Weight loss versus continuous positive airway pressure therapy for obstructive sleep apnoea on metabolic profile stratified by craniofacial restriction: abridged secondary publication

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KEY MESSAGES

1. Weight loss by lifestyle modification programme (LMP) achieved more reduction in subclinical inflammation than continuous positive airway pressure (CPAP) therapy at 6 months among obese patients with moderate to severe obstructive sleep apnoea (OSA).
2. Weight loss by LMP improved insulin sensitivity better than CPAP therapy at 6 months among obese patients with moderate to severe OSA, with smaller proportion of patients having abnormal glucose regulations by 6 months (46.1% vs 63.6%).
3. Baseline sleep apnoea severity was associated with neck circumference, mandibular length, maxillary angle, and mandibular angle.
4. Changes of subclinical inflammation and insulin sensitivity were not significantly different between patients with different degrees of craniofacial restriction.
5. Only weight loss was associated with the percentage change of apnoea-hypopnoea index at 6 months.

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Introduction

Obstructive sleep apnoea (OSA) is characterised by repetitive episodes of upper airway obstruction causing intermittent hypoxia and arousals, leading to systemic inflammation, insulin resistance, dyslipidaemia, hypertension, and cardiovascular consequences.[1] Subclinical inflammation as evidenced by elevated C-reactive protein (CRP) suggests the mechanism of increased atherosclerosis in patients with OSA. Continuous positive airway pressure (CPAP) is the first-line treatment for OSA, as it is effective in improving airway patency and the apnoea-hypopnoea index (AHI), resulting in reduced daytime sleepiness. However, wide variance (25% to 75%) in adherence may affect the effectiveness of CPAP therapy. Moreover, CPAP therapy alone does not result in improvement in visceral adiposity, insulin resistance, or metabolic dysfunction.

Obesity is a major risk factor for OSA. Weight reduction for overweight patients with OSA may improve cardiometabolic abnormalities, which are often associated with OSA. However, the chance of cure (AHI of <5 events/hr) remains low, despite substantial improvement of OSA symptoms after various weight loss programmes. Apart from obesity, craniofacial restriction is another risk factor, especially among Chinese populations. A smaller craniofacial skeletal size as determined by maxillomandibular volume (MMV) indicates more craniofacial restriction; patients with more craniofacial restriction can achieve greater benefits from weight loss.[2] Therefore, craniofacial structure is a potential predictor of effectiveness of weight loss for OSA improvement.

We hypothesised that weight loss in patients with more craniofacial restriction would result in better improvement in metabolic profile than those with less craniofacial restriction or those treated with CPAP. We compared the effect of weight loss or CPAP alone on subclinical inflammation and insulin sensitivity in obese patients with moderate to severe OSA stratified according to craniofacial restriction.

Methods

A total of 363 obese patients (body mass index [BMI], ≥25 kg/m^2) with clinical suspicion of OSA were recruited from the respiratory clinic at the Prince of Wales Hospital between 15 September 2017 and 28 January 2020. Patients underwent a home sleep study with the Embletta device, which had been validated against polysomnography in Hong Kong Chinese population.[3] Patients with AHI of ≥15/hr on home sleep study received home autoCPAP titration.

Patients with baseline blood level of high-sensitivity CRP (hsCRP) of ≥1 mg/L were randomly assigned to receive either lifestyle modification programme (LMP) or CPAP therapy for 6 months. Patients in the LMP group received dietary consultation weekly in the first 4 months, and monthly in the following 2 months. A caloric reduction of 10% to 20% in daily energy intake was set as a goal, which was adjusted based on changes in body weight with target BMI towards 23 kg/m^2. Patients were encouraged to see an exercise instructor at least once and perform 30-minute aerobic exercise two to three times a week. Patients in the CPAP group started an auto CPAP therapy nightly during the study period.

Patients were assessed at baseline and 6 months by the Epworth Sleepiness Scale (ESS), three-dimensional computed tomography of the head/neck region to evaluate the MMV for craniofacial restriction, test for serum levels of hsCRP, and oral glucose tolerance test for insulin sensitivity. Home sleep study was repeated at 6 months.

Results

A total of 194 obese patients with moderate to severe OSA were randomly assigned to receive either LMP (n=128) or CPAP therapy (n=66). At baseline, the LMP group had lower insulin resistance and fasting plasma insulin, shorter upper face height, and larger maxillary angle than the CPAP group (Table 1). Baseline AHI was correlated with insulin sensitivity as reflected by the Matsuda index (rho= -0.24, P=0.001) but not hsCRP. Following 6 months of intervention, the LMP group achieved significant improvement in body weight, ESS, AHI, hsCRP, Matsuda index, and insulin resistance, which was reflected by the homeostatic model assessment for insulin resistance (HOMA-IR). The CPAP group also achieved significant improvement in ESS, AHI, and HOMA-IR, but not hsCRP or insulin sensitivity. The objective CPAP usage was 4.02±2.0 hours, with 95th centile pressures at 12.7±1.7 cm H_2O and the residual AHI of 3.5±1.8 events/hr. The LMP group achieved greater improvement in AHI, hsCRP, and insulin sensitivity than the CPAP group did (Table 2). Significantly smaller proportion of patients having abnormal glucose regulations at 6 months in the LMP group than in the CPAP group (46.1% vs 63.6%, P=0.02).

For the radiological parameters, AHI was correlated with mandibular angle (r= -0.2, P=0.005) but not MMV. Regression analysis showed that AHI was associated with neck circumference (beta=3.63, P<0.001), ESS (beta=0.598, P=0.031), mandibular length (beta= -5.9, P=0.013), maxillary angle (beta=0.763, P=0.044), and mandibular angle (beta= -1.282, P=0.006). Patients in the LMP group were subdivided according to the mean MMV of 229.6 cm^3 into the small MMV group (n=58) and the large MMV group (n=70). Results of the two subgroups were similar with those of the overall LMP group (Table 3). More patients in the small MMV group than in the large MMV group achieved improvement in glucose regulations (41.4% vs 24.3%, P=0.024). Multivariate analysis showed that only weight loss was associated with the percentage change of AHI in 6 months (beta= -1.114, 95% confidence interval= -2.194 to -0.033, P=0.043).

Discussion

For obese patients with moderate to severe OSA, LMP was more effective to reduce AHI and body weight and improve subclinical inflammation (absolute change of hsCRP= -0.7 mg/L, -30.4% from baseline) and insulin sensitivity (absolute change of 0.6 in Matsuda index, 25.8% from baseline) than CPAP therapy. Patients in the CPAP group showed modest improvement in HOMA-IR at 6 months but not in hsCRP or insulin sensitivity. Insulin sensitivity improved significantly greater in the LMP group than in the CPAP group (0.6 vs 0.0, P<0.001). The difference in the response in HOMA-IR and the Matsuda index highlights the variability of the two evaluation tools, as the Matsuda index uses data from oral glucose tolerance test and is more accurate than HOMA-IR, which is a steady state measurement.

We have previously shown that therapeutic CPAP versus subtherapeutic CPAP at 4 cm H_2O over 6 months did not significantly reduce visceral fat thickness, levels of adipokines and severity of fatty liver. On contrary, LMP could reduce the severity of OSA and daytime sleepiness among obese Chinese patients with moderate and severe OSA. In a study of obese patients (BMI, 38.1 kg/m^2) with moderate to severe OSA who were randomised to receive CPAP (lost 0.7 kg), weight loss programme (lost 6.9 kg), or combination intervention (lost 7.1 kg), there were reduction in hsCRP (-7.24% in CPAP group, -31.4% in weight loss group, and -26.73% in combination intervention) and improvement in insulin sensitivity (0.05 vs 0.63 vs 0.44 $\times 10^{-4}$/min^{-1}/μU/mL) in the weight loss group and combination intervention group but not in the CPAP group.[4] Weight loss is superior to CPAP therapy in improving subclinical inflammation and glycaemic control. Weight-loss intervention or lifestyle modification should thus be emphasised, although CPAP therapy is still important in patients with excessive daytime sleepiness, high blood pressure or cardiovascular risk, and low BMI. Further research should focus on the cost-effectiveness of various weight loss programmes in terms of metabolic and cardiovascular outcomes among patients with sleep apnoea.

Craniofacial restriction is a risk factor for OSA, as it affects the pharyngeal airway space, especially in Chinese populations. For the same degree of obesity, Chinese patients have more severe OSA and more

TABLE 1. Baseline characteristics of patients in the lifestyle modification programme (LMP) group and the continuous positive airway pressure (CPAP) group

Variable	All (n=194)	LMP group (n=128)	CPAP group (n=66)
Age, y	50.8±10.4	50.8±10.4	50.8±10.5
Male	129 (66.5)	85 (66.4)	44 (66.7)
Weight, kg	81.4 (74-92)	81 (74-94)	83.8 (74.1-91.3)
Body mass index, kg/m^2	29.7 (27.3-32.5)	29.6 (27.4-32.5)	29.7 (27.1-32.5)
Neck circumference, cm	40±3.3	39.8±3.3	40.3±3.2
Waist circumference, cm	104±9.6	103.9±10.0	104.1±8.9
Hip circumference, cm	107.7±8.1	107.7±8.0	107.6±8.3
Waist-to-hip ratio	0.97±0.06	0.96±0.06	0.97±0.06
Smoking status			
Never	137 (70.6)	85 (66.4)	52 (78.8)
Quitted	22 (11.3)	16 (12.5)	6 (9.1)
Current	35 (18)	27 (21.1)	7 (12.1)
Physical active (counts)	86 (44.3)	55 (44)	31 (47)
Cardiometabolic illness			
Hypertension	114 (58)	78 (60.9)	36 (54.5)
Ischaemic heart disease	6 (3.1)	5 (3.9)	1 (1.5)
Known diabetes mellitus	6 (3.1)	3 (2.3)	3 (4.5)
Abnormal glucose regulation	120 (61.9)	78 (60.9)	41 (63.6)
Cerebrovascular accident	3 (1.5)	1 (0.8)	2 (3)
Inflammatory and metabolic parameter			
High-sensitivity C-reactive protein, mg/L	2.4 (1.6-4.3)	2.4 (1.6-4.3)	2.4 (1.5-4.3)
Matsuda index	2.2 (1.5-3.1)	2.3 (1.5-3.5)	2.2 (1.3-3.0)
Homeostatic model assessment for insulin resistance	3.3 (2.1-4.9)	3.1 (2.0-4.7)	3.9 (2.6-5.3)†
Plasma glucose at 0 min	95.5 (88.3 -104.5)	95.5 (88.3-102.7)	99.1 (91.9-107.1)
Plasma glucose at 30 min	182.3 (162.2-203.6)	176.6 (161.3-202.7)	184.7 (167.6-203.6)
Plasma glucose at 60 min	196.4 (162.2-199.1)	201.8 (163.1-238.7)	196.4 (157.7-231.1)
Plasma glucose at 120 min	144.1 (118.9-189.2)	145.9 (113.5-186.5)	143.2 (126.1-200.5)
Plasma insulin at 0 min	13.6 (9-20.7)	13.1 (8.4-20.1)	15.7 (10.5-21.2)†
Plasma insulin at 30 min	82.8 (52.6-145.5)	78.3 (52.1-145.9)	102.3 (55.3-146.9)
Plasma insulin at 60 min	111.4 (66.6-168.1)	111.8 (66.7-164.1)	108.1 (66.7-178.9)
Plasma insulin at 120 min	92.5 (58.7-159)	88.6 (56.1-149.5)	96.1 (58.6-195.7)
Sleep parameter			
Epworth Sleepiness Scale	11.5±5.4	11.7±5.4	10.7±5.1
Apnoea-hypopnoea index (AHI), events/hr	44.1 (26.4-62.8)	44.1 (26.3-61.1)	43.6 (29.3-71.4)
AHI (supine), events/hr	57±23.2	55.4±23.2	57.8±23.5
AHI (non-supine), events/hr	25.6 (15.2-46.5)	25.3 (14.0-44.8)	29.2 (16.7-49.8)
Minimal oxygen saturation, %	72.6±9.4	73.6±9.2	71.0±9.0
Oxygen desaturation index 3, /hr	42.1 (25.8-59.7)	42 (25.9-57.6)	44.1 (26.5-64.8)
% of total recording time of oxygen saturation <90%	8.8 (3.2 -27.7)	8.7 (2.9-24.4)	10.8 (4.4-34.2)
Radiological parameter			
Maxillomandibular volume, cm^3	229.6±37.6	231.5±36.2	227.4±38.1
Upper face height, cm	5.5±0.6	5.5±0.6	5.7±0.5*
Lower face height, cm	6.9±0.7	6.9±0.7	6.8±0.7
Total face height, cm	12.3±0.9	12.2±0.9	12.3±0.8
Maxillary length, cm	9.8±0.5	9.8±0.5	9.8±0.7
Mandibular length, cm	8.5 (8.1-8.9)	8.6 (8.1-9.0)	8.5 (8.2-8.8)
Maxillary angle, degree	71.2 (68.6-74.8)	72.2 (69.2-75.1)	70.7 (67.2-72.8)†
Mandibular angle, degree	63.1 (60.6-65.6)	63.4 (60.9-65.9)	62.8 (60.2-64.9)

* Data are presented as mean ± standard deviation, median (interquartile range), or No. (%) of patients

† P<0.05 between LMP group and CPAP group

TABLE 2. Change in body weight, sleep apnoea severity, inflammatory and metabolic parameters between the lifestyle modification programme (LMP) group and the continuous positive airway pressure (CPAP) group

Variable	LMP group (n=128)*	CPAP group (n=66)*	P value†
Body weight, kg	-4.7 (-8.2 to -2.3)	0.7 (-1.2 to 2.3)	<0.001
Body mass index, kg/m²	-1.8 (-2.9 to -0.8)	0.3 (-0.4 to 0.9)	<0.001
Epworth Sleepiness Scale	-4.2±5.4	-3.1±4.6	0.15
Apnoea-hypopnoea index (AHI), events/hr	-11.0 (-19.0 to -2.0)	-2.7 (-14.2 to 5.8)	0.02
AHI (supine), events/hr	-8.0 (-17.6 to 0.1)	-0.1 (-9.1 to 8.1)	<0.001
AHI (non-supine), events/hr	-6.9 (-20.1 to 1.7)	-2.0 (-17.7 to 12.4)	0.104
Minimal oxygen saturation, %	1.5 (-2.0 to 6.0)	5.0 (1.0 to 8.0)	0.005
Oxygen desaturation index 3, %	-10.9 (-18.3 to -2.3)	-5.0 (-19.8 to 5.5)	0.119
% of total recording time of oxygen saturation <90%	-1.3 (-8.8 to 1.2)	-3.8 (-15.5 to -0.7)	0.015
High-sensitivity C-reactive protein, mg/L	-0.7 (-1.4 to -0.0)	-0.3 (-0.9 to 0.4)	0.012
Matsuda index	0.6 (0.0 to 1.9)	0.0 (-0.5 to 0.5)	<0.001
Homeostatic model assessment for insulin resistance	-0.5 (-1.9 to 0.3)	-0.4 (-1.8 to 0.4)	0.42
Plasma glucose at 0 min, mg/dL	-2.7 (-10.8 to 0.0)	-0.9 (-4.1 to 3.6)	0.020
Plasma glucose at 30 min, mg/dL	-9.0 (-27.0 to 7.2)	-0.9 (-16.7 to 14.4)	0.015
Plasma glucose at 60 min, mg/dL	-23.4 (-43.2 to 0.9)	2.7 (-9.5 to 21.6)	<0.001
Plasma glucose at 120 min, mg/dL	-16.2 (-43.2 to 7.2)	-3.6 (-29.3 -14.4)	0.087
Plasma insulin at 0 min, μU/mL	-1.7 (-7.2 to 1.4)	-1.4 (-6.0 to 1.6)	0.39
Plasma insulin at 30 min, μU/mL	-11.7 (-35.5 to 7.4)	-3.7 (-36.5 to 30.1)	0.13
Plasma insulin at 60 min, μU/mL	-26.4 (-52.4 to 0.9)	1.7 (-10.0 to 39.0)	<0.001
Plasma insulin at 120 min, μU/mL	-19.4 (-62.8 to 7.2)	6.5 (-35.5 to 42.4)	0.001

* Data are presented as mean±standard deviation or median (interquartile range)
† Adjusted mean differences were computed from analysis of covariance model by adjusting baseline values

TABLE 3. Change in body weight, sleep apnoea severity, inflammatory and metabolic parameters among the small and large maxillomandibular volume (MMV) subgroups of the lifestyle modification programme (LMP) group and the continuous positive airway pressure (CPAP) group

Variable	LMP group		CPAP group (n=66)*	P value
	Small MMV group (n=58)*	Large MMV group (n=70)*		
Body weight, kg	-4.3 (-6.4 to -2.0)	-5.6 (-9.3 to -2.6)	0.7 (-1.2 to 2.3)	<0.001†‡
Body mass index, kg/m²	-1.7 (-2.4 to -0.7)	-1.9 (-3.1 to -0.9)	0.3 (-0.4 to 0.9)	<0.001†‡
Epworth Sleepiness Scale	-4.3±5.2	-4.2±5.6	-3.1±4.6	0.35
Apnoea-hypopnoea index (AHI), events/hr	-10.3 (-19.4 to -2.1)	-11.6 (-18.9 to 0.0)	-2.7 (-14.2 to 5.8)	0.067
AHI (supine), events/hr	-7.8 (-17.3 to 1.8)	-10.6 (-19.0 to 0.0)	-0.1 (-9.1 to 8.1)	0.002†‡
AHI (non-supine), events/hr	-6.3 (-19.3 to -0.1)	-9.4 (-24.0 to 3.8)	-2.0 (-17.7 to 12.4)	0.223
Minimal oxygen saturation, %	1.5 (-2.0 to 6.0)	1.5 (-2.0 to 7.0)	5.0 (1.0 to 8.0)	0.016‡
Oxygen desaturation index 3, %	-10.2 (-17.2 to -1.5)	-11.6 (-20.3 to -3.3)	-5.0 (-19.8 to 5.5)	0.239
% of total recording time of oxygen saturation <90%	-1.3 (-7.2 to 1.3)	-1.4 (-11.9 to 1.1)	-3.8 (-15.5 to -0.7)	0.045
High-sensitivity C-reactive protein, mg/L	-0.7 (-1.35 to -0.1)	-0.7 (-1.4 to 0.0)	-0.3 (-0.9 to 0.4)	0.039†
Matsuda index	0.5 (-0.3 to 1.9)	0.6 (0.1 to 2.0)	0.0 (-0.5 to 0.5)	<0.001†‡
Homeostatic model assessment for insulin resistance	-0.6 (-1.6 to 0.2)	-0.4 (-2.4 to 0.3)	-0.4 (-1.8 to 0.4)	0.712
Plasma glucose at 0 min	-5.4 (-10.9 to 1.8)	-1.8 (-7.7 to 0.0)	-0.9 (-4.1 to 3.6)	0.048
Plasma glucose at 30 min	-11.7 (-27.0 to 7.2)	-9.0 (-27.0 to 7.2)	-0.9 (-16.7 to 14.4)	0.052
Plasma glucose at 60 min	-16.2 (-43.2 to 7.7)	-23.4 (-43.2 to 1.8)	2.7 (-9.5 to 21.6)	<0.001†‡
Plasma glucose at 120 min	-12.6 (-45.9 to 11.3)	-19.8 (-37.8 to 3.6)	-3.6 (-29.3 -14.4)	0.219
Plasma insulin at 0 min	-1.7 (-6.4 to 1.3)	-1.8 (-8.1 to 2.1)	-1.4 (-6.0 to 1.6)	0.674
Plasma insulin at 30 min	-4.6 (-25.1 -17.4)	-14.8 (-45.6 -0.0)	-3.7 (-36.5 to 30.1)	0.029
Plasma insulin at 60 min	-21.3 (-43.4 to 12.7)	-30.4 (-71.6 - -2.3)	1.7 (-10.0 to 39.0)	<0.001†‡
Plasma insulin at 120 min	-19.4 (-64.2 to 9.5)	-19.0 (-60.7 to 1.3)	6.5 (-35.5 to 42.4)	0.005†‡

* Data are presented as mean±standard deviation or median (interquartile range)
† P<0.05 between small MMV group and CPAP group
‡ P<0.05 between large MMV group and CPAP group

craniofacial restriction than Caucasians.[5] In a study evaluating MMV of 52 obese (BMI, 34±2.7 kg/m^2) male Caucasians with moderate to severe OSA (AHI, 42.9±21.3 /hr), improvement in OSA was more evident in those with a smaller craniofacial skeleton after 6 months of weight loss programme.[2] In the present study, patients with small MMV and large MMV were comparable in terms of percentage change in AHI. This suggests complex interaction of upper airway anatomy and OSA. There was no true inferior bony border in the evaluation of the MMV and no consideration of the curvature/angles of maxilla and mandible, which play significant role in previous craniofacial studies involving OSA. Moreover, ethnicity affects the definition of craniofacial restriction; more research in this area with international collaborations is warranted.

In the present study, a validated home sleep study was used, which underestimated the true severity of OSA because the recording time was used as the denominator in calculating AHI. The CPAP group had significant improvement in sleep apnoea severity at 6 months than at baseline and better improvement in minimal oxygen saturation at 6 months than the LMP group. Actigraphic measurement should have added in the home sleep study to eliminate underestimation. One previous study reported considerable night-to-night variability of OSA, with differences in oxygen desaturation index of >10/hr between nights among 84.4% and shifts in OSA severity category in 77.9% of patients with nightly pulse-oximetry. Nevertheless, the inflammatory and metabolic parameters consistently supported the positive effects of LMP. Thus, treatment decision should be based more on clinical evaluation and outcomes than on derivatives from sleep studies.

Conclusion

Weight loss by LMP improved subclinical inflammation and insulin sensitivity among obese Chinese patients with moderate to severe OSA, irrespective of craniofacial restriction as determined by MMV.

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Disclosure

The results of this research have been previously published in:

1. Ng SSS, Tam WWS, Lee RWW, et al. Effect of weight loss and continuous positive airway pressure on obstructive sleep apnea and metabolic profile stratified by craniofacial phenotype: a randomized clinical trial. Am J Respir Crit Care Med 2022;205:711-20.

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