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Does medically induced weight loss improve obstructive sleep apnoea in the obese: review of randomized trials

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Summary

Obstructive sleep apnoea is characterized by repeated periods of breathing cessation during sleep. Obstructive sleep apnoea is both common and underdiagnosed in the obese. A recent study found that as many as 86% of older obese type 2 diabetics had obstructive sleep apnoea. Obesity is independently associated with developing obstructive sleep apnoea, and the reverse may also occur. The prevalence of obstructive sleep apnoea is therefore expected to rise in the wake of the obesity epidemic. The number of partial (hypopnoea) or complete (apnoea) airway obstructions per hour (apnoea-hypopnoea index) is used to classify obstructive sleep apnoea as mild (5–14 events per hour), moderate (15–30) or severe (>30). Severe obstructive sleep apnoea is associated with a two to sixfold increase in all-cause mortality; the impact of mild and moderate obstructive sleep apnoea is less clear. Until recently, the evidence supporting a beneficial effect of weight loss on obstructive sleep apnoea has been limited by a lack of randomized trials. In 2009, at least three randomized controlled trials evaluated whether medically induced weight loss improves obstructive sleep apnoea. The treatment effect ranged from 42% to 62% improvement, although the highest estimate was seen in a very short duration study (9 weeks). Patients who either lost 10–15 kg or more, or had severe obstructive sleep apnoea at baseline, benefited most from treatment.

Keywords: Apnoea-hypopnoea index, obstructive sleep apnoea, very-low-calorie diet, weight loss.

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Introduction

Obstructive sleep apnoea (OSA) is characterized by repeated periods of breathing cessation during sleep. The number of partial (hypopnoea) or complete (apnoea) airway obstructions per hour (apnoea-hypopnoea index, AHI) is used to classify OSA as mild (5–14 events per hour), moderate (15–30 per hour) or severe (>30 per hour) (1).

Obstructive sleep apnoea is both common and underdiagnosed in the obese. As obesity is one of strongest risk factors for developing OSA, the prevalence is expected to rise in the wake of the obesity epidemic (2–4). Among obese people, the prevalence has been reported to be greater than 30% (4). In older (mean age 61) obese patients with type 2 diabetes the prevalence has been found to be as high as 86% with the majority having moderate or more severe OSA (5). Conversely, the prevalence of overweight and obesity in patients with OSA is estimated to be 60–70% (6).

Similar to obesity, OSA is also associated with several adverse cardiometabolic outcomes, such as insulin resistance, hyperglycaemia, hypertension, type 2 diabetes, cardiovascular disease and all-cause mortality (4,7–10). Although the evidence is not conclusive, there are indications that at least some of these associations are independent

of obesity. Moreover, OSA patients are also at an increased risk of driving-related accidents, cognitive impairment and depression (11,12). Studies also suggest that health-related quality of life is lower in OSA (4).

Mild OSA does not appear to be associated with increased risk of death, whereas some, but not all, data indicate than moderate OSA is associated with an increased mortality risk (9,10,13). Severe OSA, however, has consistently been associated with a two to sixfold increase in all-cause mortality (9,10,13). The unclear association between moderate OSA and mortality can probably be explained, at least in part, by type 2 error due to small sample sizes and low number of deaths.

Continuous positive airway pressure (CPAP) has been, and remains, a mainstay in the treatment of OSA. CPAP does not, however, provide a cure for OSA and long-term compliance with CPAP remains a challenge for both patients and clinicians. There is therefore a need to find other treatment options that target the causes of OSA, such as obesity.

The aim of this review is to summarize the evidence for weight loss in improving OSA in obese patients with a focus on randomized trials, and to discuss how weight loss programmes may be implemented for optimum patient benefit.

Does medically induced weight loss improve obstructive sleep apnoea in the obese?

Although weight loss has long been recommended for improving OSA, there has been a lack of convincing scientific evidence to support such a role. Data have largely come from non-randomized intervention studies and not from randomized trials. As non-randomized studies are vulnerable to limitations such as selection bias, residual confounding and regression to the mean effects, it is important to interpret the findings from such studies with caution.

Nevertheless, non-randomized studies on the effects of bariatric surgery on OSA, for example, have consistently found large improvements in OSA after large weight losses. The AHI has been improved by 40% at worst and 100% remission at best (3). While study designs limit rigorous scientific evaluation, these data nevertheless suggest that weight loss is a clinically relevant treatment for patients with OSA.

During 2009 at least three randomized trials were published on the effects of weight loss in OSA in overweight and obese patients. All three trials found marked improvements in OSA after weight loss, mirroring the findings from the non-randomized studies (Table 1).

Table 1 Randomized controlled trials on the effects of weight loss in OSA

Paper	OSA categories	*n* randomized/ completed/analysed	Treatment	Duration	Δ weight, treated vs. controls	Δ AHI, treated vs. controls
Tuomilehto *et al.* 2009 (14)	Mild	81/72/72	12-week VLCD + maintenance	1 year	–10.7 vs. –2.4 ($P < 0.001$)	–4.0 vs. 0.3 ($P = 0.01$)
Foster *et al.* 2009 (15)	Mild to severe	264/219/264	1-year intensive lifestyle change	1 year	–10.8 vs. –0.6 ($P < 0.001$)	–5.4 vs. 4.2 ($P < 0.001$)
Johansson *et al.* 2009 (16)	Moderate to severe	63/61/63	7-week VLCD + 2-week refeeding	9 weeks	–18.7 vs. 1.1 ($P < 0.001$)	–25 vs. –2 ($P < 0.001$)

AHI, apnoea-hypopnoea index; OSA, obstructive sleep apnoea; VLCD, very-low-calorie diet.

Randomized controlled trial 1: Tuomilehto *et al.* (14)

Tuomilehto *et al*. randomly allocated patients to a passive control condition or a more intensive lifestyle change

weight loss programme. The weight loss programme started with a 12-week very-low-calorie diet (VLCD: 600–800 kcal d^{-1}) to induce a rapid weight loss in 81 overweight and obese (body mass index range 28–40 kg m^{-2}) men and women with mild OSA (defined as AHI 5–15 events per hour).

In addition to the VLCD, the 1-year programme also consisted of 14 60- to 90-min visits with a nutritionist who provided individually tailored advice on diet and lifestyle changes and check-ups of body weight and general progress including physical activity and eating behaviour. After the VLCD period, patients were recommended to eat a low-fat diet and to increase leisure time physical activity as well as planned endurance exercise and resistance exercise supervised by a physiotherapist. Seventy-two patients (89%) completed the 1-year follow-up (drop-out was similar between groups).

After 1 year, the patients in the intervention group had significantly lower AHI than the control group (6.0 vs. 9.6 events per hour, $P = 0.04$). Two out of three patients in the intervention group were classified as disease free after 1 year, compared with one out of three in the control group. There were also dose–response associations between weight loss and AHI improvement, with patients losing 15 kg or more benefiting most from treatment. No adverse events were noted.

Limitations of this trial include a difference between groups at baseline for body weight (the intervention group was 9 kg heavier) and waist circumference (intervention group was 7 cm larger), and non-inclusion of data from patients who dropped out, which may have falsely inflated the treatment effect. Furthermore the weight loss for the intervention group (–10.7 kg after 1 year) was lower than expected given the use of a 12-week VLCD protocol suggesting only partial compliance.

Randomized controlled trial 2: Foster *et al.* (15)

This large randomized controlled trial (RCT) on the effects of weight loss in OSA comes from a sub-study of the Look AHEAD trial, called Sleep AHEAD. Two-hundred and sixty-four overweight and obese type 2 diabetic men and women with a mean age of 61 years were randomized to intensive lifestyle change or a control group.

At baseline, the mean AHI was 23 events per hour and mean body mass index was 37 kg m^{-2}. Weight loss was induced by an intensive lifestyle-oriented programme with group sessions. Patients were prescribed a diet of 1200–1800 kcal d^{-1} depending on starting weight, and told to increase physical activity to reach 175 min $week^{-1}$ of moderate intensity physical activity. Forty-five out of 264 patients were lost to follow-up, with no difference in drop-out between groups.

After 1 year there were significant differences between groups for both AHI and body weight. Among the control group twice as many patients were classified as having severe OSA after 1 year compared with the intervention group. There was also a difference between groups in haemoglobin A_{1c} favouring the intervention group. A worrying finding from this trial was that the control group experienced a 4 events per hour increase in AHI despite being weight stable, suggesting in older obese type 2 diabetics OSA worsens without treatment.

Patients with high AHI at baseline benefited more than those with lower AHI, and similarly patients who lost 10 kg or more benefited more than those who lost less weight.

Randomized controlled trial 3: Johansson *et al.* (16)

Johansson *et al.* used a VLCD (554 kcal d^{-1}) for 7 weeks followed by 2 weeks refeeding to induce rapid weight loss in obese men with moderate to severe OSA, who were all treated with CPAP. There were no drop-outs during the 9 weeks.

After 9 weeks, the intervention group weighed 20 kg less than the control group and there was a reduction in AHI by two-thirds compared with no change in the control group. Similar to the two previously reported RCTs, patients who either lost 15 kg or more or had severe OSA at baseline experienced the greatest improvements in OSA.

Apart from the improvements in AHI and adiposity, the intervention group also improved metabolic risk factors and physical dimensions of quality of life. The main limitation of this trial was the short duration of 9 weeks.

How large is the treatment effect?

Despite variations in study protocols and aforementioned limitations, all three trials found a significant difference between intervention group and control group in the AHI at follow-up. Using a simple within-group analysis to estimate treatment effect the range of improvement in the AHI was 24–67%.

A more appropriate analysis of treatment effect, however, is to compare the difference in AHI at follow-up between the intervention group and the control group. In this analysis, the difference in AHI between groups, divided by the whole-sample baseline AHI, ranged from 42% to 62%. Apart from getting more robust estimates of treatment effect with a between-group analysis, the seemingly rapid natural progression of OSA, as found in the RCT on older obese type 2 diabetics by Foster *et al.* makes within-group comparisons unsuitable.

It is important to note, however, that the trial by Johansson *et al.* was only 9-week duration (1-year follow-up for the two other trials) with sleep studies performed immediately after the liquid diet programme when weight loss was

maximum (17). It is therefore likely that the treatment effect of 62% improvement in the Johansson *et al*. trial will be lower after 1 year.

What predicts improvement in obstructive sleep apnoea?

Apart from finding a mean benefit of weight loss, the trials also consistently find two predictors of OSA improvement. First, there appears to be an inverse association between weight loss and AHI improvement, with higher AHI at baseline being predictive of greater improvement.

However, it is important to observe that in these types of analyses, regression to the mean may falsely inflate the treatment effect in those with severe disease. Nevertheless the predictive value of baseline AHI on AHI at follow-up seems greater than what regression to the mean alone can explain (16). Although more research may be needed before firm conclusions can be made, it appears as if patients with higher AHI at baseline benefit more than those with lower AHI at baseline.

The second predictor was magnitude of weight loss, with patients losing more weight consistently benefiting more than patients losing less weight. All three trials performed stratified analyses of weight loss and AHI improvement and found that the category with highest weight loss was associated with the greatest improvement. The cut-offs were ≥10 kg (15), ≥15 kg (14) and ≥15 kg (16) respectively.

Two of the three trials report the strength of association between weight loss and OSA improvement. In the Foster *et al*. trial there were significant correlations between changes in waist circumference and body weight with change in AHI after 1 year ($r = 0.30$ and $r = 0.35$ respectively). The Johansson *et al*. paper report a similar strength of correlation between change in body weight and change in AHI after 9 weeks ($r = 0.40$).

While it is encouraging to find these associations, the findings also clearly demonstrate that other factors than weight loss or AHI at baseline predict a positive outcome. Much therefore remains to be clarified when trying to identify which patients can gain most from weight loss.

Recommendations for treatment

Given the dose–response association between weight loss and AHI improvement, it is important that weight loss programmes achieve a mean weight loss of at least 10 kg, although the two VLCD trials (14,16) found that 15 kg weight loss was even better. Apart from bariatric surgery, VLCD (500–800 kcal d^{-1}) followed by a maintenance programme or a weight loss drug (18,19) is probably the best way of achieving sustained weight loss of that magnitude.

Maintenance of large amounts of weight loss is arguably one of the greatest existing clinical challenges. The science behind successful weight loss maintenance has nevertheless moved forward during the last decade, in part due to studies such as the National Weight Control Registry (http://www.nwcr.ws) (20–23). Long-term maintenance of major lifestyle-induced weight loss is not an illusion, although significant effort from the patient is required. As well as restricted caloric intake, increased physical activity and behaviour changes, weight loss drugs have been shown to promote weight loss maintenance and delay weight regain (18,19).

Two of the three RCTs used formulae diet (VLCD, 500–800 kcal d^{-1}) followed by a weight loss maintenance programme to induce weight loss (14,16), and one trial used an intensive lifestyle change programme. All three trials achieved significant weight loss, with mean changes exceeding 10 kg. Unless a head-to-head study is preformed it is difficult to say which treatment will work best, although both VLCD and intensive lifestyle change appear to work well, given the relatively low drop-out and magnitude of weight loss.

Conclusions

Evidence from recently published randomized trials suggests that the treatment effect of weight loss on OSA in obese patients is considerable and clinically relevant. The mean reduction in AHI was over 40% after 1 year and may be close to 50%. Weight loss programmes should ideally produce mean weight losses of 10–15 kg or more and target patients with severe OSA, partly because mortality increases two to sixfold in severe OSA, and partly because the effects of weight loss appear greatest in severe OSA.

As all three RCTs randomly allocated patients to weight loss or control, there is only a small likelihood of selection bias, measurement error, or confounding by regression to the mean or unknown sources in the main between-group analyses of treatment effect. Moreover, the treatment effects of randomized and non-randomized studies are approximately similar, thereby adding weight to the case for weight loss in OSA in obese patients.

With the added support of randomized trials to the growing case for weight loss in OSA in the obese, the research process can now gradually shift towards translational studies so that benefit to patients can be optimized.

Conflict of Interest Statement

EH has received grants from Cambridge Manufacturing Ltd and Novo Nordisk for one of the cited RCTs (16).

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