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ORIGINAL ARTICLE

Involvement of oxidative stress in atherosclerosis development in subjects with sarcopenic obesity

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Summary

Introduction

Co-existing decreased muscle mass and increased visceral fat, an age-associated change called sarcopenic obesity, results in fragility and cardiovascular disease. To assess the pathogenesis of sarcopenic obesity, we assessed the associations of clinical parameters with psoas muscle mass in elderly male subjects with obesity and type 2 diabetes.

Methods

The subjects were 55 patients, over 65 years of age and with a visceral fat area exceeding 100 cm^2, with type 2 diabetes. The cross-sectional area of the psoas muscle is considered to provide an estimation of overall muscle mass. Sarcopenia was considered to be present when the total psoas muscle area was low, defined as a value below 500 mm^2 m^{-2} on a computed tomographic scan.

Results

The maximum intima-media thickness (max IMT) and urinary 8-isoprostane values were significantly higher in the sarcopenic group. Multiple linear regression analysis revealed max IMT to be an independent variable related to muscle mass decline. In addition, logistic analysis showed max IMT and urinary 8-isoprostane to be variables independently contributing to total psoas muscle area $<$500 mm^2 m^{-2}.

Conclusion

Worsening surrogate markers for systemic oxidative stress and atherosclerosis were associated with declining muscle mass in elderly subjects with obesity and type 2 diabetes. These results indicate that systemic oxidative stress is among the mechanisms underlying atherosclerosis development in subjects with sarcopenic obesity.

Keywords: Atherosclerosis, obesity, oxidative stress, sarcopenia.

Introduction

Sarcopenia is a qualitative and quantitative change in skeletal muscle, leading to physiological impairment (1). As the ageing of society progresses, sarcopenia-induced disability in elderly people is becoming an ever larger concern. Because skeletal muscle quality and mass are closely associated with glucose uptake function, sarcopenia often co-exists with skeletal muscle insulin resistance, resulting in the development of type 2 diabetes (2). In general, sarcopenia is defined as the loss of muscle mass and strength, but the usefulness of measuring core muscle mass by abdominal computed tomography (CT) in estimating the degree of sarcopenia is examined by recent several studies (3). Especially, cross-sectional area of psoas muscle area is thought to give a good measure of overall muscle mass (4).

On the other hand, rising proportions of people with obesity, which causes diabetes and other metabolic disorders, are a worldwide problem (5). While the grade

of obesity is obviously mild in East Asian populations as compared with that in Western countries, the body mass index (BMI) of the elderly Japanese population has been rising with each passing decade (6). In addition, Japanese subjects have a higher visceral fat area relative to abdominal subcutaneous fat area than Caucasians (7), which partially accounts for their greater predisposition to type 2 diabetes despite having only mild BMI elevation (8). Because subjects with diabetes are thought to be extremely vulnerable to impairments associated with senescence, such as atherosclerosis, bone fracture and cognitive dysfunction (9), optimally managing diabetes in the elderly population has become a major concern in Japan as this nation faces the consequences of a super-ageing society.

Ageing-associated changes in body composition, particularly the co-existence of decreased muscle mass and increased visceral fat, is called sarcopenic obesity, and results in the development of fragility and cardiovascular disease (CVD) (10). The co-existence of ageing-related risk factors, including sarcopenia, visceral obesity and diabetes, markedly accelerates multiple disorders, most notably atherosclerosis (11). In subjects with sarcopenic obesity, the incidence of cardiovascular events and all-cause mortality were significantly higher than in the non-obese, non-sarcopenic group (12,13). In a general population study of 3,366 subjects with 8 years of follow-up, the risk of CVD was not significantly increased in the sarcopenic or the obese group, but a 23% increase was noted in the group with sarcopenic obesity (14). In contrast, postmenopausal women with low muscle mass and obesity tended to have high concentrations of high-density lipoprotein cholesterol, suggesting a low risk of coronary heart disease (15). While the management of multiple geriatric disorders is regarded as a critical issue, the pathogenesis of sarcopenic obesity-related atherosclerosis remains unclear (16). Therefore, to assess the additive effects of low muscle mass on visceral fat accumulation, we examined the associations of clinical parameters, including surrogate markers of atherosclerosis, with psoas muscle mass in elderly subjects with obesity and type 2 diabetes. In particular, we hypothesized that systemic oxidative stress would play an important role in the pathophysiological mechanism of sarcopenic obesity.

Material and methods

The study subjects were males with type 2 diabetes who visited Iwate Medical University Hospital during the period from November 2011 to May 2015. Fifty-five subjects over 65 years of age, whose visceral fat area exceeded 100 cm^2 quantitated by CT (Aquilion 64 ONE: Toshiba Medical, Japan), were enrolled in this study. The study protocol was approved by the Institutional Review Board of Iwate Medical University (approval number: H27-19).

Muscle mass was estimated by measuring the cross-sectional area of the psoas muscle at the level of third lumbar vertebra on CT images (17). The cross-sectional area of the psoas muscle was reported to show a high correlation with total body skeletal muscle mass (18). Therefore, evaluation of psoas muscle area has been employed in a number of studies as a predictor of lean muscle mass (3,4). The outline of the psoas muscle was traced on cross-sectional CT image by single operator. Quantitative analyses of abdominal CT images were performed using the IMAGEJ processing system available from the National Institutes of Health. The sum of both psoas muscle areas was corrected according to the squared of height of the subject, then expressed as the total psoas area (TPA; $mm^2\ m^{-2}$). A TPA value below 500 $mm^2\ m^{-2}$ was defined as sarcopenia (19).

Laboratory values were measured employing routine techniques on blood and urine samples obtained after a 12-h overnight fast. Oxidative stress markers, such as urinary 8-isoprostane and 8-hydroxydeoxyguanosine (8-OHdG) and serum malondialdehyde-LDL cholesterol (MDA-LDL-C), were measured by SRL, Inc. (Tokyo, Japan). Hepatic steatosis was defined as a liver to spleen density ratio below 0.9, based on plain abdominal CT (20).

Quantitative data are presented as means ± standard deviation with the level of significance set at $p < 0.05$. Comparisons between the subjects with TPA ≥500 and TPA <500 were performed employing the Mann–Whitney *U*-test and the chi-squared test. Multiple linear regression analyses were performed to evaluate parameters independently showing significant correlations with TPA and maximum intima-media thickness (max IMT). Multivariate logistic analyses were performed to investigate factors potentially contributing to sarcopenic obesity. All statistical analyses were carried out using SPSS version 21 (SPSS Japan Inc., Tokyo, Japan).

Results

The clinical characteristics of the enrolled subjects are shown in Table 1. Mean age was 72 years, and the mean visceral fat area value was 185 cm^2, with visceral obesity being diagnosed based on the Japanese criterion of a visceral fat area over 100 cm^2.

Comparisons of clinical characteristics between sarcopenia and non-sarcopenia, categorized according to a TPA cut-off point of 500 $mm^2\ m^{-2}$, are shown in Table 2. The number of subjects defined as having sarcopenic obesity was 19, accounting for 35% of the

Table 1 Clinical characteristics of subjects

Characteristics	Mean ± SD (median, range)
Number	55
Age (years)	72 ± 5 (74, 65–80)
Height (m)	1.62 ± 0.48 (1.62, 1.45–1.72)
Weight (kg)	66.7 ± 8.3 (63.6, 55.7–90.8)
Body mass index (kg m^{-2})	25.4 ± 3.1 (24.5, 19.9–32.8)
Waist (cm)	92.5 ± 8.5 (91.0, 79.0–114.0)
Visceral fat area (cm^2)	185.3 ± 54.3 (175.9, 105.0–333.8)
TPA, without correction (mm^2)	1,469.4 ± 356.0 (1,426.7, 837.1–2,202.8)
TPA, corrected for height (mm^2 m^{-2})	560.6 ± 140.1 (530.7, 334.5–849.8)
Systolic blood pressure (mmHg)	128.4 ± 19.8 (130.0, 81–167)
Diastolic blood pressure (mmHg)	72.2 ± 10.9 (74.0, 45–90)
Total cholesterol (mg dL^{-1})	179.8 ± 34.9 (177.0, 107–257)
Triglyceride (mg dL^{-1})	131.1 ± 60.2 (112.0, 44–340)
LDL cholesterol (mg dL^{-1})	113.4 ± 30.4 (111.0, 60–202)
HDL cholesterol (mg dL^{-1})	42.6 ± 9.3 (111.0, 26–67)
Diabetes duration (years)	14.2 ± 11.1 (13.0, 1–35)
Fasting blood glucose (mg dL^{-1})	160.9 ± 51.7 (145.0, 80–319)
Insulin (μU mL^{-1})	8.5 ± 11.3 (6.5, 03–81.4)
HbA1c (%)	9.5 ± 1.9 (9.3, 6.3–15.9)
HOMA-IR	3.1 ± 3.0 (2.8, 0.09–19.9)
Liver/spleen ratio	1.2 ± 0.2 (1.2, 0.63–1.64)
max IMT (mm)	2.3 ± 0.8 (2.6, 0.70–4.45)
MDA-LDL-C (U dL^{-1})	139.3 ± 48.8 (131.0, 72–318)
Urinary 8-isoprostane (pg mg^{-1} Cr)	184.7 ± 81.0 (172.0, 56–393)
Urinary 8-OHdG (ng mg^{-1} Cr)	10.3 ± 4.9 (9.2, 2.4–32.2)
History of smoking *n* (%)	39 (71)
Hypertension *n* (%)	39 (71)
Dyslipidemia *n* (%)	29 (53)
History of CVD *n* (%)	11 (20)
History of CHD *n* (%)	14 (26)
Hepatic steatosis *n* (%)	4 (7)

BH, body height; CHD, coronary heart disease; CVD, cerebrovascular disease; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; max IMT, maximum intima-media thickness; MDA-LDL-C, malondialdehyde-LDL; 8-OHdG, 8-hydroxydeoxyguanosine; SD, standard deviation; TPA, total psoas area.

elderly male subjects in this study with visceral obesity and type 2 diabetes. Muscle mass was associated with weight as well as BMI, even after adjustment for height. The visceral fat area values were significantly higher in the non-sarcopenic group (TPA ≥500, 196.8 ± 55.7 cm^2 vs. TPA <500, 163.3 ± 45.0 cm^2, $p = 0.027$). While the degree of obesity was severe in the non-sarcopenic group, several parameters related to insulin resistance, such as serum insulin level and homeostasis model assessment insulin resistance (HOMA-IR), did not differ significantly between these two groups. Interestingly, the liver to spleen density ratio on plain CT was significantly lower, suggesting hepatic steatosis, in the non-sarcopenic group (TPA ≥500, 1.15 ± 0.2 vs. TPA <500, 1.3 ± 0.2, $p = 0.018$).

The max IMT, widely employed as a surrogate marker of atherosclerosis, was greater in the sarcopenic group (TPA ≥500, 2.1 ± 0.7 mm vs. TPA <500, 2.7 ± 0.9 mm, $p = 0.017$), as shown in Figure 1a. In addition, urinary 8-isoprostane, a biomarker of systemic oxidative stress, was also significantly higher in the sarcopenic group (TPA ≥500, 165.2 ± 73.5 pg mg^{-1} Cr vs. TPA <500, 221.7 ± 83.7 pg mg^{-1} Cr, $p = 0.010$), as shown in Figure 1b, although other oxidative stress markers, such as urine 8-OHdG and MDA-LDL did not differ between the two groups.

Next, to identify variables independently affecting psoas muscle mass in elderly obese subjects, we performed multiple linear regression analysis for clinical parameters, such as age, visceral fat area, diabetes

Table 2 Comparison of variables between subjects with TPA ≥500 and TPA <500

Variables	TPA ≥500 (mean ± SD)	TPA2 <500 (mean ± SD)	*p*
Number	36	19	
Age (years)	72 ± 5.0	73 ± 4.6	0.790
Height (m)	1.62 ± 0.04	1.63 ± 0.06	0.292
Weight (kg)	68.2 ± 8.4	64.0 ± 7.6	0.048
Body mass index (kg m^{-2})	26.1 ± 3.0	24.1 ± 3.0	0.017
Waist (cm)	93.6 ± 8.8	90.4 ± 7.6	0.154
Visceral fat area (cm^2)	196.8 ± 55.7	163.3 ± 45.0	0.027
TPA, without correction (mm^2)	1,658.7 ± 277.7	1,110.7 ± 150.6	<0.0001
TPA, corrected for height (mm^2 m^{-2})	636.1 ± 109.5	417.5 ± 50.7	<0.0001
Systolic blood pressure (mmHg)	128.0 ± 20.3	129.1 ± 19.4	0.846
Diastolic blood pressure (mmHg)	72.8 ± 11.9	71.0 ± 9.1	0.343
Total cholesterol (mg dL^{-1})	180.6 ± 35.0	178.4 ± 35.7	0.826
Triglyceride (mg dL^{-1})	137.4 ± 65.7	119.1 ± 47.1	0.321
LDL cholesterol (mg dL^{-1})	113.6 ± 31.9	112.9 ± 28.1	0.932
HDL cholesterol (mg dL^{-1})	41.4 ± 8.2	44.8 ± 10.9	0.205
Diabetes duration (years)	14.4 ± 12.3	13.7 ± 8.7	0.986
Fasting blood glucose (mg dL^{-1})	163.0 ± 53.5	156.8 ± 49.3	0.675
Insulin (μU mL^{-1})	9.9 ± 13.6	5.9 ± 3.0	0.219
HbA1c (%)	9.4 ± 1.9	9.8 ± 2.0	0.400
HOMA-IR	3.5 ± 3.6	2.3 ± 1.3	0.159
Liver/spleen ratio	1.15 ± 0.2	1.3 ± 0.2	0.018
max IMT (mm)	2.1 ± 0.7	2.7 ± 0.9	0.017
MDA-LDL-C (U dL^{-1})	142.6 ± 55.2	132.9 ± 34.1	0.839
Urinary 8-isoprostane (pg mg^{-1} Cr)	165.2 ± 73.5	221.7 ± 83.7	0.010
Urinary 8-OHdG (ng mg^{-1} Cr)	9.8 ± 3.5	11.4 ± 6.9	0.553
History of smoking *n* (%)	24 (67%)	15 (79%)	0.340
Hypertension *n* (%)	24 (67%)	15 (79%)	0.340
Dyslipidemia *n* (%)	19 (53%)	10 (53%)	0.992
History of CVD *n* (%)	7 (19%)	4 (21%)	0.575
History of CHD *n* (%)	10 (28%)	4 (21%)	0.420
Hepatic steatosis *n* (%)	3 (8%)	1 (5%)	0.570

t-test, Mann–Whitney *U*-test and chi-squared test.

BH, body height; CHD, coronary heart disease; CVD, cerebrovascular disease; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; max IMT, maximum intima-media thickness; MDA-LDL-C, malondialdehyde-LDL; 8-OHdG, 8-hydroxydeoxyguanosine; SD, standard deviation; TPA, total psoas area.

duration, max IMT, urinary 8-isoprostane and hepatic steatosis. Intriguingly, this analysis revealed max IMT to be negatively (β = −0.339, p = 0.010), while visceral fat area (β = 0.314, p = 0.015) and diabetes duration (β = 0.261, p = 0.045) were both positively, related independently to muscle mass decline (Table 3). Conversely, multiple linear regression analysis revealed TPA to be independently related to max IMT (β = 0.319, p = 0.010) as shown in Table 4.

The multivariate logistic regression analysis results for sarcopenic obesity are shown in Table 5. In both model 1 (adjusted for age, diabetes duration, max IMT and urinary 8-isoprostane) and model 2 (adjusted for the variables in model 1 + systolic blood pressure, LDL-C and hepatic steatosis), max IMT (β = 0.926, p = 0.036) and urinary 8-isoprostane (β = 0.009, p = 0.034) were found to contribute independently to TPA <500 mm^2 m^{-2} in elderly subjects with type 2 diabetes and visceral obesity.

Discussion

The present study demonstrated max IMT and urinary 8-isoprostane to be significantly elevated in elderly Japanese men with diabetes and sarcopenic obesity. These factors contributed independently to low psoas muscle mass, even after correction for other confounding variables related to metabolic disorders and atherosclerosis. To our knowledge, this is the first report to show the relationship between sarcopenic obesity and systemic oxidative stress.

Excessive weight and height might exert an increased mechanical load and thereby stimulate a higher accrual

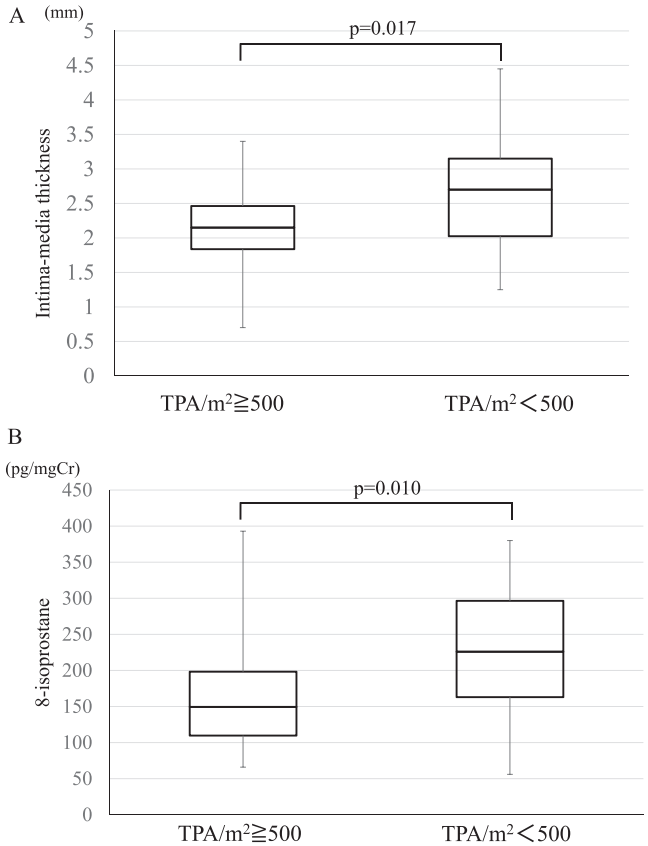

Figure 1 Box plot of maximum intima-media thickness (a) and urinary 8-isoprostane (b). TPA, total psoas area.

Table 3 Multiple regression analysis for TPA per m^2

Variable Dependent	Independent	β	*p*
TPA per m^2	max IMT	−0.339	0.010
	Visceral fat area	0.314	0.015
	Diabetes duration	0.261	0.045

Adjusted for age, visceral fat area, diabetes duration, max IMT, urinary 8-isoprostane and hepatic steatosis.
max IMT, maximum intima-media thickness; TPA, total psoas area.

Table 4 Multiple regression analysis for max IMT

Variable Dependent	Independent	β	*p*
max IMT	ABI	−0.354	0.004
	TPA	0.319	0.010
	Diabetes duration	0.283	0.020

Adjusted for systolic blood pressure, visceral fat area and 8-OHdG.
ABI, ankle brachial index; max IMT, maximum intima-media thickness; TPA, total psoas area.

Table 5 Logistic regression analysis for sarcopenic obesity

	Model 1		Model 2	
	β	*p*	β	*p*
Age	−0.10	0.881	−0.016	0.831
Diabetes duration	−0.39	0.222	−0.039	0.232
max IMT	0.877	0.045	0.926	0.036
Urinary 8-isoprostane	0.009	0.031	0.009	0.034
Systolic blood pressure			0.010	0.580
LDL cholesterol			0.004	0.734
Hepatic steatosis			−0.721	0.662

Model 1, dependent variables: age, diabetes duration, max IMT and urinary 8-isoprostane.
Model 2, dependent variables: model 1 + systolic blood pressure, LDL-C and hepatic steatosis.
LDL-C, low-density lipoprotein cholesterol; max IMT, maximum intima-media thickness.

of muscle mass, as indicated by the correlations of muscle mass with weight and height (21). Therefore, the muscle mass value was adjusted for the parameters of body size, usually corrected with height, in most prior

studies of sarcopenia (22). On the other hand, to evaluate the effect of obesity accurately, we calculated visceral fat areas employing abdominal cross-sectional images obtained by CT scan. Even after adjustment for the squared value of the subject's height, our study subjects, when limited to those having visceral obesity, showed positive associations of obesity-related parameters with TPA. Although the combination of low muscle mass and obesity was reported to exacerbate insulin resistance (23), we detected no differences in these parameters in relation to insulin resistance in the present study. This result is partially consistent with those of previous studies, which showed a diminished association between insulin resistance and sarcopenic obesity in subjects over 60 years of age (24).

Several studies have used atherosclerotic surrogate markers for evaluating whether sarcopenic obesity increases the CVD risk. Kato *et al*. reported that visceral fat accumulation and femoral muscle decline, as comorbidities, were associated with increased carotid IMT in subjects with end stage renal disease (25). In addition, a relationship between sarcopenic obesity and incremental increases in pulse wave velocity was reported in Japanese subjects (26). To our knowledge, this is the first study to focus on the association of sarcopenic obesity with an atherosclerotic surrogate marker, max IMT, exclusively in subjects with type 2 diabetes.

A few studies have investigated the mechanisms underlying the vicious cycle linking sarcopenic obesity and exacerbation of CVD risk. Generally, a reduced muscle mass results in lower total energy expenditure, leading to the development of visceral obesity. Meanwhile, visceral fat accumulation, accompanied by macrophage infiltration, induces mild chronic inflammation, resulting in an adipocytokine imbalance. Rising levels of inflammatory cytokines, such as tumour necrosis factor-α and interleukin-6, impact skeletal muscle negatively via catabolic effects (27). On the other hand, muscle mass decline potentially diminish myokine secretions, thereby possibly deteriorating inflammation and insulin resistance (28). Combinations of these alterations in humoral factors might induce or increase oxidative stress (27). In addition, oxidative stress triggers mitochondrial DNA damage, resulting in myocyte apoptosis and muscle volume decline (29). Oxidative stress is widely recognized as the key pathway in vascular endothelial damage, leading to the development of atherosclerosis (30). Taking these findings together, it is clear that oxidative stress may well form the common basis for muscle mass decline-induced and visceral fat accumulation-induced metabolic disorders and atherosclerosis development. To our knowledge, this is the first report to directly demonstrate the relationships among sarcopenic obesity, surrogate markers of atherosclerosis and clinical measurements of systemic oxidative stress.

This study showed the atherosclerosis screening test for elderly subjects with obesity and type 2 diabetes to have important clinical implications. Oxidative stress is widely regarded as being the common basis for muscle mass decline-induced and visceral fat accumulation-induced metabolic disorders as well as the development of atherosclerosis. Our study provides novel evidence indicating that systemic oxidative stress appears to be one of the mechanisms underlying atherosclerosis development in subjects with sarcopenic obesity.

The major limitation of this study is its cross-sectional design, raising the possibility that our results show only associations. Therefore, the relationships among sarcopenic obesity, oxidative stress and atherosclerosis cannot be confirmed. Second, sarcopenia status was classified based only on muscle mass. It is recommended that evaluation of sarcopenia be based on measurements of muscle mass and muscle strength. Further studies are needed to elucidate the pathogenesis of sarcopenic obesity in elderly Japanese subjects with diabetes.

In conclusion, worsening values of surrogate markers for systemic oxidative stress and atherosclerosis were associated with declining muscle mass, independently of the confounding variables known to be related to metabolic disorders, in elderly subjects with obesity and type 2 diabetes. These findings provide new insights into the vicious cycle of sarcopenic obesity, metabolic disorders, and atherosclerosis.

Conflicts of Interest Statement

The authors have no conflict of interest to declare.

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R. N. recruited patients, researched data and wrote the manuscript; N. T. conducted statistical analysis and reviewed and edited the manuscripts; M. O., M. H., R. N., S. Y., T. M., K. N. and Y. T. recruited patients and contributed to discussion; J. S. contributed to discussion and reviewed the manuscripts; and Y. I. managed study design, contributed to discussion and reviewed the manuscript.

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