Original Article

Coexistence of Visceral Fat Accumulation and Sleep-Disordered Breathing Correlates with Coronary Artery Disease

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Aim: Visceral adiposity is linked with sleep-disordered breathing (SDB) (called Syndrome Z), and both correlate with coronary artery disease (CAD). The aim of the present study was to determine the significance of excess visceral fat, SDB and circulating levels of biomarkers in CAD in Japanese men.

Methods: SDB, visceral fat area (VFA), and circulating levels of biomarkers were assessed in 60 Japanese male patients who underwent coronary angiography and overnight cardiorespiratory monitoring.

Results: Age-adjusted logistic analysis showed a significant relationship between CAD and diabetes, hypertension, dyslipidemia, SDB (AHI ≥ 5 events/hour), visceral fat accumulation (VFA ≥ 100 cm²), the combination of visceral fat accumulation and hypertension or dyslipidemia, as well as the combination of visceral fat accumulation and SDB. Patients with VFA ≥ 100 cm² and SDB had significantly lower serum adiponectin levels and higher serum soluble CD40 ligand levels than those with VFA < 100 cm² and SDB. The prevalence of CAD was significantly higher in patients with VFA ≥ 100 cm² and SDB than in patients with VFA < 100 cm² and AHI < 5 events/hour, patients with VFA < 100 cm² and AHI ≥ 5 events/hour or patients with VFA ≥ 100 cm² and AHI < 5 events/hour (93% versus 14%, $p < 0.001$, 53%, $p < 0.01$ or 63%, $p < 0.01$, respectively).

Conclusions: The present study indicates that patients with both visceral fat accumulation and SDB develop CAD in association with hypoadiponectinemia and inflammatory activity.

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Key words; Coronary artery disease, Visceral fat accumulation, Sleep-disordered breathing, Adiponectin

Introduction

Epidemiological studies have identified several independent risk factors for cardiovascular diseases (CVDs), including hypertension, dyslipidemia, diabetes, obesity and cigarette smoking¹. Lifestyle changes, such as overeating and physical inactivity, enhance the accumulation of intra-abdominal visceral fat. Insulin resistance, dyslipidemia, and hypertension based on visceral fat accumulation are common causes of atherosclerotic CVD². The combination of the latter is

recognized as metabolic syndrome³ or “Syndrome X”⁴. There is also a close link between metabolic syndrome based on visceral fat accumulation and sleep-disordered breathing (SDB), especially obstructive sleep apnea (OSA)⁵⁻⁷ (often referred to as “Syndrome Z”⁸). SDB also leads to increased CVD-related morbidity and mortality⁹⁻¹⁵.

Adipose tissue does not only act as an energy depot, but also has endocrine activity with the production of various bioactive substances, collectively known as adipocytokines¹⁶. Visceral fat accumulation results in dysregulated production of adipocytokines and increased systemic oxidative stress¹⁷. In a series of studies from our laboratories, we have recently demonstrated the dysregulated production of adiponectin in patients with severe OSA¹⁸, who also suffer from intra-abdominal obesity¹⁹. However, the associations between coronary artery disease (CAD) and excess vis-

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ceral fat, SDB, adipocytokines [adiponectin and plasminogen activator inhibitor-1 (PAI-1)], inflammatory markers, oxidative stress markers, and soluble CD40 ligand (sCD40L), which plays an important role in plaque destabilization²⁰, remain to be elucidated.

Aim

The aim of the present study was to clarify the relationship between CAD and clinical features including visceral fat, SDB and biomarkers.

Subjects and Methods

Participants

Subjects were recruited from outpatients who underwent multi-slice computed tomography (CT) coronary angiography for chest pain and then scheduled for invasive coronary angiography because of the suspicion of CAD by the results of CT coronary angiography at Kenporen Osaka Central Hospital between September 2009 and January 2012. The study subjects were 60 Japanese male patients who were admitted to the hospital for further examination of CAD and moreover underwent both fat computed tomography (CT) scan and overnight cardiorespiratory monitoring (Somté; Compumedics, Melbourne, Australia) for evaluating SDB as a cardiovascular risk. Shift workers and patients with acute coronary syndrome were excluded from the present study. This study [The Osaka University Visceral Fat Study (O-VFStudy)] is registered under number UMIN 000002997

<https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000003633&language=E>.

The Medical Ethics Committee of Osaka University and Kenporen Osaka Central Hospital approved the study. All participants were Japanese and each gave written informed consent.

Definition of CAD

CAD was finally confirmed by X-ray coronary angiography according to the standard procedures as follows: all coronary angiograms were evaluated by three experienced cardiologists. The presence of stenosis with coronary plaque was evaluated visually. Intracoronary lesion was identified as atherosclerotic stenosis of at least one segment of a major coronary artery and was considered a candidate for revascularization. Patients with intracoronary lesions were considered to have CAD.

Cardiorespiratory Monitoring

All participants underwent overnight cardiorespi-

ratory monitoring. The recorded signals [airflow, arterial oxygen saturation (SpO₂%), thoracic and abdominal wall movements] were analyzed for the number of apneas and hypopneas during sleep. The oxygen desaturation index (ODI), lowest SpO₂, baseline SpO₂, and time at desaturation <90% in minutes of total bed-time were measured for the entire night. Apnea was defined as cessation of airflow longer than 10 seconds. Hypopnea was defined as a decrease in airflow signal to <70% of the preceding level associated with >4% desaturation. Sleep apnea was categorized as obstructive, central, or mixed, into OSA, central sleep apnea (CSA), or mixed sleep apnea (MSA). OSA representing obstructive apneas were scored as the absence of airflow for ≥10 seconds but with the presence of thoracoabdominal movement (the amplitude of thoracic or abdominal efforts remained ≥15% of the baseline amplitude). CSA representing central apneas were scored in the absence of airflow for ≥10 seconds without thoracoabdominal movement (the amplitude of thoracic or abdominal efforts decreased to <15% of the baseline amplitude). MSA representing central apneas were scored in the absence of airflow for ≥10 seconds with an initial central component followed by an obstructive component. The apnea-hypopnea index (AHI) was defined as the total number of apneas/hypopneas per hour of recording time, according to the guidelines of the American Academy of Sleep Medicine Task Force^{21, 22}. An AHI ≥5 established the diagnosis of SDB. All recordings were scored manually by an experienced polysomnographer, and the duration of sleep was estimated using the self-reported sleep time and the recorded data, as we reported previously^{18, 19}.

Anthropometric Data and Laboratory Tests

Height and weight were measured in the standing position. Body mass index (BMI) was calculated using the formula [weight (kg)/height (m)²]. Waist circumference (WC) at the umbilical level was measured with a non-stretchable tape in late expiration while standing (in cm). After hospitalization, the visceral fat area (VFA) and subcutaneous fat area (SFA) were measured automatically using commercial software on CT scans taken at the umbilical level in a supine position [120 kV, 400 mAs, section thickness of 5-10 mm, field of view of 400 mm, window width of 800-1000 Hounsfield units (HU)], based on the Japanese guideline of obesity treatment (Japan Society for the Study of Obesity, in Japanese). Visceral fat accumulation measured by CT scan was defined as VFA ≥100 cm², according to the Japanese criteria²³.

Blood pressure was measured with a standard

mercury sphygmomanometer on the right arm after the patient had rested in a supine position for at least 10 minutes. Venous blood samples were collected for measurements of blood glucose, total cholesterol, triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C) after waking up while the subject was in a supine position. In each sleep study that included adiponectin monitoring, venous blood samples were obtained after overnight fasting (at ~7:00 AM) while the subject was in the supine position. For the purpose of the present study, serum and plasma samples that were obtained at baseline from each participant and stored at -80°C were thawed and assayed for serum high-sensitivity C-reactive protein (hs-CRP) (N-Latex CRP II; Dade Behring Inc., Marburg, Germany, intra-coefficients of variation (CV); 2.0%, inter-CV 2.3%, the extended measuring range [0.1–240 mg/L]), serum thiobarbituric acid reactive substances (TBARS) (Japan Institute for the Control of Aging, Nikken SEIL Co., Shizuoka, Japan, intra-CV; 3%, inter-CV 5%, range [0.001–10 $\mu\text{mol/L}$]), serum adiponectin (Otsuka Pharmaceutical Co., Tokushima, Japan, intra-CV; 3.0%, inter-CV 5.1%, range [0.375–12.0 mg/dL]), plasma total PAI-1 (LPIAtPAI test; Mitsubishi Kagaku Iatron, Tokyo, Japan, intra-CV; 3.2%, inter-CV 4.5%, range [20–155 $\mu\text{g/L}$]) and serum sCD40L levels (Quantikine Human Soluble CD40 Ligand Immunoassay, R&D Systems, Inc., Minneapolis, MN, intra-CV; 5%, inter-CV 6.2%, range [0.0625–4 $\mu\text{g/L}$]).

Smoking status was classified into current smokers, non-smokers and ex-smokers. Diabetes mellitus was defined according to the criteria of the World Health Organization and/or current treatment for diabetes mellitus (sulfonyl ureas/biguanides/ α -glucosidase inhibitors/insulin/thiazolidinedione; $n=16/10/10/5/7$). Dyslipidemia was defined as total cholesterol concentration of ≥ 220 mg/dL, TG concentration ≥ 150 mg/dL, HDL-C concentration < 40 mg/dL, and/or current treatment for dyslipidemia (statins/fibrates; $n=25/1$). Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current treatment for hypertension (calcium channel antagonists/angiotensin converting enzyme inhibitors/angiotensin receptor blockers/ β -blockers/diuretics; $n=25/0/26/6/7$). Patients with a previous diagnosis of dyslipidemia, hypertension, or diabetes mellitus and receiving drugs for any of these conditions were also included in this study. We also included subjects receiving anti-platelet drugs (aspirin/clopidogrel/cilostazol; $n=36/27/2$).

Statistical Analyses

All values are expressed as the mean $\pm$ SEM (range;

minimum-maximum). Relationships between two continuous variables were analyzed using scatter plots and Pearson's correlation coefficients. The correlations between CAD, SDB and other parameters were first analyzed by age-matched logistic regression analysis and then by multivariate analysis. Differences among groups were compared by one- or two-way analysis of variance (ANOVA) with Fisher's protected least significant difference test for multiple-group analysis or unpaired Student's *t*-test for experiments involving only two groups. The frequencies of each group were compared by the χ^2 test or Fisher's exact test. In all cases, $p < 0.05$ was considered significant. All statistical analyses were performed with StatView-J 5.0 software (Statistical Analysis System Inc., Cary, NC).

Results

Characteristics of Male Patients Hospitalized

The baseline characteristics of the 60 male patients are listed in **Table 1**. In the present study, 63% of the patients ($n=38/60$) had visceral fat accumulation (VFA ≥ 100 cm²)²² and 70% ($n=42/60$) of patients had CAD. The affected coronary artery was the left anterior descending (LAD) artery (21 lesions) in 19 patients, left circumflex (LCX) artery (14 lesions) in 12 patients and right coronary artery (RCA) (10 lesions) in 10 patients. Triple-vessel disease was identified in 16% (single/double/triple=19/16/9). All patients with CAD ($n=42$) underwent successful revascularization with percutaneous coronary intervention procedures, but not coronary artery bypass graft surgery. Based on the night-time recording, 45 patients (75%) were newly diagnosed with SDB (AHI ≥ 5 events/hour).

Relationship between CAD or SDB and Each Parameter

Age-adjusted simple logistic analysis was performed to evaluate the relationship between CAD or SDB, and each parameter is listed in **Table 2**. The analysis showed a significant relationship between age-adjusted CAD and diabetes, hypertension, dyslipidemia, SDB (AHI ≥ 5 events/hour), visceral fat accumulation (VFA ≥ 100 cm²), the combination of visceral fat accumulation and hypertension or dyslipidemia, as well as the combination of visceral fat accumulation and SDB. Age-adjusted SDB tended to be associated with decreased serum levels of adiponectin ($p=0.053$).

Table 1. Baseline characteristics of the subjects (male, $n=60$)

	Mean $\pm$ SEM (%)	range
Age (years)	66 $\pm$ 10	37-83
Body mass index (kg/m ²)	24.9 $\pm$ 3.3	17.1-32.5
Waist circumference (cm)	92 $\pm$ 9	73-121
Total fat area (cm ²)	262 $\pm$ 98	27-490
Visceral fat area (cm ²)	121 $\pm$ 56	16-277
Subcutaneous fat area (cm ²)	139 $\pm$ 54	12-329
Smoking (current-smoker)	(55)	
Diabetes mellitus	(37)	
Hypertension	(63)	
Dyslipidemia	(58)	
Coronary artery disease	(68)	
Past history		
Myocardial infarction	(15)	
Angina	(10)	
Family history of coronary artery disease	(10)	
Cardiorespiratory monitoring findings		
Baseline SpO ₂ (%)	96 $\pm$ 2	93-99
Lowest SpO ₂ (%)	83 $\pm$ 7	60-94
4% oxygen desaturation index (events/hour)	11 $\pm$ 1	0-50
% < 90% time	3 $\pm$ 7	0-42
Apnea-hypopnea index (events/hour)	16 $\pm$ 14	0-55
< 5	$n=15$ (18)	
≥ 5 to <15	$n=21$ (38)	
≥ 15 to <30	$n=16$ (29)	
≥ 30	$n=8$ (15)	
Serum adiponectin (μ g/mL)	7.9 $\pm$ 4.9	1.9-22.4
Plasma total plasminogen activator inhibitor-1 (ng/mL)	25.8 $\pm$ 13.8	11.0-75.0
Serum high sensitive C-reactive protein (mg/dL)	3.3 $\pm$ 6.9	0.0-48.6
Serum soluble CD40 ligand (pg/mL)	0.3 $\pm$ 0.2	0.0-1.1
Serum thiobarbituric acid-reacting substance (nmol/L)	6.1 $\pm$ 3.2	2.7-23.8

Characteristics of Patients with and without Visceral Fat Accumulation Stratified by SDB

Patients with both VFA ≥ 100 cm² and AHI ≥ 5 events/hour had higher BMI, higher VFA and SFA, and higher AHI than patients with VFA <100 cm² and AHI ≥ 5 events/hour and those with VFA ≥ 100 cm² and AHI <5 events/hour (**Table 3**); however, the prevalence of smoking, diabetes, hypertension and dyslipidemia was not significantly different among the four groups. Patients with VFA ≥ 100 cm² and AHI ≥ 5 events/hour had significantly lower serum adiponectin levels and higher serum sCD40L levels, and tended to have higher serum hs-CRP levels ($p=0.07$) than those with VFA <100 cm² and SDB (**Table 3**). On the other hand, there were no differences among the four groups with regard to the levels of plasma total PAI-1 and serum TBARS. The prevalence of CAD was significantly higher in patients with VFA

≥ 100 cm² and SDB than in patients with VFA <100 cm² and AHI <5 events/hour, patients with VFA <100 cm² and AHI ≥ 5 events/hour or patients with VFA ≥ 100 cm² and AHI <5 events/hour (93% versus 14%, $p<0.001$, 53%, $p<0.01$ or 63%, $p<0.01$, respectively, **Fig. 1**).

Discussion

The major findings of the present study were: 1) coexistence of visceral fat accumulation and SDB correlates with CAD, and 2) patients with coexistence of visceral fat accumulation and SDB had lower serum adiponectin levels, higher serum hs-CRP and sCD40L levels than those with VFA <100 cm² and/or SDB.

The potential mechanisms form a vicious cycle where SDB/OSA should enhance weight gain and visceral obesity should worsen OSA²⁴. It has been dem-

Table 2. Results of age-adjusted simple logistic analysis for coronary artery disease (CAD) and sleep-disordered breathing (SDB)

	With CAD		With SDB	
	<i>r</i> value	<i>p</i> value	<i>r</i> value	<i>p</i> value
Body mass index	0.25	0.196	0.31	0.102
Waist circumference	0.21	0.168	0.30	0.131
Visceral fat area (VFA)	0.22	0.089	0.12	0.802
Subcutaneous fat area	0.09	0.461	0.17	0.338
Apnea-hypopnea index (AHI)	0.41	0.010	–	–
Smoking (current-smoker)	0.26	0.060	0.24	0.564
Diabetes mellitus	0.31	0.040	0.27	0.259
Hypertension	0.35	0.027	0.24	0.555
Dyslipidemia	0.41	0.022	0.27	0.203
SDB (AHI ≥ 5 events/hour)	0.45	0.016	–	–
Visceral fat accumulation (VFA ≥ 100 cm ²)	0.41	0.001	0.12	0.473
Visceral fat accumulation + Diabetes mellitus	0.31	0.054	0.23	0.904
Visceral fat accumulation + Hypertension	0.34	0.009	0.24	0.626
Visceral fat accumulation + Dyslipidemia	0.41	0.013	0.26	0.275
Visceral fat accumulation + SDB	0.14	0.001	–	–
Serum adiponectin	–0.26	0.053	–0.30	0.081
Plasma total plasminogen activator inhibitor-1	0.12	0.572	0.22	0.547
Serum high sensitive C-reactive protein	0.15	0.468	0.27	0.371
Serum soluble CD40 ligand	0.33	0.501	0.18	0.256
Serum thiobarbituric acid-reacting substance	0.19	0.212	0.19	0.246

Significance was set at $p < 0.05$ (in bold).

onstrated that a rise in sCD40L reflects an increased risk of cardiovascular events in patients with unstable coronary artery disease²⁰. CRP is a nonspecific inflammatory marker and risk factor for atherosclerosis²⁵, and serum levels of CRP are associated with BMI in obese subjects and in patients with OSA²⁶. Repeated episodes of hypoxemia and re-oxygenation induced by SDB are reported to activate inflammatory cells, such as neutrophils and monocytes²⁷. In the present study, there was no significant relationship between VFA and AHI ($p=0.504$, data not shown). VFA correlated negatively with serum adiponectin levels ($p=0.007$, $r=-0.36$) and positively with serum hs-CRP levels ($p=0.041$, $r=0.28$), but not with serum sCD40L levels ($p=0.357$) (data not shown). There were also no significant relationships between AHI and serum adiponectin ($p=0.855$), sCD40L ($p=0.828$), and hs-CRP levels ($p=0.868$) (data not shown). However, the present study suggests that the coexistence of visceral fat accumulation and SDB may play at least some role in the development of CAD through hypoadiponectinemia, and high serum levels of hs-CRP and sCD40L (**Table 3**). Metabolic syndrome based on visceral fat accumulation and SDB/OSA, “Syndrome Z”⁸, may represent two sides of the same coin, given

the common pathophysiological processes evident in both conditions, such as insulin resistance, hypertension and dyslipidemia.

Conclusion

The results of the present study indicated that patients with both visceral fat accumulation and SDB develop CAD in association with hypoadiponectinemia and inflammatory activity. In such patients, amelioration of SDB and reduction of visceral fat seem important for the prevention of CAD events.

Study Limitations

The present study has several limitations. First, all patients in this study were Japanese men and any differences from other ethnicities are unknown. The numbers of Japanese females were very small and therefore were excluded from the present study. Second, there is bias in single center trials. Third, based upon 80% power to detect statistically significant differences ($p=0.05$; two-sided), a sample size of at least 25 patients in each group was required (total sample size=50). The number of patients may still be small

Table 3. Comparison of patients with and without excess visceral fat (cutoff visceral fat area (VFA); 100 cm²) and/or sleep-disordered breathing (SDB) (cutoff apnea-hypopnea index (AHI); 5 events/hour)

	VFA <100 cm ²		VFA ≥100 cm ²	
	SDB (-)	SDB (+)	SDB (-)	SDB (+)
Age (years)	53 ± 13	70 ± 7 [*]	69 ± 8 [*]	66 ± 9 [*]
Body mass index (kg/m ²)	23.4 ± 2.7	22.1 ± 2.5	24.7 ± 2.5 [¶]	27 ± 3 ^{*¶}
Visceral fat area (cm ²)	70 ± 43	62 ± 26	145 ± 43 ^{*¶}	152 ± 42 ^{*¶}
Subcutaneous fat area (cm ²)	105 ± 41	101 ± 41	141 ± 54	162 ± 50 ^{*¶}
Apnea-hypopnea index (events/hour)	2.4 ± 1.9	16.9 ± 13.8 [*]	3.7 ± 0.8 [¶]	22.6 ± 14.5 ^{*§}
Smoke (current)	1 (14%)	5 (53%)	8 (75%)	29 (73%)
Diabetes mellitus	0 (0%)	8 (53%)	3 (38%)	11 (37%)
Hypertension	2 (29%)	8 (53%)	6 (75%)	22 (73%)
Dyslipidemia	2 (29%)	8 (53%)	5 (63%)	20 (67%)
Serum adiponectin (μg/mL)	6.5 ± 0.8	12.5 ± 1.7 [*]	5.3 ± 1.0 [¶]	6.5 ± 0.5 [¶]
Plasma total plasminogen activator inhibitor-1 (ng/mL)	30.0 ± 9.1	24.1 ± 4.9	26.4 ± 4.2	25.7 ± 2.3
Serum high sensitive C-reactive protein (mg/dL)	2.1 ± 0.3	2.5 ± 1.1	2.2 ± 1.0	4.6 ± 1.7
Serum soluble CD40 ligand (pg/mL)	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
Serum thiobarbituric acid-reacting substance (nmol/L)	4.6 ± 0.7	6.9 ± 1.3	5.6 ± 0	6.0 ± 0.4 [¶]

Data are the mean ± SEM or percentage (%) of patients.

^{*}*p* < 0.01, compared to without both visceral fat accumulation and SDB

[¶]*p* < 0.01, [†]*p* < 0.001, compared to without visceral fat accumulation and with SDB

[§]*p* < 0.01, compared to with visceral fat accumulation and without SDB

and further investigations might be required to confirm the present results. Fourth, we used conventional overnight cardiorespiratory monitoring to assess SDB without electroencephalography. The duration of sleep by self-reported sleep time and the recorded data might overestimate the real sleeping time based on the electroencephalogram and thus underestimate AHI. Although polysomnography is required to assess sleep duration and structure and is currently considered the 'gold standard' method for the diagnosis of OSA whether attended or not, the time spent on analysis and interpretation of the recorded data by technical and medical staff means it may not be the most cost-effective or convenient method for the assessment of SDB in a large number of patients who present with CAD and require secondary prevention of adverse outcomes in this urgent setting. Finally, CSA (some OSA also) is known to be strongly influenced by cardiac function and diastolic function as well as systolic function. All the study subjects including previous myocardial subjects (*n* = 15, **Table 1**) did not undergo cardiac function marker measurement, i.e. left ventricular ejection fraction, diastolic parameters, and plasma B-type natriuretic peptide. Further studies are required.

Authors' Contributions

Y.N. and K.K. recruited the patients, collected

Fig. 1. Prevalence of coronary artery disease in patients with and without visceral fat accumulation (visceral fat area (VFA) cutoff value; 100 cm²) stratified by sleep-disordered breathing (SDB) (apnea-hypopnea index cutoff; 5 events/hour).

The frequencies were compared by exact test (extended).

and analyzed the data, and wrote the manuscript. K.K. also participated in the concept and design of the study, interpretation of data and reviewed/edited the manuscript. K.Y. recruited and examined the patients. T.F. and I.S. contributed to the discussion and wrote the manuscript. All authors read and approved the final version of the manuscript.

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Declaration

Ken Kishida and Tohru Funahashi are members of the "Department of Metabolism and Atherosclerosis," a sponsored course endowed by Kowa Co. Ltd. and a company researcher is dispatched to the course. All other authors declare no competing interests.

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