely linked with the metabolic dysregulation.

Thus, much has been written about the uni-directional relationship between obesity and OSA pathogenesis, however, the potential reciprocal role of OSA in the causation of obesity is less clear. Limited evidence available raises the possibility of OSA contributing to the development of weight gain[9] or resistance to weight loss[10] mediated by changes in energy intake, lifestyle and energy expenditure which we will review in this article. A summary of the main areas is highlighted in Fig. 1.

Review aims

We review the available evidence for the bidirectional relationship between obesity and OSA and examine the mechanistic role of both conditions in each other's pathogenesis.

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Abbreviations

AHI   apnoea hypopnoea index
BMI   body mass index
COPD   chronic obstructive pulmonary disease
CPAP   continuous positive airway pressure
EE   energy expenditure
FRC   functional residual capacity
OHS   obesity hypoventilation syndrome
OSA   obstructive sleep apnoea
Pcrit   critical closing pressure
REE   resting energy expenditure
SDB   sleep disordered breathing
SEE   sleep energy expenditure
TEE   total energy expenditure
VLCD   very low calorie diet

Obesity effects in OSA

No review article of this area would be complete without first examining the role of obesity in the pathogenesis of OSA. Considerable progress has been made in the last several decades investigating the pathogenesis of OSA and whilst a detailed discussion is beyond the scope of this review, an appreciation of the role of obesity in this process requires some understanding of present knowledge in this area.

Clinical and epidemiological studies linking OSA and obesity

Association data linking obesity and OSA have been well described in large cohort studies. The Wisconsin Sleep Cohort Study, a prospective study of the natural history of SDB, followed 690 individuals over one decade, re-evaluating each subject twice at 4 year intervals. The study found that a 10% weight gain predicted a corresponding 32% increase in the apnoea hypopnoea index (AHI) and six-fold increase in the risk for developing moderate to severe OSA.[11] The converse was also present, with weight loss associated with reductions in AHI, albeit to a smaller degree, suggesting that weight gain may have a stronger impact on AHI than does weight loss. Importantly, the results were independent of potential confounding factors, such as age, baseline body habitus measures (including height, weight, and waist, neck, and hip girths), and smoking habits. These data were later confirmed by the Sleep Heart Health Study,[12] which examined a community based cohort of similar middle-aged and elderly subjects for predictors of SDB. The study demonstrated that a one standard-deviation increase in BMI was associated with a four-fold increase in prevalence of OSA.

The Cleveland Family Study, published in the same period, confirmed the effects of body weight on disease progression with increasing incidence of OSA independently determined by body weight, age and gender.[13] The study also showed that, with advancing age, the influence of body weight and gender on disease incidence diminished, with disease risk in both genders equalizing after the age of 50 years.

In 2009, three landmark randomized controlled trials addressing the role of weight loss in the treatment of mild, moderate and
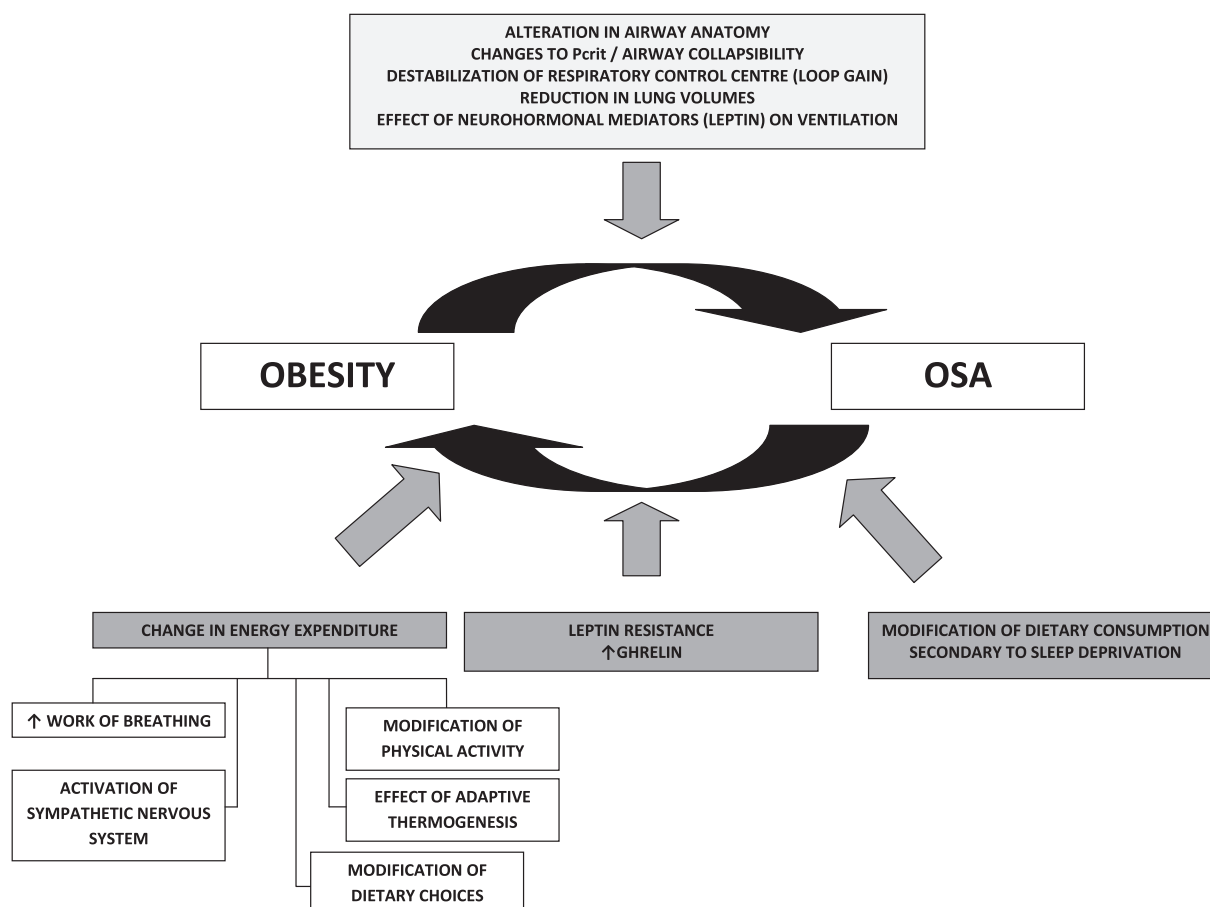

Fig. 1. Summary of the possible reciprocal relationships between obesity and obstructive sleep apnoea.

severe OSA were published, thus providing the first high quality evidence for the role of obesity in causing OSA and the subsequent benefits of weight loss. Tuomilehto et al.,[14] studied 72 overweight and obese subjects (mean BMI 32 kg/m^2) with mild OSA (AHI 5–15/h) who were randomized to either a combination of a very low calorie diet (VLCD) for 12 weeks and a supervised lifestyle programme or a control group which consisted of a single session of lifestyle counselling. Despite the chance occurrence of the treatment group being heavier than the controls (randomization was not stratified by BMI), 63% of patients in the active treatment arm achieved OSA remission (AHI < 5/h) after one year compared to only 35% of controls.

Johansson et al. conducted a randomized controlled trial (RCT) of 63 obese males (mean BMI 34.8 kg/m^2) with continuous positive airway pressure (CPAP)-treated, moderate to severe OSA (mean AHI 37/h) who were randomized to receive either VLCD or a usual diet.[15] After nine weeks, the treatment group achieved greater weight loss compared to the control group (−18.7 versus 1.1 kg; $p < 0.001$), greater reduction in BMI (−5.7 versus 0.3 kg/m^2; $p < 0.001$) and most crucially, a substantial reduction in mean AHI (12/h versus 35/h; $p < 0.001$). The study showed that patients with severe OSA derived more benefit from weight loss compared to those with moderate disease at baseline despite little differences in the amount of weight lost. The one year follow-up study[17] of this population (controls crossed over to VLCD diet and weight maintenance program as well) confirmed this trend and demonstrated maintenance of most of the AHI improvements at one year.

The third study from Foster et al.[16] investigated patients with obesity and untreated, moderate to severe OSA (mean AHI 23.2/h) with the additional co-morbidity of type II diabetes mellitus. The authors randomized 264 obese subjects (mean BMI 36.7 kg/m^2) to either intense lifestyle intervention with portion-controlled diet and prescribed exercise or to standard support. After one year, the treatment group had lost significantly more weight (−10.8 versus −0.6 kg; $p < 0.001$) compared to the controls and had significant reductions in AHI (−5.4 versus 4.2/h; $p < 0.001$). The prevalence of OSA in the intervention group fell from 28% to 18% while the control group experienced an increase from 29 to 38%, interestingly, without significant change in weight suggesting that in this particular group of patients, untreated OSA may follow a relatively rapid progression of disease severity. In addition to improvements in AHI with weight loss, the findings from Foster et al.[16] are also in line with those of Johansson et al.[15] in that patients with greater severity of OSA stood to benefit more from weight loss compared to those with mild disease.

The effect of obesity on the pathogenesis of OSA

OSA is the result of recurrent collapse of the upper airway during sleep resulting in arousals, sleep fragmentation and oxyhaemoglobin desaturation. Collapsibility is promoted by the combination of intraluminal negative pressure generated by the diaphragm during inspiration and extraluminal forces exerted by tissue and bony structures surrounding the airway which essentially, is a hollow, collapsible tube. Collapsing forces are opposed by the action of the pharyngeal dilator muscles as well as the caudal/longitudinal traction on the airway from lung inflation. The transmural pressure required to collapse the airway is termed the critical closing pressure (Pcrit), a concept developed by Schwartz and colleagues[18] which essentially represents a measure of the airway's tendency (or resistance) to collapse.[19] Other factors involved in the initiation and propagation of airway collapse in OSA include an unstable respiratory control system (with elevated "loop gain") and low arousal threshold, both of which promote oscillations in ventilation.[20]

Obesity is thought to play a role in the pathogenesis of OSA in a number of ways, including alterations in upper airway structure and function promoting greater collapsibility, reduction in resting lung volume, and a disturbance of the relationship between respiratory drive and load compensation. Obesity-related changes that predispose to airway collapse include deposition of adipose tissue around the upper airway and increases in neck circumference. These changes reduce intraluminal airway calibre and increase extraluminal tissue pressure[20] resulting in increased passive Pcrit as a consequence of elevated mechanical loading of pharyngeal structures.[19] In non-obese individuals, mandibular advancement potentially enlarges the bony compartment of the upper airway and reduces Pcrit. This effect however, is not seen in obese individuals likely due to the deposition of adipose tissue in peripharyngeal fat pads which cause collapse of the lateral pharyngeal structures as opposed to just the anterior wall.[19,21,22] A variety of imaging studies, using both computed tomography and magnetic resonance imaging have been used to measure pharyngeal fat deposition in various areas of the upper airway[21,23,24] and have demonstrated increased AHI with diminishing retroglossal cross-sectional dimensions.

In addition to local pharyngeal factors lung inflation applies longitudinal traction to the larynx and trachea,[25,26] which increases airway rigidity and reduces collapsibility.[27] This effect is diminished in obesity and, in particular, central obesity,[19] where deposition of fat in the thorax and abdomen results in decreased lung compliance[28] and a reduction in functional residual capacity (FRC).[29] Low FRC not only increases passive collapsibility of the airway via reduced caudal traction,[25,29] but predisposes to instability of the respiratory control system by reducing the "plant gain" of the feedback control loop.[30] A further detrimental effect at low lung volumes, is a tendency for the small peripheral airways to collapse leading to a reduction in ventilation of the lung bases, ventilation-perfusion mismatch and widening of the alveolar-arterial PO$_2$ difference.[29] The presence of recurrent airway obstruction, intermittent hypoxia and accompanying arousals causes oscillation of the systemic and pulmonary arterial blood pressures, heart rate and cardiac function which exacerbates systemic hypertension[31–34] and existing heart failure.[35,36]

The mechanical effects of the physical sites of excess fat deposits are unlikely to be the only factors in the pathophysiology of OSA.[37] While weight loss has been shown to increase velopharyngeal volume, changes in upper airway length appear to have greater influence on the frequency of apnoeas,[38] reinforcing the point that inter-individual variability in the effects of weight on OSA severity cannot be explained in terms of change in upper airway structure and local deposition alone. Although poorly delineated, there are indicators that obesity, in itself, has an effect on neuromuscular control within the upper airway. The effect is suggested by studies demonstrating improvements in Pcrit and OSA following weight loss[39] but direct clinical studies in human cohorts demonstrating this pathway is lacking. Recently, using a mouse model, Polotsky et al. demonstrated that the mechanical loading imposed by increasing weight was more significant in older mice which resulted in a greater susceptibility to airway collapse.[40] The authors hypothesized that with age and increasing weight, tonic neuromuscular responses are reduced and the phasic muscle responses responsible for overcoming the obstruction are altered. This model may be relevant in ageing, obese human OSA populations.

Hormonal changes associated with obesity may also affect the pathogenesis of OSA. Leptin is a key hormone involved in the regulation of energy intake and expenditure.[41] It is produced by adipocytes and acts in the hypothalamus to inhibit appetite. Most subjects with obesity have elevated leptin levels (due to increased adipocytes and fat mass), suggesting that in the presence of obesity

a degree of insensitivity to changes in leptin may occur.[42] OSA itself is also associated with raised leptin levels.[43] Leptin has inhibitory effects on respiratory drive and thus may play a role in the pathogenesis of OSA and obesity hypoventilation syndrome (OHS). Direct examination of this issue in human clinical populations was conducted by Campo et al.[44] who measured fasting leptin, anthropometry and hypercapnic ventilatory responses in 245 patients with obesity. This group reported higher concentrations of serum leptin associated with reduced respiratory drive and reduced hypercapnic response, mechanisms that underlie OHS. This was a cross-sectional study, which does not show causality, and the absence of arterial blood gasses to screen for existing OHS limits the interpretation of these findings. Nevertheless, this study does lend support to previous association studies[45,46] of leptin's influence in modulating the respiratory centre and consequently, its potential influence on the severity of both OHS and OSA.

Obesity induces an inflammatory state directly because adipose tissue is an abundant source of pro-inflammatory cytokines including tumour necrosis factor (TNF-α)[47] and interleukin-6 (IL-6).[48] These cytokines may be responsible for the observation that obesity and visceral obesity in particular, are associated with defects in neuromuscular control of the upper airway which lead to greater susceptibility and severity of OSA.[49] TNF-α in particular, exerts somnogenic effects on the central nervous system[50] by stimulating membrane expression and release of its soluble receptor TNF-α receptor I. The levels of soluble TNF-α receptor in plasma fall with the use of CPAP,[51] which corroborates the potential role of inflammation in the natural history of OSA.

OSA effects on obesity

As discussed so far, obesity exerts a significant direct effect on the pathophysiology of OSA through mechanical effects on the upper airway, influences on respiratory control, possible alterations of neuromuscular control and direct effects of adipokines on ventilation. But what of the reciprocal effects of OSA on the development and maintenance of obesity? Approximately 70% of those with OSA are obese.[52] The literature has previously reported that weight gain follows the onset of OSA symptoms and has also occurred in the 12 months prior to diagnosis.[9,43] For example, in a retrospective analysis, Phillips et al. reported a mean weight gain of 7.4 kg (standard deviation 1.5) in the year prior to the diagnosis of OSA - raising the possibility of OSA-related effects on weight gain.

The effect of CPAP on weight homeostasis in OSA patients has been unclear, with early studies reporting weight loss[53,54] but others reporting no change.[55,56] The two positive studies were published in the late 1990s. Loube et al.[53] reported weight loss greater than 4.5 kg in patients who were CPAP-compliant compared to those who were not, following a period of more than 50 months of CPAP use. The study was limited by its retrospective nature relying on chart reviews and patient self-reports for CPAP adherence. The measurement of weight loss was also reliant upon weight measurements performed 6–9 months apart from initial commencement, with no further weights recorded from long term follow-up. Secondly, Chin et al.[54] examined 22 severe OSA patients (AHI > 50/h) for changes in visceral and subcutaneous body fat (as well as serum leptin) following 6 months of CPAP use. Results were mixed, with 9 patients exhibiting mean BMI reductions of 2 kg/m^2, but 13 patients experiencing no change. The study was intended to examine visceral fat accumulation, which is a better predictor of coronary artery disease and in this regard, it demonstrated significant reductions independent of BMI.

Studies which did not demonstrate weight loss with CPAP were of a more recent nature with Redenius et al.[56] publishing a retrospective study of OSA patients adherent to CPAP, compared to

a control group of untreated or inadequately treated OSA patients. There was no difference in BMI between treated and control groups after one year. Interestingly, gender stratified analysis suggested that female patients gained weight following treatment with CPAP. The study was limited by the small study population and unequal distribution of patients in the study groups increasing the risk of systematic bias. The study also did not control for significant confounders including concurrent medications, diet and sleep duration, smoking and exercise, all of which may have affected weight over the course of a year. Finally, there were no indicators of treatment adequacy with CPAP, only assessments of adherence; which raised the possibility that even adherent patients may have had their OSA sub-optimally addressed. The second negative study was a prospective study from Ferland et al. who studied patients in two treatment arms comparing sibutramine assisted weight loss against CPAP therapy. The choice of treatment was selected by patients to "mimic" clinical reality and hence was not randomized. Sibutramine resulted in a 5% reduction in body weight without change to sleep parameters, whilst CPAP normalized sleep and cardiovascular parameters (blood pressure, heart rate) without significant change to weight or BMI. Overall, these studies suggest that OSA patients on CPAP do not experience marked weight reduction following initiation of therapy, and in some cases, they continue to gain significant weight but are all limited by their inadequate measurement of energy balance.

A recent well designed study has helped clarify this area and suggests that CPAP may indeed modify weight and metabolic parameters.[57] The authors conducted a randomized sham CPAP controlled crossover study with 3 months of active treatment in patients with severe OSA. In 20% of patients with metabolic syndrome, CPAP therapy led to a resolution of the metabolic syndrome, generally due to a significant reduction in one of the components (rather than all). CPAP treatment also led to a small, but significant improvement in weight, BMI, and visceral and subcutaneous fat. The study did not address mechanisms by which CPAP led to an improvement in weight and visceral fat, but it could be either due an effect on energy intake or energy expenditure.

Overall, there is a distinct lack of well-designed studies investigating the effects of OSA on obesity. Many of the studies in this field are limited by major flaws in design and short follow-up periods. Consequently, there is a clear need for future research to be directed at investigating the effects of OSA on obesity.

Energy expenditure, OSA and obesity

It is evident that a large proportion of patients with OSA are obese. This raises the possibility of abnormalities in energy regulation within this patient group, which contribute to the development and reinforcement of the obese state. The current simplistic understanding of weight homeostasis involves balance between energy intake and energy expenditure (EE), with a net increase in caloric intake resulting in weight gain.[58] Sleep plays a significant part in this process given that a large proportion of the human existence is spent in sleep and one of the prevailing theories for the function of sleep is the conservation of energy.[59] The energy conservation theory is supported by the finding of decreased EE during sleep in healthy individuals and the energy waste that occurs from sleep deprived states.[60]

OSA may potentially affect both EE and caloric intake in a number of ways:

1) Increased work of breathing from airway obstruction
2) Activation of the sympathetic nervous system with arousals and intermittent hypoxia
3) Alteration of EE with sleep fragmentation

4) Alteration to dietary habits in favour of energy dense foods
5) Modification of physical activity, via lethargy and daytime sleepiness

Although the effect of work of breathing in OSA on EE has never been independently assessed, the large intrathoracic pressure swings generated during periods of obstructed breathing may lead to an increase in EE, such as is observed in patients with chronic obstructive pulmonary disease (COPD).[61–63] It is also possible that the respiratory system could incur a penalty from the secondary hypoxia stemming from obstructive events. In COPD patients,[63] a reduction in respiratory mechanical efficiency is observed and hypoxia is hypothesized to be a contributor.

The activation of the sympathetic nervous system during periods of sleep arousal with secondary body movements from fragmented sleep has been associated with an increase in EE. Bonnet et al.[64] demonstrated this by exposing study subjects to acoustic stimuli (experimental arousals) and measuring the resting metabolic rate of study subjects with a face mask and metabolic cart setup. There was a clear increase in metabolic variables on the night of artificially induced sleep fragmentation compared to the baseline values obtained on the first night. Furthermore, there was reversal back to baseline levels on the night of recovery sleep. This concept of elevation in metabolic rate from sleep fragmentation was demonstrated in OSA populations by Kezirian et al.[65] who examined resting EE in 212 patients with varying severities of OSA. The authors found that increased resting EE was associated with increasing severity of OSA. This study was limited by its cross sectional design and more importantly by the possible confounding effect of weight. Results were also not adjusted for lean body mass, which is of particular importance given that muscle has inherently greater metabolic activity than adipose tissue and is the major predictor of total resting EE.

There are several other studies examining EE in OSA populations however, the data available are conflicting (See Table 1). Stenlof et al.[66] demonstrated an increase in total 24 h EE (TEE) and sleep related EE (SEE) in patients with severe OSA (AHI > 30/h) compared to non-severe OSA controls. Due to difficulties in recruiting weight matched obese controls without OSA, the authors used a control group of asymptomatic snorers, but who still had at least mild-moderate OSA. Of note, this control group had elevated SEE compared to quiet wakefulness, suggesting that even mild OSA could influence EE. In addition, O'Driscoll et al.[67] found that OSA is associated with increased SEE when measured via a multiple physiological sensor (SenseWear). Contradictory results were found by Ryan et al.[68] who found no difference in resting energy expenditure (REE) and dietary thermogenesis between patients with moderate to severe symptomatic OSA (mean AHI 68 ± 20/h) and BMI-matched controls (following adjustment for lean body mass) even after treatment with CPAP. Small paediatric studies by Bland et al.[69] and Li et al.[70] also demonstrated little relationship in TEE and SEE respectively between OSA and controls.

Interventional studies regarding EE in treated OSA have been more consistent in their findings. Stenlof et al. reported reduced SEE after 3 months of CPAP treatment, but no change to weight or body composition. A reduction in SEE with OSA treatment (laser-assisted uvulopalatoplasty) was also demonstrated by Lin et al.[71] Patients were divided into surgical responders (AHI reduced to < 20/h) and non-responders (AHI > 20/h). Despite only 6 out of 25 being classified as surgical responders, this group displayed significant reductions in SEE.

If sleep EE does genuinely increase in OSA the consequence would be to favour negative energy balance. However, it is clear that patients with untreated OSA do not follow a natural of history of weight loss, but many exhibit weight gain leading up to diagnosis.[9] Potential explanations for this include a reduction in EE during the daytime, mediated by tiredness and daytime sleepiness with a consequent reduction in physical activity. This would counter the increased EE at night from airway obstruction. To date, there have been no well designed studies to clarify this possibility. A reduction in daytime physical activity and therefore EE is potentially modulated by associated depression. High rates of this mood disorder have been reported in OSA populations, with community samples yielding rates of 17% and sleep clinic cohorts ranging between 21% and 41%.[72] Both depression and OSA are independent predictors of excessive daytime sleepiness[73] and their presence together are potentially additive in their effect, resulting in further reduction in physical activity and therefore affecting energy balance.

The lack of weight loss seen in CPAP-treated obese OSA patients[56,74] may also be partly explained by considering daytime

Table 1
Summary of studies of energy expenditure in OSA populations.

Study	Study type	Sample	Measurement method	Intervention	Intervention duration	Primary endpoints	Energy expenditure findings
Ryan et al. (1995)[68]	Non randomized Observational	14 moderate to severe OSA, 14 controls	Metabolic cart	CPAP	12 ± 5 weeks	Resting EE Dietary Thermogenesis	No change in resting EE corrected for LBM & weight at baseline and following CPAP
Stenlof et al. (1996)[66]	Non randomized Observational	5 severe OSA, 14 snoring controls	Metabolic chamber	CPAP	12 weeks	Daily EE Sleep EE	↓ Daily EE corrected for LBM ↓ Sleep EE corrected for LBM following CPAP
Lin et al. (2002)[71]	Non randomized Observational	25 moderate to severe OSA, 15 healthy controls	Metabolic cart	Laser UVP	One-off, but measurements of EE made after 3 months	Sleep EE	↑Sleep EE in OSA group compared to healthy controls ↓Sleep EE in UVP responsive OSA patients
Hins et al. (2006)[85]	Observational	8 OSA	Metabolic chamber Oximetry	–	–	Daily EE Sleeping MbR	↑ Hypoxia associated with ↑ difference between predicted and measured daily EE
Kezirian et al. (2008)[65]	Cross sectional	212 moderate OSA	Indirect calorimetry PSG	–	–	REE AHI	↑ Resting EE associated with ↑ AHI (but not corrected for weight/LBM)
O'Driscoll et al. (2012)[67]	Observational	13 no OSA, 17 mild OSA, 20 moderate to severe OSA	SenseWear	–	–	Sleep EE	↑Sleep EE associated with ↑ AHI (but not corrected for weight/LBM)

(AHI = apnoea-hypopnoea index, CPAP = continuous positive airway pressure, EE = energy expenditure, LBM = lean body mass, MbR = metabolic rate, PSG = polysomnography, UVP = uvulopharyngoplasty).

physical activity and EE. West et al.[75] conducted a RCT using therapeutic and sham CPAP in 36 male subjects with newly diagnosed moderate to severe OSA (4% oxygen desaturation index > 10/h) and excessive sleepiness as measured by the Epworth sleepiness score (ESS). Activity levels were measured over a week by means of a wrist actigraphy device before and after 3 months of CPAP therapy. The group receiving therapeutic CPAP showed an improvement in the ESS along with parameters on a modified wakefulness test (MWT), but failed to record an increase in daytime activity or an improvement in obesity parameters such as BMI, neck size or waist-hip ratio. Whilst the adherence to CPAP over the 3 month period was modest (mean usage 3.8 h/night), and a longer period of observation may have been helpful in clarifying the effects of CPAP on daytime activity and anthropometric measures, this study remains the first systematic examination of CPAP and physical activity. Regardless, given that CPAP does not change lifestyle habits, it remains that lifestyle intervention should also always be part of the treatment for all obese patients with OSA.

The perpetuation of obesity is also potentially influenced by a change in dietary habits in favour of high caloric items that lead to positive energy balance. The Swedish Obese Subjects Study[76] was the first to demonstrate that patients reporting symptoms consistent with a high pre-test probability of OSA were noted to have higher energy intake compared to equally obese but asymptomatic subjects. Similar results have recently been seen in children with OSA. Beebe et al.[77] examined dietary choices on the evening prior to diagnostic polysomnogram in obese paediatric subjects (aged 10–16.9 years). Of note, those with more severe OSA preferred calorie dense food items high in fats and carbohydrates, independent of obesity. Direct confirmation of OSA increasing caloric intake is still required in adult populations, including the size of meals, but there are biologically plausible reasons why this could occur. These include promotion of hyperphagia due to OSA-induced fragmented sleep/reduced sleep duration,[78,79] accentuation of underlying dietary preferences for energy rich foods as seen in paediatric populations[80] and alteration of eating habits as a form of stress response as evidenced by binge eating and drinking in patients with disordered coping behaviour.[81]

The long term success of weight loss maintenance programs is low, despite attempts to modify both sides of the energy balance equation (energy intake and expenditure).[82] OSA patient groups are no different. Low patient adherence to physical activity regimens and dietary advice (in part due to mechanisms listed above) are obvious factors, but a metabolic concept called adaptive thermogenesis, has been mooted as a potential factor in impeding weight loss and compromising the maintenance of reduced body weight. Adaptive thermogenesis is described as the reduction in EE beyond what can be predicted from the changes in fat mass or fat-free mass under conditions of standardized physical activity, in response to a reduction in energy intake.[83] Put another way, patients with

obesity who are able to adhere to a weight reduction program demonstrate a greater than predicted reduction in their EE, which may promote a positive energy balance and therefore, weight regain. It has been postulated that hunger and dysphoria accompany this state of reduced EE, which may promote increased food intake which is linked to leptin and other hormonal drivers of appetite and satiety.[84] The concept is relevant in OSA, which has been shown in a small study to have an effect on adaptive thermogenesis.[85] In this study 8 OSA patients had daily EE and sleeping EE measured in a whole body calorimetry chamber for 24 h. Oxygen desaturation was measured using nocturnal home oximetry. The authors did not find an overall difference in predicted and measured EE, but did find an inverse association between the duration spent in hypoxia (defined as SpO2 < 90%) and the difference between predicted and measure EE. In other words, the greater the duration of hypoxia experienced, the greater the reductions in total and sleep EE, which again, tips the energy balance in favour of weight gain.

Metabolic dysfunction, OSA and obesity

The maintenance of a stable body weight is complicated further by dysfunction of hormones involved in appetite control of which leptin and ghrelin are the most prominent. Leptin is an adipocyte-derived hormone that regulates body weight through control of appetite and EE.[86] Leptin acts on the hypothalamus of the brain[87] where it inhibits the effects of the appetite stimulating gut-secreted neuropeptide Y and the hormone anadamine. It is correlated with BMI and insulin levels and its secretion is further modulated by the stress system and cytokines.[88] The end result of an elevated leptin level is increased satiety and reduced food intake. Ghrelin on the other hand, is responsible for appetite stimulation.[89] It is secreted from P/D1 cells from the gastric fundus[90] and epsilon cells of the pancreas.[91] Given their functions, it is obvious that dysregulation of either hormone can shift the energy balance equation in favour of weight gain.

Leptin resistance in obese populations has been known for some time[42] and is postulated to arise from impaired leptin transport across the blood–brain barrier[92,93] or altered receptor signalling pathways. Leptin levels in OSA populations are higher than what would be expected because of existing obesity alone[43,94] reflecting further leptin resistance due to the OSA itself. Correction of OSA with even short duration of CPAP use can reduce circulating leptin levels.[54,95] Harsch et al.[95] measured leptin and ghrelin levels in 30 obese male patients with OSA before and after 8 weeks of CPAP and found significantly reduced levels of both hormones without significant change to BMI. This study raises the possibility of CPAP treatment as a means of reversing leptin resistance. Reductions in serum leptin following CPAP treatment have been repeated in other studies[54,96–98] and there is indication that changes occur after as

Table 2
Summary of studies of leptin and ghrelin following treatment with CPAP in OSA populations.

Study	Study type	Sample	Intervention duration	Change in BMI/weight	Change in visceral fat	Leptin	Ghrelin
Chin et al. (1999)[54]	Observational	22 severe OSA	3–4 days	↔	↓	↓	–
Harsch et al. (2003)[95]	Observational	30 severe OSA	2 months (leptin) 2 days (ghrelin)	↔	–	↓	↓
Sanner et al. (2004)[97]	Observational	86 moderate OSA	3 months	↔	–	↓	–
Takahashi et al. (2008)[99]	Observational	21 severe OSA	1 month	↔	–	–	↓
Drummond et al. (2008)[98]	Observational	98 moderate to severe OSA	6 months	–	–	↓	–
Cuhadaroglu et al. (2009)[96]	Observational	31 moderate to severe OSA	2 months	–	–	↓	–
Garcia et al. (2011)[100]	Observational	20 severe OSA	6 months	↑	–	↔	↓
Sharma et al. (2011)[57]	Double blinded placebo controlled trial	86 moderate to severe OSA	3 months	↓	↓	–	–

(CPAP = continuous positive airway pressure, OSA = obstructive sleep apnoea).

little as 4 days of CPAP use.[54] Studies examining CPAP effects on ghrelin are few,[95,99,100] but all demonstrate reductions, which would be expected to down-regulate appetite and promote better weight control in OSA patients (See Table 2).

Sleep deprivation and obesity

There are limited data examining appetite control and sleep fragmentation from untreated OSA, but one can extrapolate some of the effects that sleep restriction in other settings has over weight homeostasis, energy balance and its relationship to obesity. As mentioned earlier, there is some indication that patients with OSA demonstrate higher energy intake and a preference for calorie-dense foods.[76,77] It is unclear if this preference is due to sleep fragmentation and/or sleep restriction, but a number of recent publications have raised the role of short sleep duration in the hormonal regulation of food intake.[101–103] Spiegel et al.[103] studied 12 non-obese male subjects and measured levels of leptin, ghrelin, subjective feelings of hunger and appetite as well as dietary choices, following 2 days of sleep restriction followed by sleep extension under laboratory conditions (controlled for physical activity and diet). Although a small sample size, sleep curtailment for even such short periods led to measureable reduction of the anorexigenic (−18%) hormone leptin, elevation (+28%) of the oroxegenic hormone ghrelin, and increased sensations of hunger and appetite with dietary choices shifting to a preference for calorie-dense carbohydrate rich food items. The tendency to gain weight in the setting of restricted sleep may be further modulated by an underlying disinhibited eating behaviour trait in susceptible patients, as demonstrated by a recent six-year longitudinal study in Canada by Chaput et al.[104] The incidence of overweight/obesity in individuals with disinhibited eating traits and short sleep (≤6 h/night) were 2.5 times more frequent compared to similar short sleepers without the behaviour trait. Given the few studies examining sleep deprivation and obesity, there is a clear need for further research in the area including confirmation of previous findings.

The association between short sleep duration and obesity is still being investigated. Several reviews published in 2008[105–107] suggest that an association between sleep restriction and obesity exists, more consistently in paediatric populations than in adults. The difficulty in determining a cause and effect relationship between short sleep duration and the subsequent development of obesity has been highlighted by recent meta-analyses of the subject.[108] The major problem is disentangling the contributions of other parallel factors such as depression and other psychosocial conditions, which can serve as significant confounders. Similar challenges exist when attempting to study the contribution of sleep restriction in clinical OSA populations and a more pragmatic approach through interventional studies may be required. In the meantime, it is not possible to state that sleep restriction arising from OSA is a definitive contributor to obesity, but there are reasonable grounds to consider that this may be so.

Summary

Obesity is a significant risk factor in the pathogenesis of OSA, but there is emerging evidence that sleep disordered breathing itself feeds back into a complex mechanism that leads either to the development or reinforcement of the obese state. Current evidence does not permit us to make claims to our patients that correction of OSA has a direct effect on weight loss, but it does suggest that the potential role OSA plays in obesity deserves further research.

Practice points

Obesity has a direct role in the pathogenesis of OSA through changes in:

- airway anatomy
- airway collapsibility
- neural compensation and stability of respiratory control centres
- lung volume

OSA has a potential role in the development and reinforcement of obesity via changes to:

- energy expenditure during sleep and wake periods
- dietary habits in favour of excess consumption of calories and altered food preferences in favour of energy-dense items
- the neurohormonal mechanisms that control satiety and hunger
- sleep duration arising from fragmented sleep

There is insufficient evidence to advocate treatment of OSA as a method for weight loss and recommendations for OSA treatment should be based on established benefits such as effects on daytime sleepiness.

Research agenda

The effect of OSA on both caloric intake and energy expenditure needs to be assessed together in the same patient population. Ideally, this should use methods that do not restrict the patient's activities in any way or confine to laboratory conditions, allowing quantification of not only EE during sleep, but also during the daytime in the free living state.

The effect of treating OSA with CPAP on the neurohormonal mediators of appetite and in energy intake and expenditure using larger sample sizes and longer durations needs to be conducted to establish long term effects of correction of SDB on weight homeostasis.

Disclosure

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