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Research Article

Weight Loss Ameliorates Markers of Systemic Inflammation and Endothelial Dysfunction in Obstructive Sleep Apnea Obese Patients

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Abstract

Background: Obstructive sleep apnea (OSA) is the most common sleep disorder in clinical practice. Its growing worldwide prevalence may be due to the rising incidence of obesity in the public. OSA has been increasingly recognized as a major public health issue, as it has a significant influence on the incidence and prognosis of cardiovascular diseases. Although, these abnormalities could be modulated with weight reduction, there is limitation in clinical studies have addressed the beneficial effects of weight reduction in modulating biomarkers of endothelial dysfunction and cytokines for obesity associated with OSA.

Objective: This study was designed to detect the effects of weight loss on the inflammatory cytokines and adhesive molecules in obese patients with obstructive sleep apnea.

Methods: Seventy obese patients with moderate to severe OSA (the apnea-hypopnea index (AHI)>15 events/hour), their age ranged from 36-50 years and their body mass index ranged from 26-31kg/m^2 were equally assigned into two groups: the weight reduction group received aerobic exercises, diet regimen, where the control group received no intervention for 12 weeks.

Results: The mean values of body mass index (BMI), apnea-hypopnea index (AHI), tumor necrosis factor –alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), inter-cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin were significantly decreased in the training group, however the results of the control group were not significant. In addition, there were significant differences between both groups at the end of the study.

Conclusion: Weight loss ameliorates inflammatory cytokines and adhesive molecules among obese patients with obstructive sleep apnea.

Keywords: Obstructive sleep apnea, Obesity, Adhesive molecules, Cytokines, Weight reduction

Introduction

Obstructive sleep apnea (OSA) is a clinical condition characterized by recurrent episodes of obstruction (apnea or hypopnea) of the upper airway, which can lead to intermittent hypoxia, hypercapnia and significant negative intrathoracic pressure during sleep.[1,2] Obstructive sleep apnea is common and affects 3%-7% of the general population.[3] OSA is quantified based on the apnea-hypopnea index (AHI), which represents the average number of apneas and hypopneas per hour of sleep. The diagnosis of OSA is made when AHI is >five events/hour of sleep and its severity can be classified according to the AHI into mild (>5 and <15 events/hour), moderate (≥15 and ≤30 events/hour) and severe (>30 events/hour).[4] OSA affects all age groups and is prevalent across different populations globally.[5] In the Wisconsin Sleep Cohort Study, the prevalence of undiagnosed OSA in adults was 9% for women and 24% for men[6] and 13% and 6%, respectively, have moderate-to-severe disease.[7]

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Obesity is an important risk factor for OSA[8] and their shared pathways of oxidative stress and inflammation make discerning independent roles in cardiovascular disease difficult.[9] Obesity stimulates an inflammatory state, as adipose tissue has resident macrophages and is a rich source of pro-inflammatory cytokines.[10] An increased prevalence of OSA has been associated with some risk factors including age, male sex, and obesity.[11] Obesity is one of the strongest risk factors and mild to moderate obesity has been associated with markedly increased sleep apnea prevalence.[12] Obesity promotes enlargement of soft tissue structures within, and surrounding, the airway, thereby contributing significantly to pharyngeal airway narrowing and to the development of OSA.[13]

OSA is associated with an increased risk of cardiovascular events and mortality.[14,15] Obstructive sleep apnea (OSA) is associated with an increased risk of cardiovascular disease (CVD). In addition, obese individuals OSA is independently associated with inflammation and insulin resistance.[16] However, it remains debated whether this relationship is independent of confounding factors such as age, sex, and obesity. The mechanisms responsible for the development of atherosclerosis triggered by OSA are not completely known. Several pathogenic factors are proposed as intermediate mechanisms linking OSA with cardiovascular disease (CVD). There is evidence that sleep apnea mainly by chronic intermittent hypoxia is associated with sympathetic activation, oxidative stress, systemic inflammation, hypercoagulability, endothelial dysfunction, and metabolic dysregulation.[17] These mechanisms are closely interrelated and are observed in individuals with excessive body weight.[18]

Obstructive sleep apnea (OSA) has been independently associated with endothelial dysfunction, which may explain the increased risk for cardiovascular and all-cause mortality in this population. Obstructive sleep apnea (OSA) have a high burden of cardiovascular disease.[19] Inflammatory markers, such as C-reactive protein (CRP), IL-6, IL-8, and tumor necrosis factor a (TNF-a), which have been proposed to be linked to the pathogenesis of systemic inflammation in cardiovascular disease, have been reported to be elevated in OSA patients.[20-23] Elevated levels of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), E-selectin and P-selectin may contribute to cardiovascular disease and are associated with obstructive sleep apnea (OSA) and obesity;[24,25] most observe higher ICAM-1 levels with more obesity[26] and reduced levels after weight loss.[27] Circulating ICAM-1, but not VCAM-1, is a consistent predictor of cardiovascular risk in healthy populations, while VCAM-1 predicts future cardiovascular risk within patients with pre-existing disease.[28,29]

Obstructive sleep apnea (OSA) remains both an under recognized and under-treated disease despite extensive research supporting its deleterious effects and the benefits of therapeutic intervention. However, little is known about the effect of lifestyle intervention on inflammatory cytokines and circulating levels of adhesion molecules among obese patients with OSA. The aim of this study of an existing randomized controlled trial was to determine the impact of lifestyle changes for 12 weeks aimed at weight reduction on inflammatory biomarkers and adhesion molecules in obese patients with OSA.

Patients and methods

Subjects

Seventy obese patients with moderate to severe OSA (AHI >15 events/hour) investigated by polysomnography in the Sleep Unit of the Internal Medicine Department at King Abdul Aziz University Hospital, their age ranged from 36-50 year. Exclusion criteria included patients undergoing any kind of active treatment for OSA, as well as pregnant women, those with chronic kidney or liver disease, diabetes, rhinitis, sinusitis, respiratory infections, patients with body mass index ≥40kg/m^2, systemic infections, those with untreated thyroid disease any cardiopulmonary, endocrine, or sleep disorders other than OSA, or consumption of any medications that could affect either cardiopulmonary function or sleep, including antihypertensive. A cardiologist conducted an initial clinical examination for all participants who were randomized for a weight reduction group (group A) or control group (group B). All participants signed the informed consent.

Measurements

Sleep recordings and daytime sleepiness (Polysomnography)

All the subjects were evaluated for one night in the Sleep Unit of the Internal Medicine Department at King Abdul Aziz University Hospital, where they were continuously monitored for 8 hours using a portable device, the Embletta system (Flaga, Reykjavik, Iceland). Recording was performed after one night of adaptation to the hospital setting. Airflow was monitored by a nasal pressure transducer. The thoracoabdominal movements of all the subjects were detected through two piezoelectric belts. Continuous overnight recordings of oxygen saturation were obtained by finger pulse oximetry. Snoring was recorded by a microphone placed at the neck, and note was taken of electrocardiogram findings and sleep position. Apnea was defined as the cessation of airflow lasting 10 seconds whereas hypopnea was defined as a discrete reduction (two thirds) of airflow and/or abdominal ribcage movements lasting 10 seconds associated with a 3% decrease in oxygen saturation. The number of events per hour was obtained by dividing the total number of events by total minutes of recording time and was defined as the apnea hypo apnea index (AHI). In addition, the number of dips 4% of basal SaO_2%/hour (oxygen desaturation index [ODI]) was measured. The study was scored by a single physician specializing in sleep medicine, whom was the same person scoring all the studies.[30]

Measurement of biomarkers of endothelial function

Biomarkers of endothelial function include sinter-cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin that were measured from frozen serum samples stored at −80°C. Enzyme-linked immunosorbent assays (ELISAs) were used to measure soluble levels of E-selectin, ICAM-1 and VCAM-1 (R&D Systems, France).

Measurement of inflammatory cytokines

Venous blood samples after a 12 hours fasting were centrifuged at +4°C (1000=g for 10min). Interleukin-6 (IL-6) levels were analyzed by "Immulite 2000" immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) levels were measured by ELISA kits (ELX 50) in addition to ELISA microplate reader (ELX 808; Bio Tek Instruments, USA).

Measurement of anthropometric parameters

Body weight of all participants was measured with (HC4211, Cas Korea, South Korea) while wearing hospital gowns and undergarments. Where the height was measured with a digital stadiometer (JENIX DS 102, Dongsang), so Body Mass Index (BMI) was computed as BMI=Body weight/Height^2. All assessment of BMI, AHI, ODI, TNF-α, CRP, IL-6, ICAM-1, VCAM-1 and E-selectin were taken before the starting and at the end of the study.

Procedures

All participants were divided randomly into the following groups:

1. Group (A): Thirty-five obese patients with moderate to severe OSA were submitted to the aerobic exercise training to complete a 12 week aerobic exercise on a treadmill which was conducted according to recommendation of American College of Sports Medicine regarding aerobic exercise application.[31] Training program included 5 minutes for warming –up in the form of range motion and stretching exercises, 30 minutes of aerobic exercise training (60-70% of maximum heart rate) and 10 minutes of cooling down (on treadmill with low speed and without inclination). Participants had 3 sessions/week for 3 months with close supervision of physical therapist. In addition, a dietician performed an interview-based food survey for all participants of group (A) for detection of feeding habits, abnormal dietary behavior and to prescribe the balanced low caloric diet that provide 1200 Kilocalories/day for 12 weeks.

2. Group (B): Thirty-five obese patients with moderate to severe OSA conducted their ordinary life style and received no intervention for 3 months.

Statistical analysis

The mean values of the investigated parameters obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups (P<0.05).

Results

Seventy obese patients with moderate to severe untreated OSA completed the screening evaluation. The baseline characteristics of the participants are shown in Table 1. Most participants (65%) were men. Thirty-five participants were assigned group (A) (n=35; 24 males and 11 females) and group (B) (n=35, 22 males and 13 females). None of the baseline characteristics differed significantly between the two groups. The mean values of BMI, AHI, ODI, TNF-α, IL-6, CRP, ICAM-1, VCAM-1 and E-selectin were significantly decreased in the training group (Table 2), however the results of the control group were not significant (Table 3). In addition, there were significant differences between both groups at the end of the study (Table 4).

Table 1: Mean value of baseline characteristics of subjects for participants in both groups.

	Group (A)	Group (B)	Significance
Age (year)	43.57±5.62	45.12±4.81	P>0.05
Gender (male/female)	24/11	22/13	P>0.05
BMI (kg/m^2)	33.25±2.71	32.58±3.14	P>0.05
Neck circumference (cm)	40.81±2.93	39.75±3.16	P>0.05
Waist circumference (cm)	110.17±8.52	108.64±9.13	P>0.05
SBP (mmHg)	132.25±10.44	129.87±8.79	P>0.05
DBP (mmHg)	87.38±5.61	85.52±6.17	P>0.05
AHI (events/hour)	43.27±6.82	42.64±5.95	P>0.05
ODI/hour	22.43±7.21	21.18±8.12	P>0.05
HOMA-IR	3.54±1.63	3.32±1.75	P>0.05
SaO_2 (%)	94.23±1.27	95.45±1.35	P>0.05

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HBA1c: Glycosylated haemoglobin; AHI: Apnea Hypopnea Index; ODI: Oxygen Desaturation Index; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; SaO2: Arterial Oxygen Saturation.

Table 2: Mean value and significance of BMI, TNF-α, IL-6, CRP, AHI, ODI, ICAM-1, VCAM-1 and E-selectin in group (A) before and at the end of the study.

	Mean +SD		T-value	Significance
	Pre	Post		
BMI (kg/m^2)	33.25±2.71	26.46±2.23*	7.65	*P<0.05*
TNF-α (pg/mL)	4.85±1.39	3.14±1.12*	6.76	P<0.05
IL-6 (pg/mL)	2.64± 0.95	1.81±0.83*	5.48	P<0.05
CRP (pg/mL)	4.28± 1.16	2.42±0.92*	7.83	P<0.05
AHI (events/hour)	43.27±8.82	29.38±7.43*	8.19	P<0.05
ODI/hour	22.43±7.21	18.16±5.92*	6.78	P<0.05
ICAM-1 (ng/ml)	93.21±9.51	81.45±8.26*	8.52	P<0.05
VCAM-1 (ng /ml)	815.68±30.15	732.11±25.28*	10.17	P<0.05
E-selectin (ng/ml)	16.57±4.13	10.88±3.17*	6.53	P<0.05

BMI: Body Mass Index; TNF-α: Tumor Necrosis Factor–alpha; IL-6: Interleukin-6; CRP: C-Reactive Protein; AHI: Apnea Hypopnea Index; ODI: Oxygen Desaturation Index; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference, P< 0.05.

Table 3: Mean value and significance of BMI, TNF-α, IL-6, CRP, AHI, ODI, ICAM-1, VCAM-1 and E-selectin in group (B) before and at the end of the study.

	Mean +SD		T-value	Significance
	Pre	Post		
BMI (kg/m^2)	32.58±3.14	32.87±3.16	1.13	*P>0.05*
TNF-α (pg/mL)	4.24±1.52	4.52±1.50	0.84	*P>0.05*
IL-6 (pg/mL)	2.68±0.91	2.87±0.94	0.86	*P>0.05*
CRP (pg/mL)	4.13± 1.17	4.45±1.26	0.92	*P>0.05*
AHI (events/hour)	42.82±7.93	43.94±8.12	1.24	*P>0.05*
ODI/hour	21.86±7.12	23.35±7.25	1.38	*P>0.05*
ICAM-1 (ng/ml)	91.45±8.73	94.21±8.97	1.66	*P>0.05*
VCAM-1 (ng /ml)	812.22±28.56	820.42±30.15	1.93	*P>0.05*
E-selectin (ng/ml)	15.18±3.74	17.25±3.91	1.42	*P>0.05*

BMI: Body Mass Index; TNF-α: Tumor Necrosis Factor–alpha; IL-6: Interleukin-6; CRP: C-Reactive Protein; AHI: Apnea Hypopnea Index; ODI: Oxygen Desaturation Index; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule.

Table 4: Mean value and significance of BMI, TNF-α, IL-6, CRP, AHI, ODI, ICAM-1, VCAM-1 and E-selectin in group (A) and group (B) at the end of the study.

	Mean +SD		T-value	Significance
	Group (A)	Group (B)		
BMI (kg/m^2)	26.46±2.23	32.87±3.16	8.14	P <0.05
TNF-α (pg/mL)	3.14±1.12	4.52±1.50	7.23	P <0.05
IL-6 (pg/mL)	1.81±0.83	2.87±0.94	6.11	P <0.05
CRP (pg/mL)	2.42±0.92	4.45±1.26	8.91	P <0.05
AHI (events/hour)	29.38±7.43	43.94±8.12	8.76	P <0.05
ODI/hour	18.16±5.92	23.35±7.25	7.18	P <0.05
ICAM-1 (ng/ml)	81.45±8.26	94.21±8.97	9.23	P <0.05
VCAM-1 (ng /ml)	732.11±25.28	820.42±30.15	10.84	P <0.05
E-selectin (ng/ml)	10.88±3.17	17.25±3.91	6.92	P <0.05

BMI: Body Mass Index; TNF-α: Tumor Necrosis Factor –alpha; IL-6: Interleukin-6; CRP: C-Reactive Protein; AHI: Apnea Hypopnea Index; ODI: Oxygen Desaturation Index; ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; (*) indicates a significant difference, P < 0.05.

Discussion

Obstructive sleep apnea (OSA) is a leading public health problem as it is usually associated with elevated cardiovascular risk, and inflammation plays an important role in the development of cardiovascular disease, it is reasonable to suspect that OSA may confer risk through an inflammatory mechanism. As adhesion molecules are a key component of the inflammatory process, it is likely that, if OSA is associated with increased inflammation, OSA will also be associated with increased adhesion molecules. Obesity is the most common predisposing factor for OSA.[32] Also, obesity induces an inflammatory state, as adipose tissue has resident macrophages and is an abundant source of pro-inflammatory cytokines such as TNF-α, CRP & IL-6[33,34] and cellular adhesion molecules include ICAM-1, VCAM-1, P-selection and L-selection.[35,36] With a significant

positive correlation between circulating levels of adhesion molecules and AHI among patients with OSA[37] The optimal management of obesity starts with a combination of diet, physical activity, and behavioral modification. Previous studies demonstrated beneficial effects of exercise training and caloric restrictions on pro-inflammatory state associated with endothelial dysfunction after weight loss.[38-40]

The main finding of the present study was that weight reducing program reduced AHI, ODI and ameliorated inflammatory cytokines (TNF-α, IL-6 and CRP) and markers of endothelial function (ICAM-1 VCAM-1 and E-selectin) in obese patients with OSA as a result of weight loss, these results are in line with many previous studies.

Mitchell and coworkers stated that meta-analyses were conducted for four RCTs proved that weight loss via intensive lifestyle interventions could be encouraged as a treatment for OSA.[41] However, Thomasouli and colleagues conducted a systematic review and meta-analysis of twelve randomized controlled trials and founded that intensive lifestyle management can significantly reduce obesity indices and improve AHI.[42] While, Ashrafian et al. had a systematic literature review revealed 19 surgical and 20 non-surgical studies of weight loss interventions in OSA treatment and confirmed that both bariatric surgery and non-surgical weight loss may have significant beneficial effects on OSA through BMI and AHI reduction. However, bariatric surgery may offer markedly greater improvement in BMI and AHI than non-surgical alternatives.[43] A prospective analysis from the Wisconsin Sleep Cohort demonstrated that there is a dose-response relationship between weight and AHI as a 10% weight loss was associated with a 26% reduction in AHI.[44] Moreover, several RCTs investigating the impact of weight loss on severity of OSA have reported that a mean range of weight loss by 10% to 16% can reduce AHI by 20% to 50%.[45-47] Similarly, three uncontrolled before-after studies on weight loss also reported that the average weight reduction by 13% and 30% is associated by decrease in AHI by 10% to 50%.[48-50]

Significant reductions of TNF-α, CRP and IL-6 concentrations were observed in group (A) as a result of weight loss. However, the differences were statistically significant between the groups. There is evidence for an association between OSA and elevated levels of CRP, IL-6 and TNF-α.[51,52]There is a lack of studies regarding impact of weight loss on inflammatory marker among obese patients with OSA. In our study, improving nocturnal breathing was found to be significantly related to CRP and TNF- α. In previous reports it has been shown that hypoxia and AHI are predictors of these cytokines.[53-55] It has been proposed that it is the excessive fat tissue, and not OSA per se, which explains the elevation of CRP and IL-6 in overweight patients with OSA.[56-58] Additionally, both of these biomarkers, and TNF-a, are associated with obesity, and are known to decrease by weight loss.[59-61] Three recent randomized studies have demonstrated that lifestyle intervention is an effective treatment for obese patients with OSA, and it also reduces other risk factors that tend to cluster with obesity and OSA, highlighting feasibility of the treatment as an early intervention modality.[62-64] Furthermore, lifestyle intervention results in a decrease of low-grade inflammation in individuals at high risk of diabetes, most of whom carry excess weight and other metabolic abnormalities similar to OSA patients.[65] While, Cotie et al. proved that 16 weeks of combined aerobic/resistance training and diet-induced weight loss improved endothelial function and interleukin-6 (IL-6) in overweight and obese young women.[66] Similarly, Lang et al. investigated the effects of an 8 week weight-control program on serum TNF-α, and blood lipid level profiles in 3 obese men and 11 obese women, their findings suggest that weight reduction through an 8 week weight loss program may have anti-inflammatory and antiatherogenic effects.[67] However, Madsen et al. concluded that weight loss of > 10% is necessary to significantly improve inflammatory markers in obese individuals.[68] Moreover, Sheu et al. enrolled 21 non-diabetic obese women in a 12 week caloric restriction and light exercise-based weight loss program. Ten lean women served as controls. Weight loss by 5% of initial weight in non-diabetic obese women led to significant reduction in TNF-α and IL-6.[69] Reductions in pro-inflammatory cytokines concentrations after weight loss is explained by reduction in fat mass.[70] Finally, Sahlman et al. conducted a study on 28 patients with overweight patients with mild OSA who were enrolled in a one year supervised lifestyle intervention and proved that weight loss resulted in reductions in concentrations of TNF-α, IL-6 and C-reactive protein (CRP) associated with apnea-hypopnea index, and improving night-time oxygen saturation.[71]

An improvement in the markers of endothelial function was observed because of weight reducing program in group (A). There were reductions in sVCAM-1, sICAM-1 and E-selectin observed at the end of the study. Nevertheless, the current data are comparable with previous studies conducted in obese populations that have shown reductions in PAI-1.[72-74] VCAM-1[75] and sICAM-1[75-77] following weight loss. However, Sharman and Volek conducted a 6 week crossover dietary intervention with reduced energy diets (low fat vs very low carbohydrate ~1500kcal) in 15 overweight men, resulted in reduction in plasma TNF-α, IL-6, CRP and sICAM-1.[78] While, Forsythe et al. conducted a parallel study with longer period dietary intervention (12 weeks) in a group of overweight individuals with dyslipidemia and stated that weight reduction was achieved which led to reduction in TNF-α, IL-6, IL-8, E-selectin, ICAM and plasminogen activator inhibitor-1 (PAI-1).[79] Similarly, Thomson et al. conducted a study on 50 overweight/obese women with polycystic ovary syndrome (PCOS) to determine if 20 weeks of a high-protein energy-restricted diet with or without exercise in women with PCOS could improve endothelial function. Participants were randomly assigned by computer generation to one of three 20 weeks interventions: diet only (6000kJ/day), diet and aerobic exercise (6000kJ/day and 5

walking sessions/week) and diet and combined aerobic-resistance exercise (6000kJ/day, three walking and two strength sessions/week). All three treatments resulted in significant weight loss, also sVCAM-1, and sICAM-1 and PAI-1 levels decreased with weight loss with no differences between treatments.[80] Also, bariatric surgery rapidly improved endothelial function.[81,82] The mechanisms of endothelial dysfunction amelioration are not clearly elucidated, but some studies suggest that reduction in circulating level of markers of endothelial activation and oxidative stress[83,84] as well as increases in nitrous oxide (NO) bioavailability through repetitive increase of shear stress may serve as mechanisms.[85,86]

Conclusion

Weight loss ameliorates inflammatory cytokines and adhesive molecules among obese patients with obstructive sleep apnea.

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Conflicts of Interest

Author declares that there is no conflict of interest.

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