Gerontology & Geriatric Medicine
Volume 9: 1–5

DOI: 10.1177/23337214231179847
journals.sagepub.com/home/ggm
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Influence of Metabolic Syndrome on Small, Dense LDL, and Subclinical Atherosclerosis in Older Subjects

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Abstract

Aging is known as one of the important risk factors for coronary artery disease (CAD). We explore whether an association of metabolic syndrome (Met-*S*) increases subclinical atherosclerosis among elderly diabetic subjects estimating the plaque score (*PS*) of the carotid artery. A total of 187 subjects were enrolled. Middle-aged and older groups were divided into two groups. *T*-test and Chi-square test were also employed. Simple regression analysis for the *PS* was performed with respective risk factors as independent variables. After selection of independent variables, multiple regression analysis was performed to estimated the association of *PS* and dependent variable of the study. There were significant differences in body mass index (BMI) ($p < .001$), HbA1c ($p < .01$), TG ($p < .05$), and PS ($p < .001$) . Multiple regression analysis in middle-aged subjects showed that the determinant of *PS* were age ($p < .001$), BMI ($p = .006$), Met-*S* ($p = .004$), and hs-CRP ($p = .019$). Multiple regression analysis in older subjects showed that neither age nor Met-*S* was included as significant determinant of *PS*. An association of Met-*S* is an important factor for progression of subclinical atherosclerosis, but it cannot be a significant determinant of *PS* if the subjects are limited within older group.

Keywords

metabolic syndrome, older, plaque score, subclinical atherosclerosis, type 2 diabetes

Manuscript received: April 2, 2023; **final revision received:** May 8, 2023; **accepted:** May 16, 2023.

Introduction

The definition and diagnostic criteria for metabolic syndrome (Met-*S*) in Japan were established in April 2005 (Nippon Naikagakkai, 2005). Japanese criteria are based on the following inclusion criteria: (a) Waist circumference ≧85 cm for men and ≧90 cm for women are essential conditions, plus two or more of the following three criteria: (b) Fasting blood glucose ≧110 mg/dL or taking diabetes medication; (c) Triglyceride ≧150 mg/dL mmol/L or HDL-C < 40 mg/dL or taking lipid-lowering medication: and (d) Systolic blood pressure ≧130 mmHg or Diastolic blood pressure ≧85 mmHg or taking hypertension drugs (Nippon Naikagakkai, 2005).

It is now well-known that the presence of Met-*S* is associated with increased coronary artery disease (CAD) events and cardiovascular mortality (Gui et al., 2017; Mottillo et al., 2010; Ninomiya et al., 2007). Met-*S* is also reported to be a predictor of subclinical atherosclerosis. Also, the purpose of diagnosis and intervention for Met-*S* is not only early detection of subclinical atherosclerosis but also the prevention of development of type 2 diabetes mellitus. Patients with diabetes mellitus are at increased risk for CAD (Singh et al., 2013; Turner et al., 1998). Therefore, if patients with Met-*S* develop type 2 diabetes mellitus, their risk for CAD may further increase. Indeed, our previous observation revealed that the metabolic syndrome subjects with type 2 diabetes mellitus, are at a further elevated risk for CAD than the non-metabolic syndrome subjects with type 2 diabetes mellitus (Nakano et al., 2010).

Small, dense LDL cholesterol (sLDL-*C*) has been demonstrated to be a residual risk factor for the development of CAD in Western countries as well as in Japan (Duran et al., 2020; Koba et al., 2002). LDL size is usually measured by gradient gel electrophoresis using polyacrylamide gel (Krauss & Burke, 1982). This

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Table 1. Characteristics of Subjects.

	Middle-aged $n = 122$	Older $n = 65$
Age (year)	49.5 ± 10.8*	71.5 ± 5.9*
Gender (M/F)	85/37	37/28
BMI	27.6 ± 5.9*	23.4 ± 3.4*
DM (*n*)	88 (72.1%)	47 (72.3%)
HT (*n*)	56 (45.9%)	35 (53.8%)
DL (*n*)	82 (67.2%)	51 (78.5%)
Met-*S* (*n*)	63 (51.6%)	32 (49.2%)
HbA1c (%)	7.1 ± 2.0**($n = 106$)	6.4 ± 1.1**($n = 62$)
LDL-*C* (mg/dl)	137.6 ± 35.4	130.8 ± 38.9
TG (mg/dl)	175.5 ± 151.8***	133.1 ± 73.2***
HDL-*C* (mg/dl)	49.8 ± 13.1	52.3 ± 14.2
sLDL-*C* (mg/dl)	47.9 ± 22.4	47.6 ± 24.8
hs CRP(mg/dl)	0.14 ± 0.11	0.17 ± 0.10
PS	4.47 ± 5.1*	8.25 ± 5.6*

BMI: Body mass index, DM: Diabetes Mellitus, HT: Hypertension, DL: Dyslipidemia.
Met-*S*: Metabolic syndrome, LDL-*C*: fasting low-density lipoprotein cholesterol, TG: fasting triglyceride, HDL-*C*: fasting high-density lipoprotein cholesterol, sLDL-*C*: small, dense cholesterol, hs CRP: high sensitivity *C*-reactive protein, PS: plaque score.
Data are expressed as mean ± *SD* *,**,***:significantly different between the groups.
*$p < .001$. ** $p < .01$. ***$p < .05$.

standard assay procedure requires long assay time and high cost. Meanwhile, Hirano et al. developed a simple and rapid assay system for the measurement of concentration of sLDL-*C* using heparin-magnesium precipitation and direct LDL assay (Hirano et al., 2003).

On the other hand, aging itself is known as one of the important risk factors for CAD. Our previous observation revealed that older diabetic subjects had increased sLDL-*C* even if their LDL-cholesterol is not elevated (Yoshino et al., 2015). Also, we have reported that the Met-*S* subjects with type 2 diabetes mellitus, are at a further elevated risk for CAD compared to non-metabolic syndrome subjects with type 2 diabetes mellitus (Nakano et al., 2010).

Using data, we continued to explore whether the CAD risk of the older patients with Met-*S* who develop type 2 diabetes mellitus increases more than that of older type 2 diabetic subjects without Met-*S* estimating plasma high sensitivity *C*-reactive protein (hs-CRP), sLDL-*C*, and plaque score of the carotid artery (*PS*).

Methods

Study Design

The present study is a cross-sectional study.

Participants

A total of 187 subjects including 85 middle-aged and 37 older male and 37 middle-aged and 28 older females, ranging from 30 to 80 years-old, were recruited from individuals visiting Toho University Medical Center Ohmori Hospital or participating in a local health check program at several private companies.

Evaluation

Age, gender, body mass index (BMI), type 2 diabetes mellitus (*DM*), hypertension (*HT*), dyslipidemia (*DL*), metabolic syndrome, hemoglobin A1c (HbA1c), fasting low-density lipoprotein cholesterol (LDL-*C*), fasting triglyceride (*TG*), fasting high-density lipoprotein cholesterol (HDL-*C*), sLDL-*C*, hs-CRP, *PS* were investigated. Kawai et al. reported that PS predicted the onset of stroke more accurately than the mean intima Media Thickness (IMT) (Kawai et al., 2013). Therefore, *PS* was introduced in the present study.

The subjects who had hepatic, renal, or thyroid diseases were excluded by routine serum biochemical analysis. Fibrate- and statin-users were also excluded. Two age groups were divided according to their age (above and below 65 years). The presence of Met-*S* was diagnosed according to the Japanese Guidelines for the Definition of Metabolic Syndrome (Nippon Naikagakkai, 2005). The diagnosis of diabetes mellitus was based on a fasting plasma glucose level of ≧126 mg/dL, a random plasma glucose level of ≧200 mg/dL, or HbA1c (NGSP) level of ≧6.5% (American diabetes association, 2011). The normotensive subjects who were receiving drugs for hypertension were estimated as having hypertension. After informed consent was given, waist circumference and blood pressure (at supine position) were measured. Blood sampling was done after overnight fast. Blood glucose, HbA1c, and plasma lipids were measured using standard laboratory methods. LDL-*C* and sLDL-*C* were measured by homogenous direct assay method and the combination of heparin-magnesium precipitation and homogenous direct assay method, respectively (Hirano et al., 2003; Okada et al., 1998). *PS* was estimated according to Tanaka et al (Tanaka et al., 1992). Hs-CRP in plasma was measured according to Ledue et al (1998).

Statistical Analysis

All values are expressed as mean ± *SD*. A cross-sectional analysis of age groups was performed using Student's *T*-test for continuous data and the Chi-square test for categorical data. Simple regression analysis for the *PS* was performed with respective risk factors as independent variables. After selection of appropriate independent variables, multivariate regression analysis was then performed to estimated the association of *PS*, and dependent variable of the study using SPSS for Windows (Ver 28, IBM, Tokyo, Japan). A significant difference was defined as $p < .05$, $p < .01$, and $p < .001$.

Results

Clinical characteristics of middle-aged and older subjects are shown in Table 1. The average age of middle-aged and older subjects were 49.5 ± 10.8 years and 71.5 ± 5.9 years, respectively. The number of type 2 diabetes mellitus were also 88 and 47 respectively. There were significant differences in age, BMI, HbA1c, *TG*, and *PS* between the two

Table 2. Simple Regression Analysis Exploring the Determinants of Plaque Score.

a.

Middle-aged	*p*	β	95% CI
Age	<.001	.468	[0.153, 0.312]
Gender	.016	.218	[0.449, 4.208]
BMI	.026	−.202	[−0.327, 0.021]
DM	<.001	.316	[1.645, 5.534]
HT	.254	.104	[−0.772, 2.897]
DL	.988	−0.001	[−1.973, 1.943]
Met-*S*	<.001	.303	[1.326, 4.832]
LDL-*C*	.565	.053	[−0.018, 0.034]
TG	.698	.063	[−0.005, 0.007]
HDL-*C*	.704	−0.035	[−0.084, 0.057]
hs CRP	.018	.214	[1.726, 18.072]
sLDL-*C*	.155	.130	[−0.011, 0.070]

b.

older	*p*	β	95% CI
Age	.840	.025	[−0.215, 0.263]
Gender	.554	.075	[−1.954, 3.613]
BMI	.089	.213	[−0.055, 0.757]
DM	<.001	.442	[2.655, 8.196]
HT	.635	.060	[−2.108, 3.428]
DL	.696	.049	[−2.700, 4.017]
Met-*S*	.134	.188	[−0.654, 4.778]
LDL-*C*	.058	.236	[−0.001, 0.068]
TG	.072	.225	[−0.002, 0.036]
HDL-*C*	.925	−0.012	[−0.104, 0.094]
hs CRP	<.001	.554	[19.063, 42.223]
sLDL-*C*	<.001	.558	[0.079, 0.173]

BMI: Body mass index, DM: Diabetes Mellitus, HT: Hypertension, DL: Dyslipidemia.
Met-*S*: Metabolic syndrome, LDL-*C*: fasting low-density lipoprotein cholesterol, TG: fasting triglyceride, HDL-*C*: fasting high-density lipoprotein cholesterol, hs CRP: high sensitivity *C*-reactive protein. sLDL-*C*: small, dense cholesterol.

groups (Table 1). Simple regression analysis in middle-aged subjects revealed that the determinant of *PS* were age, gender, BMI, DM, Met-*S*, and hs-CRP (Table 2a). Multiple regression analysis in middle-aged subjects showed that the determinant of PS were age, BMI, Met-*S*, and hs-CRP (Table 3a). On the other hand, Simple regression analysis in older subjects revealed that the determinant of *PS* were *DM*, hs-CPR, and sLDL-C (Table 2b). Multiple regression analysis in older subjects showed that neither age nor Met-*S* was included as significant determinant of *PS*. On the other hand, hs- CRP, and s LDL-*C* were significant determinants of *PS* (Table 3b).

Discussion

Visceral fat accumulation has been recognized as an important risk factor for CAD (Kim et al., 2004; Matsuzawa et al., 1999) since Fujioka et al. reported the contribution of intra−abdominal fat accumulation (visceral obesity) to the glucose and lipid metabolism in human obesity (Fujioka et al., 1987). Met-S is a clinical entity characterized by visceral obesity, hypertension, hypertriglyceridemia, low HDL-cholesterol, and glucose intolerance, although there are some incompatibilities of diagnostic criteria among countries. In Japan, the definition of and diagnostic criteria for Met-*S* were established in April, 2005, in which an association of increased waist circumference was emphasized as the most important component reflecting increased intra−abdominal fat accumulation (Nippon Naikagakkai, 2005). The presence of Met-*S* is associated with increased CAD events, cardiovascular mortality(Gui et al., 2017; Mottillo et al., 2010; Ninomiya et al., 2007). Met-*S* is also reported to be predictive of subclinical atherosclerosis (Hulthe et al., 2000). Since a component of Met-*S* involves glucose intolerance, it is obvious that the patients with Met-*S* without any clinical intervention may finally develop type 2 diabetes mellitus. Thus, the purpose of diagnosis and intervention for Met-*S* is not only early detection of subclinical atherosclerosis but also the prevention of developing type 2 diabetes mellitus. It is well-known that patients with diabetes mellitus are at increased risk for CAD (Singh et al., 2013; Turner et al., 1998). Therefore, if patients with metabolic syndrome develop type 2 diabetes mellitus, their risk for CAD will further increase. Indeed, our previous observation revealed that the patients with type 2 diabetes mellitus and metabolic syndrome had higher s LDL-*C* and hs-CRP than patients with type 2 diabetes without metabolic syndrome (Nakano et al., 2010). Furthermore, presence of Met-*S* is often associated with increased sLDL-*C* (Sugino et al., 2011).

Recent research into the inflammatory nature of atherosclerosis suggests that inflammatory-response proteins may serve as potential predictors of clinical events. In particular, one of the inflammatory-response proteins, hs-CRP, has been the focus of much attention. Epidemiological data have shown an independent association between hs-CRP elevation and coronary risk (Iso et al., 2009; Li et al., 2017). Recently, several investigators found that human atherosclerotic lesions, coronary artery smooth muscle cells, aortic endothelial cells, and adipocytes express CRP (Calabró et al., 2003; Calabro et al., 2005; Yasojima et al., 2001). Therefore, persistent production of small amounts of CRP by atherosclerotic lesions and coronary artery smooth muscle cells may lead to slight but chronic CRP elevation. Thus, the hs-CRP assay is now useful and popular for predicting CAD risk (Piepoli et al., 2016)

Aging itself is known as the most important risk factor for CAD. Therefore, it has been a matter of debate whether the CAD risk of elderly patients with Met-*S* more than non-Met-*S* elderly subjects. According to Vinluan CM et al, the modified WHO definition of Met-*S* was associated with increased risk for cerebrovascular events in over 65 years old subjects (Vinluan et al., 2012). On the other hand, according to Sakurai et al, Met-*s* of Japanese criteria did not always appear to be associated with cardiovascular disease (Sakurai et al., 2010) . In the present study, *PS* of older subjects was significantly higher than middle-aged subjects. In multiple regression analysis, determinant of *PS* were age, BMI, Met-*S* and

Table 3. Multiple Regression Analysis Exploring the Determinants of Plaque Score.

a.			
Middle-aged	*P*	β	95% CI
age	<.001	.362	[0.101, 0.259]
gender	.159	.109	[−0.462, 2.792]
BMI	.006	−0.249	[−0.366, 0.63]
DM	.065	.146	[−0.103, 3.416]
Met-*S*	.004	.282	[0.846, 4.240]
hs CRP	.019	.202	[1.581, 17.092]
b.			
older	*p*	β	95% CI
DM	.357	.106	[−1.507, 4.114]
hs CRP	.002	.357	[7.491, 31.99]
s LDL-*C*	.002	.363	[0.032, 0.132]

BMI: Body mass index, DM: Diabetes Mellitus, Met-S: Metabolic syndrome, sLDL-C: small, dense cholesterol, hsCRP: high sensitivity C-reactive protein, PS: plaque score.

hs-CRP in middle-aged subjects. On the other hand, in spite of correlation with hs- CRP and sLDL-*C*, age, and Met-*S* were not included as significant determinants of *PS* in older subjects. Furthermore, not only Met-*S* but also *DM* was not affected *PS* in older subjects.

There are two reasons that we speculated. First, frequency of dyslipidemia in middle-aged subjects were smaller than older subjects. Therefore, sLDL-*C* was not an explanatory variable in middle-aged subjects. Second, BMI in older subjects was lower than middle-aged subjects. Hence, Met-*S* could not be an explanatory variable for *PS* older subjects.

There were two study limitations. First, eating habit of subjects were not monitored in the present study. Second, the present study was only a cross-sectional. Therefore, a randomized control trial may be essential for determining whether intervention is obligatory for the prevention of subclinical atherosclerosis within older type 2 diabetes mellitus subjects with metabolic syndrome.

In conclusion, Met-*S* is an important factor for progression of subclinical atherosclerosis, but it can no longer be a significant determinant of *PS* if the subjects are limited within an older group. An association of hs CRP and sLDL-*C* may be a more powerful determinant of *PS* of older people than the presence of metabolic syndrome; therefore, it can be a matter of debate whether an aggressive intervention for Met-*S* still must be obligatory for older subjects from the standpoint of progression of subclinical atherosclerosis.

Authors' Note

This manuscript will not be submitted, in part or entirety, elsewhere for publication before the decision.

Author's Contributions

HY was responsible for database search and writing of the article. ™ was responsible for correction of the article. GY was responsible for correction of the article and supervision.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

All study protocols and procedures were approved by Ethics committee of Toho University Medical Center Ohmori Hospital. Written informed consent was obtained from all participants.

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