Original Article

Effects of Weight Reduction Therapy on Obstructive Sleep Apnea Syndrome and Arterial Stiffness in Patients with Obesity and Metabolic Syndrome

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***Aim*: Obesity and metabolic syndrome (MetS) and obstructive sleep apnea (OSA), which are often accompanied by obesity, are each independently associated with cardiovascular disease (CVD). However, the influence of OSA on arterial stiffness in obese patients remains unclear. We herein examined the relationships between the severity of OSA and CVD risk factors, including the severity of MetS and arterial stiffness, in obese patients. In addition, we evaluated the effects of weight reduction therapy on OSA and arterial stiffness.**

***Methods*: Among the 60 overweight or obese Japanese outpatients enrolled, 46 (76.7%) met the MetS criteria.**

***Results*: The apnea-hypopnea index (AHI) and cardio-ankle vascular index (CAVI), a new index of arterial stiffness, were significantly higher in the MetS patients than in the non-MetS patients, whereas there were no significant differences in body mass index, blood pressure or the low-density lipoprotein cholesterol level. A multivariate regression analysis revealed that waist circumference, the C-reactive protein level and CAVI were independently correlated with AHI. In addition, age, SBP, IRI and AHI were independently correlated with CAVI. Furthermore, weight reduction therapy, including diet and exercise, over a three-month period significantly decreased the AHI and CAVI values in parallel with a reduction in BMI.**

***Conclusions*: This study demonstrated that the severity of OSA is significantly correlated with the severity of MetS and arterial stiffness in obese patients. Short-term weight reduction therapy improves not only metabolic dysfunction, but also the severity of OSA and arterial stiffness, as measured according to the CAVI. Such changes may help to prevent atherosclerosis in obese patients.**

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Key words: Arterial stiffness, Obesity, Metabolic syndrome, Cardiovascular risk factors, Blood pressure, Obstructive sleep apnea syndrome

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by upper airway collapse causing sleep fragmentation, repetitive hypoxemia and sympathetic surges that is independently associated with death due to cardiovascular disease (CVD)[1]. Epidemiological studies have demonstrated that obesity and metabolic syndrome (MetS), a cluster of multiple atherogenic risk factors, including obesity, hypertension, hyperglycemia and dyslipidemia, increase the risk of cardiovascular morbidity and mortality[2]. Obesity is the most common risk factor for OSA, and the prevalence of OSA is undoubtedly rising given the epidemic of obesity[3]. MetS has also recently been postulated to be

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closely associated with OSA[3]. It is therefore important to promptly detect OSA and its effects on the risk of CVD in obese patients. To date, the impact of OSA in patients with obesity and MetS has not been elucidated.

OSA is recognized to be a secondary cause of hypertension and may contribute to insulin resistance, diabetes and dyslipidemia, all of which are components of MetS[4]. Given the known pathophysiological triggers of intermittent hypoxia and sleep fragmentation in patients with OSA, the potential mechanisms underlying the OSA-obesity-MetS interaction involve sympathetic activation, oxidative stress, inflammation and neurohumoral changes[3]. However, the magnitude of the impact of OSA on the progression of atherosclerosis in patients with obesity and MetS, as compared to other risk factors, is not well established. Recently, as an index of arterial stiffness, the cardio-ankle vascular index (CAVI), was developed. This parameter is independent of blood pressure and thus superior to the brachial-ankle pulse wave velocity (baPWV)[5, 6]. We previously demonstrated that the CAVI levels in obese patients exhibit a significant association with the number of components of MetS, which has been reported to be associated with the risk of incident CVD[6]. Kumagai *et al.* also reported that the CAVI levels in patients with moderate-to-severe OSA are significantly higher than those observed in patients with mild OSA, despite a lack of significant differences in baPWV[7]. However, there are no detailed studies regarding the relationship between the CAVI and the severity of OSA in obese patients.

Weight reduction therapy is an essential first step in the management of obesity and obesity-related complications[6, 8]. We previously demonstrated that short-term, successful weight reduction in obese patients markedly alleviates several CVD risk factors, particularly the level of oxidative LDL and arterial stiffness measured according to the CAVI[6, 8]. Although there are many studies concerning the effects of weight loss following continuous positive airway pressure (CPAP) treatment or bariatric surgery in improving OSA[9], few studies have examined the influence of weight loss alone achieved via lifestyle modification with diet and exercise therapy on the severity and outcomes of OSA in obese patients. In addition, most studies have reported limited effects of weight loss achieved with conservative lifestyle modification therapy in improving OSA in comparison with CPAP therapy or bariatric surgery[10]. In addition, there are no available studies regarding the effects of short-term weight reduction on OSA in obese Japanese patients.

Accordingly, it is important to establish the clinical relevance of OSA and the risk of CVD in patients with obesity and MetS. In this study, we examined the relationships between the severity of OSA and CVD risk factors, including the components of MetS and arterial stiffness in obese patients in order to elucidate the significance of the influence of OSA on the progression of CVD in obese patients. Because weight reduction improves atherogenic CVD risk factors[6, 8], we also evaluated the effects of weight reduction therapy on the severity of OSA. We herein demonstrate significant correlations between OSA and arterial stiffness and the severity of MetS in obese patients. Interestingly, diet- and exercise-induced weight reduction effectively improved OSA in parallel with refinement of arterial stiffness in the obese patients. The findings of this study suggest the importance of screening for OSA in obese patients in order to effectively prevent the progression of CVD in patients with obesity and MetS.

Materials and Methods

Subjects

A total of 60 overweight or obese Japanese outpatients (24 men and 36 women, mean age: 48.6 years, mean body mass index [BMI]: 31.2 kg/m^2) were consecutively enrolled at the outpatient clinic of the National Hospital Organization Kyoto Medical Center during the period from April 2007 to March 2009. We recruited obese subjects with a BMI of ≥ 25 kg/m^2. This study is a part of the Japan Obesity and Metabolic Syndrome Study (JOMS), which has undergone clinical trial registration in the University Hospital Medical Information Network (UMIN) system (UMINStudyID: UMIN 000000559)[6]. The exclusion criteria were a previous history of CVD, other vascular diseases, apparent renal disease, severe liver dysfunction or secondary obesity due to endocrine disorders, such as Cushing's syndrome, polycystic ovary syndrome, acromegaly or hypothyroidism. None of the patients had received anti-obesity drugs. The study protocol was approved by the ethics committee for human research at Kyoto Medical Center, and all participants provided their written informed consent.

Diagnostic Criteria for Metabolic Syndrome

All overweight and obese patients were classified as having (MetS group) or not having (non-MetS group) MetS according to the criteria proposed by the US National Cholesterol Education Program-Adult Treatment Panel Ⅲ (NCEP-ATP Ⅲ) with a slight modification of waist circumference, as a representative criterion of this syndrome, as previously described[6, 11].

The criterion for waist circumference was set at ≥85 cm for men and ≥90 cm for women, based on the National Metabolic Syndrome Criteria Study Group of Japan[12].

Data Collection and Laboratory Assay Methods

At the beginning of and three months after the initiation of weight reduction therapy, MetS-related parameters (BMI, waist circumference and systolic and diastolic blood pressure [SBP and DBP, respectively]) and blood parameters were measured as previously described[6]. Fasting blood samples were obtained from the antecubital vein in the morning after a 12-hour fast without the prescription of drugs, and the levels of fasting plasma glucose (FPG), hemoglobin A1c (HbA1c) (measured according to the National Glycohemoglobin Standardization Program [NGSP])[13], immunoreactive insulin (IRI), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) were determined according to standard procedures[6, 8]. The serum levels of C-reactive protein (CRP), an inflammatory marker, leptin and adiponectin were also determined as previously described[6]. PWV, an index of arterial stiffness, and CAVI, a newly developed indicator of arterial stiffness that is independent of BP, were determined using a Vasera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan), as previously reported[6].

Measurement of the Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI)

Sleep studies were conducted to determine the apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) using a PulSleep LS-100 (Fukuda Denshi, Tokyo, Japan), a portable sleep apnea monitor that digitally records the nasal airflow (via nasal cannula), oxygen saturation and snoring sounds[14]. The AHI was defined as the total number of apnea and hypopnea events divided by the total sleep time[15]. Apnea was defined as the cessation of airflow for at least 10 seconds, and hypopnea was defined as an 80% or greater reduction in airflow for at least 10 seconds, regardless of the amplitude. ODI was defined as the number of significant episodes of desaturation ($\Delta > 4\%$) per hour of sleep[14]. Accepted definitions and scoring methods for the diagnosis of OSA were used. The patients with OSA were classified according to the AHI as follows: $5 \leq$ AHI < 15 events per hour indicated mild OSA and AHI ≥ 15 events per hour indicated moderate-to-severe OSA[15, 16].

Weight Reduction Therapy

Among the 60 enrolled patients, 27 obese patients were excluded for the following reasons: 12 patients stopped consulting the clinic, two patients experienced serious adverse events, six patients withdrew their consent and seven patients did not approve of our weight reduction protocol. Accordingly, 33 obese patients (11 men and 22 women, mean age: 51.0 years, mean BMI: 31.0 kg/m^2) underwent weight reduction therapy including lifestyle modification to reduce energy intake and increase physical activity for three months, as previously described[6, 8]. All patients undergoing weight reduction therapy were instructed to maintain the same levels of energy intake and physical activity for the entire period, as recommended by the Japan Atherosclerosis Society's Guidelines for the Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases[6, 8]. The diet therapy consisted of 25 kcal/kg of ideal body weight per day. The patients consumed 60% of the total energy as carbohydrates, 20-25% as fat and 15-20% as protein. They were also instructed to exercise for more than 30 minutes at moderate intensity at least three days/week[6, 8]. In this study, all patients were instructed to follow our weight reduction protocol throughout the three-month treatment period. To ensure adherence to the weight reduction therapy during this period, we interviewed and instructed all patients regarding our weight reduction protocol and checked the daily patients' records in our outpatient clinic every month. Before and three months after the initiation of the weight reduction therapy, we measured metabolic parameters, CAVI, AHI and ODI. Smoking habits and prescribed drugs were not altered. We classified the patients who were able to reduce their body weight by more than 3% of their baseline BW as being successful in achieving weight reduction and those who reduced their BW by less than 3% as being unsuccessful, as previously reported[8].

Statistical Analysis

The data are presented as the mean ± SE, and a p value of < 0.05 was considered to be significant. A two-tailed, unpaired t-test and the χ^2 test were used to assess differences between the two groups for continuous and categorical variables, respectively. If the data were not normally distributed, the Wilcoxon test was used. A two-way repeated-measures ANOVA (unsuccessful and successful weight reduction groups × before and after treatment) was employed to assess the comparative effects of weight reduction therapy on the measured variables. Then, for significant variables identified in the ANOVA, a two-tailed, paired t-test

Table 1. Baseline characteristics of the patients with and without MetS according to the criteria for metabolic syndrome proposed by the NCEP

	Non-MetS	MetS	*p* value
Male/Female	6/8	18/28	n.s.
Age (years)	46.0 ± 3.3	49.4 ± 1.9	n.s.
BMI (kg/m^2)	29.4 ± 0.5	32.7 ± 0.5	n.s.
Waist circumference (cm)	94.3 ± 3.5	99.4 ± 1.3	n.s.
Systolic blood pressure (mmHg)	135 ± 5.4	140 ± 2.2	n.s.
Diastolic blood pressure (mmHg)	80.4 ± 3.5	85.1 ± 1.3	n.s.
Fasting plasma glucose (mmol/L)	5.6 ± 0.4	7.0 ± 0.3	< 0.01
HbA1c (%)	6.3 ± 0.3	7.1 ± 0.2	< 0.01
IRI (pmol/L)	76.2 ± 16.2	123.6 ± 14.4	n.s.
Triglyceride (mmol/L)	2.6 ± 0.2	4.3 ± 0.3	< 0.01
HDL-C (mmol/L)	1.4 ± 0.1	1.4 ± 0.0	n.s.
LDL-C (mmol/L)	3.2 ± 0.2	3.2 ± 0.1	n.s.
Leptin (ng/mL)	7.8 ± 1.3	9.7 ± 0.7	n.s.
Adiponectin (μg/mL)	6.7 ± 0.8	5.7 ± 0.4	n.s.
CRP (μg/mL)	0.81 ± 0.2	1.26 ± 0.2	n.s.
CAVI	7.43 ± 0.3	8.27 ± 0.2	< 0.05
AHI	11.4 ± 2.9	24.3 ± 2.9	< 0.05
ODI	7.99 ± 2.3	15.3 ± 2.4	n.s.

The data are expressed as the mean ± SEM. BMI: body mass index; HbA1c: hemoglobin A1c; IRI: immunoreactive insulin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CRP: high-sensitivity C-reactive protein; CAVI: cardio-ankle vascular Index; AHI: apnea hypopnea index; ODI: oxygen desaturation index.

was applied to evaluate changes in conditions from before to three months after the initiation of therapy[6]. An analysis of covariance (ANCOVA) adjusted for gender and age was performed to assess the trends in the mean values of AHI, ODI and CAVI stratified according to the number of MetS components; the trend test was based on the linear contrast. Pearson's correlation coefficients were used to investigate the correlations between AHI, ODI, CAVI and metabolic parameters at baseline and between changes in these parameters during the weight reduction period. Changes from baseline to three months after the initiation of therapy were abbreviated as Δ. A multivariate stepwise regression analysis was performed to identify factors related to the baseline AHI, ODI, and CAVI values and changes in AHI, ODI and CAVI during the three-month study period. We employed a multivariate regression analysis with a forward stepwise procedure.

All statistical analyses were performed using the SPSS 15.0 software program for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline Clinical Characteristics of the Patients with and without MetS

Table 1 summarizes the characteristics of the study cohort, comparing those with and without MetS. The prevalence of MetS among the obese patients in this study was 76.7% according to the NCEP-ATPⅢ guidelines. The levels of FPG, HbA1c and TG were significantly higher in the MetS group than in the non-MetS group, while the proportion of men, age, BMI, waist circumference, SBP, DBP and levels of HDL-C, LDL-C, adiponectin and CRP were not different between the two groups. The levels of IRI, leptin and CRP were slightly higher in the MetS group than in the non-MetS group; however, the differences were not significant. Moreover, the CAVI values were significantly higher in the MetS group than in the non-MetS group (non-MetS group, 7.43 ± 0.3; MetS group, 8.27 ± 0.2, $p < 0.05$). The AHI values were also significantly higher in the MetS group than in the non-MetS group (non-MetS group, 11.4 ± 2.9; MetS group, 24.3 ± 2.9, $p < 0.05$). The ODI values were slightly higher in the MetS group than in the non-MetS group; however, the differences were not significant (**Table 1**). Among men, only DBP, TG and

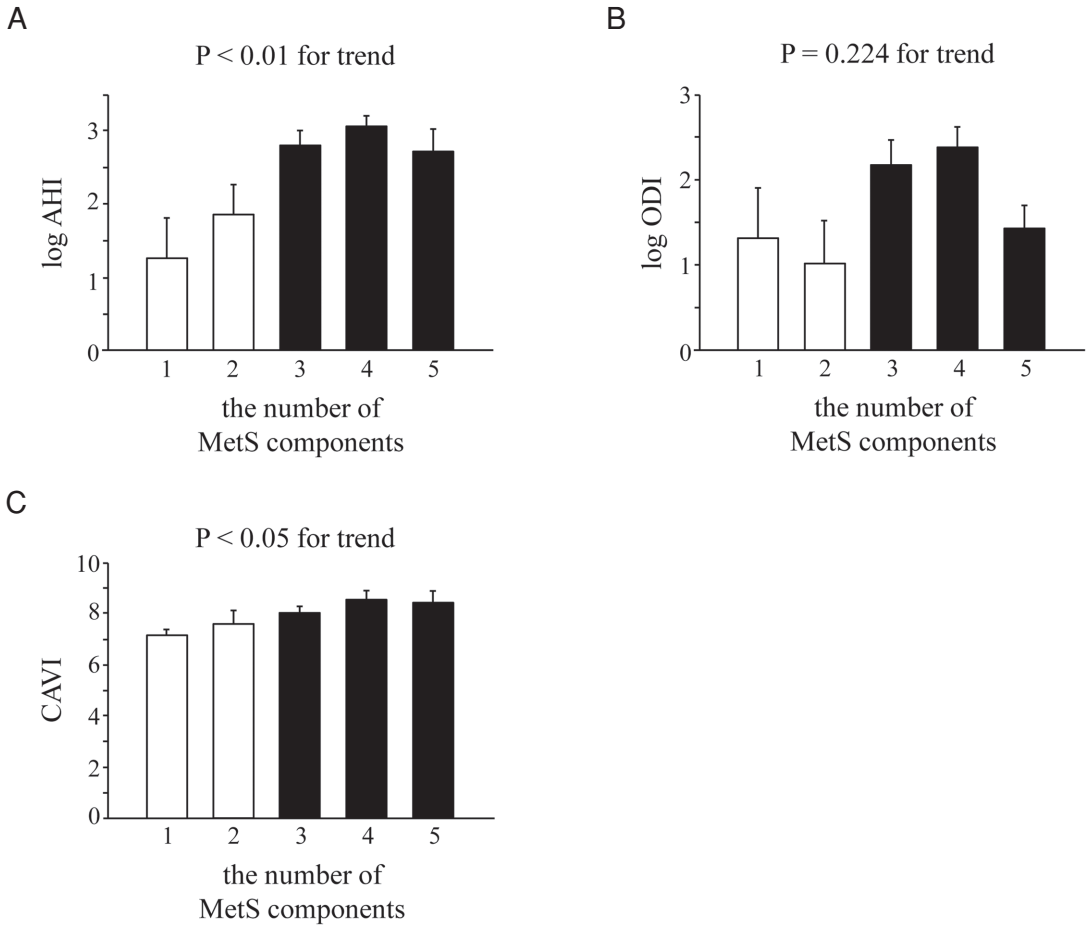

Fig. 1. AHI, ODI and CAVI stratified according to the number of MetS components.

The values of log AHI (A), log ODI (B) and CAVI (C) stratified according to the number of components of metabolic syndrome following adjustment for gender and age. The data are shown as the mean ± SEM. The trends in the mean values in all groups were assessed using ANCOVA with a linear contrast model adjusted for gender and age. Non-metabolic syndrome and metabolic syndrome are indicated by open and closed bars, respectively.

CAVI were significantly higher in the MetS group than in the non-MetS group, whereas AHI and ODI were not significantly different between the two groups (**Supplemental Table 1A**). On the other hand, among women, BMI, waist circumference, TG, AHI and ODI were significantly higher in the MetS group ($p<0.05$) (**Supplemental Table 1B**).

AHI, ODI and CAVI Stratified According to the Number of MetS Components

We also examined the mean levels of log AHI, log ODI and CAVI stratified according to the number of MetS risk factors in all patients. When both gender and age were taken into account, both log AHI and CAVI were found to be significantly associated with the number of risk factors (log AHI, $p<0.01$; CAVI, $p<0.05$; age- and gender-adjusted) (**Fig. 1A** and **C**), whereas log ODI was not (**Fig. 1B**).

Baseline Correlations between AHI, ODI, CAVI and the MetS-Related Parameters

Among all parameters, AHI exhibited significant positive correlations with BMI, waist circumference, leptin, CRP, CAVI and ODI (waist circumference, CAVI and ODI, $p<0.01$; BMI, leptin and CRP, $p<0.05$). ODI also demonstrated significant positive correlations with BMI, waist circumference, leptin, CRP and AHI (waist circumference and AHI, $p<0.01$; BMI, leptin and CRP, $p<0.05$). In addition, CAVI exhibited significant positive correlations with age, SBP, IRI, TG and AHI (age, IRI and AHI, $p<0.01$; SBP and TG, $p<0.05$) (**Table 2A**).

Table 2

A. Baseline correlations between AHI, ODI and CAVI and various parameters

	AHI[a]	ODI[a]	CAVI
	r	*r*	*r*
Age	0.227	0.154	0.671**
BMI	0.296*	0.269*	−0.154
Waist circumference	0.323**	0.321**	−0.005
Systolic blood pressure	0.094	0.058	0.322*
Diastolic blood pressure	0.145	0.095	0.202
Fasting plasma glucose	0.137	0.072	0.169
HbA1c[a]	0.093	0.011	0.129
IRI[a]	0.082	0.060	0.381**
Triglyceride[a]	0.166	0.104	0.273*
HDL-C	0.017	0.078	0.006
LDL-C	0.046	−0.100	0.229
Leptin	0.285*	0.284*	0.044
Adiponectin	−0.012	0.056	0.017
CRP[a]	0.257*	0.255*	−0.087
CAVI	0.351**	0.185	−
AHI[a]	−	0.881**	0.351**
ODI[a]	0.881**	−	0.185

The abbreviations in this table are the same as those used in Table 1. *r*: correlation coefficient. *$p<0.05$, **$p<0.01$. [a]Logarithmic transformation was performed because the variable had a skewed distribution.

B. Step-wise multiple regression analysis of AHI, ODI and CAVI

Dependent variables	Independent variables	β	*p*	R^2
AHI[a]	Waist circumference	0.326	0.004	0.310
	CRP[a]	0.266	0.036	
	CAVI	0.376	<0.001	
ODI[a]	Waist circumference	0.321	0.006	0.103
CAVI	Age	0.598	<0.001	0.640
	SBP	0.341	<0.001	
	IRI[a]	0.168	0.019	
	AHI[a]	0.182	0.010	

β: Standardized regression coefficient. The abbreviations in this table are the same as those used in Table 1. In a stepwise multivariate regression analysis of AHI and ODI as dependent variables, the independent variables were the baseline parameters of age, gender, BMI, waist circumference, systolic blood pressure, fasting plasma glucose, HbA1c, IRI, triglycerides, HDL-C, LDL-C, leptin, adiponectin, CRP and CAVI. In a model of CAVI as the dependent variable, the independent variables were the baseline parameters of age, gender, BMI, waist circumference, systolic blood pressure, fasting plasma glucose, HbA1c, IRI, triglycerides, HDL-C, LDL-C, leptin, adiponectin, CRP, AHI and ODI.
[a]Logarithmic transformation was performed because the variable had a skewed distribution.

Among men, the leptin and CRP levels exhibited significant positive correlations with the AHI values; these associations were not observed in women. In contrast, in women, waist circumference was significantly correlated with AHI, whereas no such correlation was observed in men (**Supplemental Tables 2A and B**). In men, ODI was found to be correlated with AHI only. Meanwhile, in women, ODI exhibited correlations with both waist circumference and AHI. In men, CAVI demonstrated significant positive correlations with age, IRI and AHI. In contrast, in women, CAVI exhibited significant positive correlations with age, SBP and AHI.

A stepwise multivariate regression analysis revealed that waist circumference, log CRP and CAVI were independently associated with log AHI (waist circum-

Table 3. Effects of weight reduction on the metabolic variables, AHI and ODI in the obese patients

	Group unsuccessful in weight reduction		Group successful in weight reduction	
	before	3 months	before	3 months
Male/Female	7/12		4/10	
Age (years)	48.7 ± 2.8		54.1 ± 2.7	
BMI (kg/m^2)	32.1 ± 1.3	32.4 ± 1.3	29.4 ± 1.1	27.2 ± 1.0**
Waist circumference (cm)	98.8 ± 5.6	101 ± 2.6	93.1 ± 1.3	89.6 ± 1.7**
Systolic blood pressure (mmHg)	139 ± 3.8	143 ± 3.1	141 ± 5.3	129 ± 4.2*
Diastolic blood pressure (mmHg)	86.2 ± 2.4	86.4 ± 1.5	83.4 ± 2.1	80.3 ± 2.1
Fasting plasma glucose (mmol/L)	7.3 ± 0.2	6.4 ± 0.2	6.8 ± 0.5	5.6 ± 0.3
HbA1c (%)	7.1 ± 0.3	7.3 ± 0.3	6.9 ± 0.3	6.4 ± 0.2
IRI (pmol/L)	106 ± 12	113 ± 22	92.4 ± 17	59 ± 14
Triglyceride (mmol/L)	1.4 ± 0.1	1.7 ± 0.2	2.8 ± 0.1	1.4 ± 0.2
HDL-C (mmol/L)	1.5 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.5 ± 0.1
LDL-C (mmol/L)	3.1 ± 0.2	3.1 ± 0.1	3.4 ± 0.2	3.1 ± 0.2
Leptin (ng/mL)	10.0 ± 2.0	11.3 ± 2.0	10.5 ± 1.6	10.3 ± 1.5
Adiponectin (μg/mL)	6.50 ± 0.8	6.13 ± 0.6	5.01 ± 0.6	6.23 ± 0.6
CRP (μg/mL)	1.09 ± 0.3	0.95 ± 0.2	1.05 ± 0.3	0.72 ± 0.2
CAVI	8.17 ± 0.3	8.20 ± 0.4	8.49 ± 0.3	7.98 ± 0.3*
AHI	19.3 ± 2.7	21.1 ± 2.9	18.0 ± 2.9	9.61 ± 1.9*
ODI	11.5 ± 2.7	12.3 ± 2.1	6.16 ± 1.8	4.02 ± 0.8

The abbreviations in this table are the same as those used in Table 1.
*$p<0.05$, **$p<0.01$ vs. baseline measurement as determined using a two-way repeated measures ANOVA (groups x before and three months after the initiation of weight reduction therapy).

ference: $\beta=0.326$, $p=0.004$; log CRP: $\beta=0.266$, $p=0.036$; CAVI: $\beta=0.376$, $p<0.001$; total $R^2=0.310$) and that waist circumference only was an independent determinant of ODI ($\beta=0.321$, $p=0.006$, total $R^2=0.103$) (**Table 2B**). On the other hand, age, SBP, log IRI and log AHI were found to be independently associated with CAVI (age: $\beta=0.598$, $p<0.001$; SBP: $\beta=0.341$, $p<0.001$; log IRI: $\beta=0.168$, $p=0.019$; log AHI: $\beta=0.182$, $p=0.010$; total $R^2=0.640$) (**Table 2B**).

Effects of Body Weight Reduction on Metabolic Parameters, CAVI and AHI in the Obese Subjects

Of the 33 patients, 14 (42.4%) successfully reduced their body weight by more than 3%. Among those who were successful in achieving weight reduction, BMI, waist circumference, SBP and CAVI were significantly decreased three months after the initiation of the weight reduction therapy (BMI, waist circumference, $p<0.01$; SBP, CAVI, $p<0.05$). The AHI values were significantly decreased three months after the initiation of weight reduction therapy ($p<0.05$). Similarly, the ODI values also decreased, but not significantly (**Table 3**). Among those unsuccessful in achieving body weight reduction ($n=19$), none of the above parameters changed throughout the study period (**Table 3**).

Correlations between Changes in AHI, ODI, CAVI and the MetS-Related Parameters

Table 4A lists the data for all subjects regarding the simple correlations between ΔAHI, ΔODI and ΔCAVI and the baseline values and changes in all parameters during the weight reduction period. Among all study subjects, Pearson's correlation coefficients revealed that a decrease in AHI was strongly correlated with a low adiponectin level at baseline, decreases in BMI, waist circumference, the LDL-C level, the leptin level, CAVI and ODI and an increase in the adiponectin level (adiponectin at baseline, $r=0.399$; ΔBMI, $r=0.652$; Δwaist circumference, $r=0.437$; ΔLDL-C, $r=0.349$; Δleptin, $r=0.361$; ΔCAVI, $r=0.369$; Δadiponectin, $r=-0.361$; ΔODI, $r=0.504$; $p<0.05$). A decrease in ODI was strongly correlated with a high ODI and AHI at baseline (AHI at baseline, $r=-0.504$; ODI at baseline, $r=-0.598$; $p<0.01$); however, a decrease in ODI was not significantly correlated with changes in any parameters, except for ΔAHI (**Table 4A**). In addition, a decrease in CAVI induced by weight reduction therapy was significantly correlated with decreases in BMI and AHI only ($r=0.349$ and

Table 4

A. Correlations between changes in AHI, ODI and CAVI from baseline and changes in parameters

	ΔAHI	ΔODI	ΔCAVI
	r	*r*	*r*
Parameters at baseline			
Age	−0.145	−0.275	0.136
BMI	0.154	0.093	−0.041
Waist circumference	0.071	0.110	−0.153
Systolic blood pressure	0.054	−0.175	0.032
Diastolic blood pressure	0.063	−0.147	−0.143
Fasting plasma glucose	0.077	0.132	0.176
HbA1c[a]	0.120	0.150	−0.031
IRI[a]	0.131	0.113	0.238
Triglyceride[a]	−0.061	−0.024	−0.062
HDL-C	0.080	0.053	0.035
LDL-C	−0.164	0.072	0.083
Leptin	−0.306	−0.103	−0.152
Adiponectin	0.399*	0.051	0.212
CRP[a]	0.151	0.255	−0.224
CAVI	−0.186	−0.287	−0.016
AHI[a]	−0.307	−0.504**	−0.052
ODI[a]	−0.017	−0.598**	−0.088
changes of parameters			
ΔBMI	0.652**	0.284	0.349*
ΔWaist circumference	0.437**	0.111	0.303
ΔSystolic blood pressure	0.210	0.213	0.317
ΔDiastolic blood pressure	−0.022	0.064	0.067
ΔFasting plasma glucose	0.113	0.079	0.030
ΔHbA1c	0.108	−0.085	0.269
ΔIRI	0.290	0.045	0.123
ΔTriglyceride	0.113	−0.087	0.088
ΔHDL-C	−0.154	−0.140	0.008
ΔLDL-C	0.349*	−0.111	0.227
ΔLeptin	0.361*	−0.022	0.286
ΔAdiponectin	−0.361*	0.010	−0.121
ΔCRP	0.067	−0.220	0.055
ΔCAVI	0.369*	−0.063	−
ΔAHI	−	0.504**	0.369*
ΔODI	0.504**	−	−0.063

The abbreviations in this table are the same as those used in Table 1. *r*: correlation coefficient. *$p<0.05$, **$p<0.01$. [a]Logarithmic transformation was performed because the variable had a skewed distribution.

B. Step-wise multiple regression analysis of changes in AHI, ODI and CAVI

Dependent variables	Independent variables	β	*p*	R^2
ΔAHI	ΔBMI	0.652	<0.001	0.425
ΔODI	nothing	−	−	−
ΔCAVI	ΔAHI	0.369	<0.001	0.136

β: Standardized regression coefficient. The abbreviations in this table are the same as those used in Table 1. In a stepwise multivariate regression analysis of ΔAHI and ΔODI as the dependent variables, the independent variables were the baseline parameters of age, gender, ΔBMI, Δsystolic blood pressure, Δfasting plasma glucose, ΔHbA1c, ΔIRI, Δtriglycerides, ΔHDL-C, ΔLDL-C, Δleptin, Δadiponectin and ΔCRP. In a model of ΔCAVI as the dependent variable, the independent variables were the baseline parameters of age, gender, ΔBMI, Δsystolic blood pressure, Δfasting plasma glucose, ΔHbA1c, ΔIRI, Δtriglycerides, ΔHDL-C, ΔLDL-C, Δleptin, Δadiponectin, ΔCRP, ΔAHI and ΔODI.

0.369, respectively; $p<0.05$), although a decrease in CAVI was not significantly correlated with any parameters at baseline (**Table 4A**). A multivariate regression analysis revealed that a decrease in BMI was an independent determinant of a reduction in AHI during the weight reduction period ($\beta=0.652$, $R^2=0.425$, $p<0.001$) (**Table 4B**). There were no independent determinants of the changes in ODI. A decrease in AHI was found to be the only independent determinant of a reduction in CAVI during the weight reduction period ($\beta=0.369$, $R^2=0.136$, $p<0.001$) (**Table 4B**).

Discussion

We herein demonstrated for the first time that the severity of OSA is significantly associated with the number of MetS components and arterial stiffness in obese patients. This study also revealed that successful short-term weight reduction therapy with diet and exercise significantly reduced the severity of OSA in parallel with a decrease in body weight and that the reduction in arterial stiffness was not influenced by BP.

An epidemiological study reported that OSA is associated with a four-fold higher incidence of MetS compared to that observed in patients without OSA[17]. It has also been shown that, independent of visceral fat obesity, OSA is associated with hypertension, dyslipidemia and hyperglycemia, all of which are components of MetS[18]. On the other hand, few data are available regarding the rate and severity of OSA in patients with obesity and MetS. In this study, we verified that the AHI values are significantly higher in MetS patients than in non-MetS patients and that the mean levels of AHI are significantly elevated according to the number of risk factors of MetS in obese patients. The mechanisms whereby OSA induces the progression of MetS components are considered to involve increased catecholamines, sleep deprivation, insulin resistance and other pathophysiological characteristics; therefore, OSA may predispose obese patients to develop MetS[19]. In this study, our data showed that AHI was significantly correlated with BMI, waist circumference, leptin and the level of CRP, suggesting that not only visceral obesity, but also adipocytokine dysregulation and inflammation, may affect the severity of OSA in obese patients. Previously, we reported the role of the sympathetic activation of leptin in regulating body weight[20]. Animal studies have also provided evidence indicating that leptin is a stimulant of ventilation[21]. Chin K and others reported that higher leptin levels are observed in patients with OSA, independent of the body fat content[22], which suggests that leptin resistance (resistance to the weight-reducing effects of leptin) in patients with obesity and MetS promotes the progression of OSA. Taken together, our findings suggest that OSA and MetS reciprocally interact and deteriorate each other's pathological condition via various common mechanisms, as described above.

This study is the first to demonstrate that AHI is significantly associated with CAVI, an index of arterial stiffness that is not influenced by changes in BP, in obese patients. It has also been reported that severe OSA and hypertension are associated with baPWV and structural cardiac abnormalities[23]. However, baPWV is affected by BP and the activity of the autonomic nervous system[24]. We previously reported that CAVI is less influenced by BP and more closely correlated with the severity of MetS and MetS-related parameters relative to baPWV and is thus superior to baPWV in obese patients[6]. It has also been reported that significantly higher CAVI values are observed in patients with moderate-to-severe OSA than in patients with mild OSA, whereas no significant differences are observed in baPWV[7]. In this study, a multivariate regression analysis revealed that AHI, not age, SBP or IRI, was an independent determinant of CAVI, suggesting that the severity of OSA in obese patients is closely associated with arterial stiffness, independent of BP. Furthermore, our results also revealed that waist circumference, CRP and CAVI only are independent determinants of the AHI values in obese patients. Our data correspond to the findings of a report that revealed that the levels of pentraxin 3 and CRP, inflammatory markers, are higher in patients with moderate-to-severe OSA than in patients without OSA and are correlated with higher CAVI values[25]. These results suggest that low-grade systemic inflammation is a key mediator linking obesity-MetS-OSA and may be contribute to the progression of atherosclerosis. Evidence suggests that chronic intermittent hypoxia and sleep loss and fragmentation associated with OSA increase the levels of various markers of inflammation and oxidative stress, thus contributing to the development of endothelial and metabolic dysfunction, including atherosclerosis[26]. Collectively, our data support the idea that the presence of OSA in patients with obesity and MetS significantly contributes to the development of systemic inflammation and atherosclerosis.

Interestingly, our longitudinal study is the first study to show that successful short-term weight reduction markedly reduces the AHI values in obese patients. Many studies have reported that CPAP treatment reduces AHI, daytime sleepiness and the risk of

fatal and nonfatal cardiovascular events in patients with OSA[9]. In addition, bariatric surgery significantly reduces AHI and improves the severity of OSA by significantly reducing BMI[27]. However, it is thought that weight reduction alone based on lifestyle modification has little effect on improving OSA due to a lack of well-executed studies of OSA. Tuomilehto HP *et al.* reported that a very low calorie diet combined with active lifestyle counseling resulting in marked weight reduction (-3.5 kg/m^2 of BMI) is an effective treatment for the majority of patients with mild OSA and that changes in AHI are strongly associated with changes in weight and waist circumference[28]. A recent randomized study demonstrated that, among a group of obese patients with OSA, the use of bariatric surgery compared with conventional weight loss therapy did not result in significantly greater reductions in AHI despite major differences in weight loss[29]. Our results correspond with the findings of these reports and further demonstrated that weight loss of only 3% over three months in a group of obese Japanese patients exhibiting successful weight reduction (-2.2 kg/m^2 of BMI) significantly reduced the AHI values by approximately 50%. In addition, in this study, a decrease in AHI achieved with weight reduction therapy was significantly correlated with decreases in BMI, waist circumference, the LDL-C level, the leptin level and CAVI and an increase in the adiponectin level. Furthermore, a multivariate regression analysis revealed that a decrease in BMI achieved with weight reduction therapy was the sole independent determinant of a reduction in AHI, findings that correspond to the results of a previous study[28]. Collectively, our results provide important evidence revealing that moderate weight loss via lifestyle modification can improve the severity of mild OSA, partly by improving dysregulation of adipocytokine production.

We previously reported that three months of weight reduction therapy significantly reduces several cardiovascular risks factors, such as the level of oxidized LDL, an atherogenic lipoprotein, and CAVI, an atherogenic index[6, 8]. In this study, we found that three months of weight reduction therapy significantly reduced both AHI and CAVI and that decreases in BMI and AHI only were significantly correlated with a reduction in CAVI, while a decrease in AHI was the sole independent factor associated with a decrease in CAVI in obese patients. Evidence has accumulated showing that OSA is closely associated with atherosclerosis and cardiovascular disease[19, 23, 26]. A prospective cohort study reported that long-term CPAP therapy significantly reduces the carotid artery intima-media thickness[30]. However, until recently, the effects of weight reduction achieved via lifestyle modification on the OSA status and atherosclerosis in obese patients have remained unknown, although weight reduction is essential for treating obesity-related complications[6, 8, 10]. Accordingly, this study is the first report to show that short-term weight reduction therapy using only diet and exercise contributes to reducing AHI and subsequently improving arterial stiffness. Our data, therefore, newly support the concept that improving the severity of OSA via weight loss largely contributes to decreasing arterial stiffness in obese patients.

Some limitations of this study merit consideration. First, we specifically focused on metabolic parameters and OSA; no cardiovascular end points were examined. Second, the use of polysomnography, along with a portable sleep apnea monitor, during hospitalization for OSA is preferable for examining the severity of OSA. Finally, the follow-up used in the weight reduction program was relatively short, and it is necessary to conduct long-term prospective cohort studies with larger sample sizes in order to clarify the long-term effectiveness of weight reduction therapy in treating cardiovascular disease.

In conclusion, this study revealed that the severity of OSA is significantly associated with cardiovascular risk factors, such as the severity of MetS and arterial stiffness, in obese patients. In addition, moderate weight loss, even that achieved via short-term weight reduction therapy, improves not only metabolic dysfunction, but also the severity of OSA, thus reciprocally helping to prevent atherosclerosis. Therefore, screening for OSA and monitoring the severity of the condition is extremely important for the early detection and prevention of cardiovascular disease in obese patients. In addition, even short-term, moderate weight loss achieved through lifestyle modification is very important for preventing atherosclerosis and cardiovascular disease in patients with obesity and MetS.

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Conflicts of Interest

None.

Disclosures

None.

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Supplemental Table 1

A. Baseline characteristics of the patients with and without MetS according to the criteria for metabolic syndrome proposed by the NCEP (Men)

	Non-MetS ($n=6$)	MetS ($n=18$)	p value
Age (years)	39.3 ± 4.4	49.2 ± 2.6	n.s.
BMI (kg/m^2)	31.5 ± 2.4	30.4 ± 1.0	n.s.
Waist circumference (cm)	102 ± 6.8	99.8 ± 2.0	n.s.
Systolic blood pressure (mmHg)	132 ± 4.0	141 ± 3.0	n.s.
Diastolic blood pressure (mmHg)	73.8 ± 3.4	87.7 ± 1.6	<0.01
Fasting plasma glucose (mmol/L)	5.2 ± 0.2	6.9 ± 0.5	n.s.
HbA1c (%)	5.8 ± 0.2	7.0 ± 0.3	n.s.
IRI (pmol/L)	84 ± 28	128 ± 22	n.s.
Triglyceride (mmol/L)	1.1 ± 0.2	2.0 ± 0.2	<0.05
HDL-C (mmol/L)	1.2 ± 0.1	1.3 ± 0.1	n.s.
LDL-C (mmol/L)	3.2 ± 0.3	3.1 ± 0.2	n.s.
Leptin (ng/mL)	7.6 ± 2.2	6.7 ± 0.7	n.s.
Adiponectin (μg/mL)	6.4 ± 1.1	4.8 ± 0.4	n.s.
CRP (μg/mL)	0.8 ± 0.3	1.0 ± 0.3	n.s.
CAVI	6.8 ± 0.3	8.4 ± 0.3	<0.01
AHI	14.2 ± 6.1	22.8 ± 3.6	n.s.
ODI	13.1 ± 4.4	14.7 ± 3.9	n.s.

The data are expressed as the mean ± SEM. IRI: immunoreactive insulin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CRP: high-sensitivity C-reactive protein.

B. Baseline characteristics of the patients with and without MetS according to the criteria for metabolic syndrome proposed by the NCEP (Women)

	Non-MetS ($n=8$)	MetS ($n=28$)	p value
Age (years)	51.0 ± 4.2	49.5 ± 2.7	n.s.
BMI (kg/m^2)	27.6 ± 0.9	31.8 ± 0.9	<0.05
Waist circumference (cm)	88.3 ± 2.0	99.1 ± 1.7	<0.01
Systolic blood pressure (mmHg)	137 ± 9.2	140 ± 3.0	n.s.
Diastolic blood pressure (mmHg)	85.4 ± 5.0	83.4 ± 1.8	n.s.
Fasting plasma glucose (mmol/L)	5.9 ± 0.7	7.0 ± 0.3	n.s.
HbA1c (%)	6.6 ± 0.4	7.1 ± 0.2	n.s.
IRI (pmol/L)	70.8 ± 22	121 ± 19	n.s.
Triglyceride (mmol/L)	1.1 ± 0.1	1.8 ± 0.1	<0.01
HDL-C (mmol/L)	1.6 ± 0.1	1.5 ± 0.1	n.s.
LDL-C (mmol/L)	3.1 ± 0.2	3.3 ± 0.1	n.s.
Leptin (ng/mL)	7.9 ± 1.7	11.7 ± 0.9	n.s.
Adiponectin (μg/mL)	6.9 ± 1.2	6.2 ± 0.6	n.s.
CRP (μg/mL)	0.8 ± 0.2	1.4 ± 0.3	n.s.
CAVI	7.9 ± 0.4	8.2 ± 0.3	n.s.
AHI	9.3 ± 2.6	25.3 ± 4.2	<0.05
ODI	4.2 ± 1.3	15.7 ± 3.2	<0.05

The abbreviations in this table are the same as those used in Supplemental Table IA.

Supplemental Table 2

A. Baseline correlations between AHI, ODI and CAVI and various parameters (Men)

	AHI[a]	ODI[a]	CAVI
	r	*r*	*r*
Age	0.385	0.236	0.729**
BMI	0.237	0.266	−0.160
Waist circumference	0.100	0.187	−0.041
Systolic blood pressure	0.079	−0.030	0.224
Diastolic blood pressure	0.117	0.037	0.196
Fasting plasma glucose	0.022	−0.014	0.206
HbA1c[a]	0.127	0.125	0.097
IRI[a]	−0.092	−0.165	0.414*
Total cholesterol	−0.122	−0.129	0.031
Triglyceride[a]	0.357	0.233	0.386
HDL-C	0.036	0.108	−0.057
LDL-C	−0.167	−0.249	0.088
Leptin	0.452*	0.380	0.192
Adiponectin	−0.304	−0.128	−0.206
CRP[a]	0.398*	0.311	0.071
CAVI	0.392*	0.120	−
AHI[a]	−	0.843**	0.392*
ODI[a]	0.843**	−	0.120

The abbreviations in this table are the same as those used in Supplemental Table IA. *r*: correlation coefficient. [a]Logarithmic transformation was performed because the variable had a skewed distribution. *$p<0.05$, **$p<0.01$.

B. Baseline correlations between AHI, ODI and CAVI and various parameters (Women)

	AHI[a]	ODI[a]	CAVI
	r	*r*	*r*
Age	0.163	0.122	0.634**
BMI	0.312	0.294	0.265
Waist circumference	0.469**	0.416*	0.069
Systolic blood pressure	0.098	0.098	0.376*
Diastolic blood pressure	0.159	0.127	0.214
Fasting plasma glucose	0.203	0.140	0.132
HbA1c[a]	0.058	0.020	0.142
IRI[a]	0.178	0.172	0.301
Total cholesterol	0.205	0.132	0.235
Triglyceride[a]	0.044	−0.030	0.178
HDL-C	−0.005	0.098	−0.021
LDL-C	0.183	0.056	0.305
Leptin	0.246	0.309	0.112
Adiponectin	0.073	0.148	0.242
CRP[a]	0.198	0.240	−0.103
CAVI	0.340*	0.300	−
AHI[a]	−	0.912**	0.340*
ODI[a]	0.912**	−	0.300

The abbreviations in this table are the same as those used in Supplemental Table IA. *r*: correlation coefficient. [a]Logarithmic transformation was performed because the variable had a skewed distribution. *$p<0.05$, **$p<0.01$.