Metabolically healthy obesity and risk of leukoaraiosis; a population based cross-sectional study

Takuro Okamura¹⁾, Yoshitaka Hashimoto¹⁾, Masahide Hamaguchi²⁾, Akihiro Ohbora³⁾, Takao Kojima³⁾ and Michiaki Fukui¹⁾

¹⁾ Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan

²⁾ Department of Diabetology, Kameoka Municipal Hospital, Kyoto 621-8585, Japan

³⁾ Department of Gastroenterology, Murakami Memorial Hospital, Asahi University, Gifu 500-8523, Japan

Abstract. Metabolically healthy obese (MHO) individual is known to be defended from the metabolic complications of obesity. Leukoaraiosis, which is commonly detected on brain magnetic resonance imaging (MRI), is now recognized as a risk of stroke, dementia and death. However, the association between MHO and the prevalence of leukoaraiosis is unclear. In this cross-sectional study of 796 participants who received a medical examination program, we investigated the association between MHO and the prevalence of leukoaraiosis. We used common clinical markers for definition of metabolic healthy status: blood pressure, fasting plasma glucose, triglycerides and high-density lipoprotein cholesterol concentrations. Obesity was defined by body mass index ≥ 25.0 kg/m². We diagnosed leukoaraiosis by fluid-attenuated inversion recovery without hypointensity on T1-weighted images or the presence of a hyperintensity on T2-weighted images. The crude prevalence proportion of leukoaraiosis was 44.5% (case/*n* = 171/384) in metabolically healthy nonobese (MHNO) individual, 46.3% (44/95) in MHO individual, 62.3% (114/183) in metabolically unhealthy nonobese (MUNO) individual or 56.6% (77/136) in MUO individual. The odds ratios of prevalence of leukoaraiosis were 1.19 (95% CI 0.74–1.90, *p* = 0.471) for MHO, 1.79 (1.22–2.62, *p* = 0.003) for MUNO and 1.56 (1.03–2.37, *p* = 0.037) for MUO individuals after adjusting for sex, age, smoking status, habit of exercise and alcohol, compared with MHNO individual. We revealed that MHO individuals were not related with the higher risk of leukoaraiosis, whereas MUNO and MUO individuals were.

Key words: Obesity, Stroke, Cerebral white matter, Metabolic syndrome, Epidemiology

BOTH OBESITY [1] and metabolic syndrome [2] are major problems of public health all over the world and often exist together. Metabolically healthy obese (MHO) phenotype is known as a subset of obese phenotype, that burden of metabolic abnormalities associated with fat accumulation is low, including low prevalence of hypertension, hyperlipidemia and hyperglycemia [3–5]. In fact, we previously reported that not MHO but metabolically unhealthy obese (MUO) individual was associated with the risk of incident chronic kidney disease [6].

Leukoaraiosis, which is commonly detected on brain magnetic resonance imaging (MRI), is now recognized

as a risk of dementia, stroke and death [7]. Both obesity [8, 9] and metabolic syndrome [10–13] are reported as risk factors for leukoaraiosis; however, the relation between MHO individual and leukoaraiosis remains to be elucidated. Thus, in this cross-sectional study, we investigated the relationship between metabolic phenotype and the prevalence of leukoaraiosis.

Materials and Methods

Study participants and study design

In this cross-sectional study of a medical examination program at Murakami Memorial Hospital (Gifu, Japan), we made an investigation of the relationship between MHO phenotype and the prevalence of leukoaraiosis. The aim of a medical examination program and the feature of participants of this cohort study were reported previously [14]. After receiving informed consent and

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Correspondence to: Masahide Hamaguchi, MD, PhD, Department of Diabetology, Kameoka Municipal Hospital, 1-1 Noda, Shinochoshino, Kameoka, Kyoto 621-8585, Japan.

E-mail: mhama@koto.kpu-m.ac.jp

de-identifying the personal information data, we served the results of the medical examination of the participants to a database. We extracted the participants who received brain MRI in the current study. Exclusion criteria was current use of any medication. This study was approved by the ethics committee of Murakami Memorial Hospital.

Data collection and Measurements

A standardized self-administered questionnaire was used to obtain the medical history and lifestyle factors of all participants, with habits of smoking or alcohol and physical activity. We evaluated alcohol consumption by asking the participants about the type and amount of alcohol consumption per week during the past month, then estimating the mean ethanol intake per week. We categorized participants into the following four groups: nonor minimal, <40 g/week; light, 40–140 g/week; moderate, 140–280 g/week; or heavy alcohol consumption, >280 g/week [15, 16]. We also categorized participants into three groups by smoking status; never, ex-smoker or current smoker. We investigated the participants' recreational or sports activities [17]. We defined regular exercisers as participants who played any kind of sports over once a week regularly [18].

Definition of metabolic syndrome and metabolic phenotypes

We diagnosed metabolic syndrome by a joint interim statement of the National Heart, Lung and Blood Institute; the International Diabetes Federation Task Force on Epidemiology and Prevention; the World Heart Federation; the American Heart Association; the International Association for the Study of Obesity; and the International Atherosclerosis Society, using the criteria for Asians [19]. The participants were diagnosed as metabolic syndrome when over 3 of the following criteria were present: hyperglycemia (fasting plasma glucose ≥ 5.6 mmol/L); hypertension (blood pressure $\geq 130/85$ mmHg); low high-density lipoprotein (HDL) cholesterol levels (serum HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women); hypertriglyceridemia (serum triglycerides ≥ 1.70 mmol/L); and abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women). We did not measure waist circumference of all study participants, therefore we adopted a body mass index of ≥ 25 kg/m² as a cut-off for the diagnosed of obesity [20]. This definition was often used for Japanese individuals [21, 22]. We defined the metabolic syndrome score as the presence of metabolic syndrome component

(from 0 to 5) [23].

To define whether participant was metabolically healthy or metabolically unhealthy, we used 4 metabolic parameters; hypertension, impaired fasting glucose or diabetes, low HDL-cholesterol concentration and hypertriglyceridemia. We considered that they were metabolically healthy state, when none or 1 of the metabolic factor was present. On the other hand, when 2 or more metabolic factors were present, we considered that they were metabolically unhealthy state [6]. We categorized participants into 4 groups: 1) metabolically healthy non-obese (MHNO), 2) MHO, 3) metabolically unhealthy nonobese (MUNO) and 4) MUO.

Definition of leukoaraiosis

On brain MRI features with a 3.0 T MR scanner with a standard head coil (GE Signa VH/I; GE Medical Systems, Milwaukee, WI, USA), leukoaraiosis was diagnosed. The collection of T1- and T2-weighted images, and fluid-attenuated inversion recovery (FLAIR) images were included in the MRI protocol. In MRI image diagnosis, one experienced radiologist blindly evaluated the presence or absence of leukoaraiosis according to the diagnostic criteria described later and did not know the aim of this study. He diagnosed leukoaraiosis by the existence of a hyperintensity on FLAIR or T2-weighted images without hypointensity on T1-weighted images [24], and assessed on precontrast images.

Statistical analysis

Continuous variable was expressed as mean $\pm$ standard deviation and categorical variable was expressed as number. We used unpaired student *t* tests or χ^2 tests to assess the statistical differences between participants with and without leukoaraiosis. In addition, categorical variables were compared among the groups by Pearson's chi-squared test, and continuous variables were compared by one-way ANOVA and Tukey HSD test to assess the statistical differences among the participants for four phenotypes. Logistic regression analyses were used to analyze the correlations between the prevalence of leukoaraiosis and the metabolic syndrome or metabolic phenotype adjusting for known cardiovascular risk factors.

A *p* value less than 0.05 was considered statistically significant and the JMP version 12.0 software (SAS Institute Inc., Cary, North Carolina) was used for statistical analyses.

Results

The participants' characteristics are shown in Table 1 and Table 2. From June 1st in 2009 to Dec 31st in 2013, among the 796 study participants, 406 participants diagnosed leukoaraiosis. Age, fasting plasma glucose, blood pressure, metabolic syndrome score and percentage of metabolic syndrome of participants with leukoaraiosis were higher than those of without leukoaraiosis. The crude proportions of leukoaraiosis were 44.5% in MHNO, 46.3% in MHO, 62.3% in MUNO and 56.6% in MUO, respectively.

The results of univariate analyses of factors associated with prevalence of leukoaraiosis are shown in Table 3. Age, blood pressure, fasting plasma glucose, metabolic syndrome score, presence of metabolic syndrome and ex-smoking were associated with a prevalence of leukoaraiosis. On the other hand, sex and BMI were not associated with a prevalence of leukoaraiosis.

The results of multivariate analyses of factors related with prevalence of leukoaraiosis are shown in Table 4. Not blood pressure but hypertension was associated with prevalence of leukoaraiosis, after adjusting for covariance (Model 1 and Model 2). Compared with MHNO phenotype, adjusting OR of prevalence of leukoaraiosis was 1.19 (95% CI 0.74–1.90, $p = 0.47$) for MHO, 1.79 (1.22–2.62, $p = 0.003$) for MUNO and 1.56 (1.03–2.37, $p = 0.037$) for MUO (Model 3).

Discussion

In this study, we found that MHO individual was not related with higher risk of leukoaraiosis, whereas MUNO and MUO individuals were related with. It has been documented that MHO individual is known to be defended from the metabolic complications of obesity [4, 5]. As far as we examine, this study is first investigation of the association between MHO and the prevalence of leukoaraiosis.

Table 1 Characteristics of participants at baseline examination

	ALL	Participants without leukoaraiosis	Participants with leukoaraiosis	<i>p</i>
<i>N</i>	798	392	406	—
Age (years)	56.2 ± 8.6	53.9 ± 7.7	58.4 ± 8.8	<0.001
Sex (male/female)	536/262	259/133	277/129	0.517
Body mass index (kg/m ²)	23.5 ± 3.2	23.5 ± 3.2	23.5 ± 3.1	0.951
Systolic blood pressure (mmHg)	124.4 ± 15.6	122.6 ± 15.1	126.1 ± 15.9	0.002
Diastolic blood pressure (mmHg)	78.4 ± 10.7	77.6 ± 10.8	79.1 ± 10.7	0.055
Fasting plasma glucose (mmol/L)	5.7 ± 1.1	5.6 ± 1.0	5.8 ± 1.1	0.007
HbA1c (%)	5.6 ± 0.7	5.5 ± 0.6	5.7 ± 0.7	0.017
Total cholesterol (mmol/L)	5.3 ± 0.9	5.3 ± 0.9	5.3 ± 0.9	0.456
Triglycerides (mmol/L)	1.1 ± 0.8	1.0 ± 0.7	1.1 ± 1.0	0.111
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	0.269
Uric acid (μmol/L)	313.3 ± 80.2	309.1 ± 75.4	317.3 ± 84.5	0.149
Smoking (Non/Ex/Current)	379/284/135	200/126/66	179/158/69	0.1
Alcohol (Non/Light/Moderate/Heavy)	480/139/97/82	232/72/45/43	248/67/52/39	0.761
Habit of exercise (–/+)	629/169	312/80	317/89	0.601
Metabolic syndrome score	1.5 ± 1.2	1.3 ± 1.2	1.7 ± 1.2	<0.001
Metabolic syndrome (–/+)	715/83	362/30	353/53	0.006
MHNO/MHO/MUNO/MUO	384/95/183/136	213/51/69/59	171/44/114/77	<0.001

Data are number of subjects or mean ± SD, HDL, High-density lipoprotein; MHNO, Metabolically healthy non-obesity; MHO, Metabolically healthy obesity; MUNO, Metabolically unhealthy non-obesity; MUO, Metabolically unhealthy obesity. Unpaired student *t* tests or χ^2 tests was conducted to assess the statistical significance of differences between participants without leukoaraiosis and participants with leukoaraiosis.

Table 2 Characteristics of participants at baseline examination

	MHNO	MHO	MUNO	MUO	<i>p</i>
<i>N</i>	384	95	183	136	—
Age (years)	55.7 (8.6)	53.5 (8.4)	58.7 (7.7) ^{†,‡}	56.8 (8.8) [‡]	<0.001
Sex (male/female)	220/164	59/36	145/38	112/24	<0.001
Body mass index (kg/m ²)	21.7 (1.9)	26.8 (1.6) [†]	22.6 (1.7) ^{†,‡}	27.6 (2.7) ^{†,‡,§}	<0.001
Systolic blood pressure (mmHg)	117.5 (14.3)	123.7 (12.7) [†]	131.9 (14.1) ^{†,‡}	134.7 (12.8) ^{†,‡}	<0.001
Diastolic blood pressure (mmHg)	74.0 (10.0)	78.3 (9.1) [†]	83.3 (10.0) ^{†,‡}	84.4 (8.6) ^{†,‡}	<0.001
Fasting plasma glucose (mmol/L)	5.3 (0.6)	5.5 (1.1)	6.1 (1.1) ^{†,‡}	6.5 (1.2) ^{†,‡,§}	<0.001
HbA1c (%)	5.4 (0.4)	5.5 (0.8)	5.8 (0.7) ^{†,‡}	6.0 (0.9) ^{†,‡,§}	<0.001
Total cholesterol (mmol/L)	5.3 (0.8)	5.4 (0.9)	5.2 (1.0)	5.3 (1.0)	0.113
Triglycerides (mmol/L)	0.8 (0.4)	1.0 (0.4)	1.4 (1.2) [†]	1.5 (1.0) ^{†,‡}	<0.001
HDL cholesterol (mmol/L)	1.6 (0.4)	1.5 (0.3) [†]	1.3 (0.4) ^{†,‡}	1.2 (0.3) ^{†,‡}	<0.001
Uric acid (μmol/L)	290.3 (75.6)	313.6 (68.3) [†]	331.2 (80.9) [†]	353.6 (78.9) ^{†,‡}	<0.001
Smoking (Non/Ex/Current)	215/117/52	48/30/17	67/73/43	49/64/23	<0.001
Alcohol (Non/Light/Moderate/Heavy)	244/68/39/33	67/12/8/8	97/33/29/24	72/26/21/17	0.477
Habit of exercise (−/+)	304/80	81/14	141/42	33/103	0.943
Leukoaraiosis	171 (44.5%)	44 (46.3%)	114 (62.3%)	77 (56.6%)	0.003

Data are number of subjects or mean ± SD, HDL, High-density lipoprotein; MHNO, Metabolically healthy non-obesity; MHO, Metabolically healthy obesity; MUNO, Metabolically unhealthy non-obesity; MUO, Metabolically unhealthy obesity.

p values by one-way analysis of variance for continuous variables and chi-squared test for categorical variables.

The analyses of continuous variables among four groups were performed by Tukey HSD test: [†], *p* < 0.05 versus MHNO, [‡], *p* < 0.05 versus MHO, [§], *p* < 0.05 versus MUNO.

Table 3 Univariate analyses of factors associated with the prevalence of leukoaraiosis

	Odds ratio (95% CI)	<i>p</i>
Age, 10 year	1.92 (1.61–2.31)	<0.001
Men	0.91 (0.68–1.22)	0.521
Body mass index	0.99 (0.95–1.04)	0.81
Systolic blood pressure, 10 mmHg	1.17 (1.07–1.28)	<0.001
Diastolic blood pressure, 10 mmHg	1.15 (1.01–1.31)	0.039
Fasting plasma glucose, mmol/L	1.20 (1.05–1.39)	0.007
Triglycerides, mmol/L	1.15 (0.97–1.39)	0.112
HDL-cholesterol, mmol/L	0.82 (0.58–1.17)	0.273
Uric acid, 10 mmol/L	1.01 (1.00–1.03)	0.102
Metabolic syndrome score	1.27 (1.13–1.43)	<0.001
Metabolic syndrome	1.63 (1.15–2.32)	0.006
Habit of exercise	1.10 (0.78–1.54)	0.588
Ex-smoker	1.43 (1.06–1.95)	0.021
Current smoker	1.12 (0.76–1.65)	0.57

CI, Confidence interval; HDL, High-density lipoprotein. Sex was defined as female (=0) or male (=1), habit of exercise was defined as non-exerciser (=0) or exerciser (=1), smoking status was defined as nonsmoker (=0), ex-smoker (=1) or current smoker (=2).

Leukoaraiosis, which is an expression of ischemic injury in white-matter substances, represents atherosclerosis of small arteries [25, 26]. Visceral obesity is related with the prevalence of leukoaraiosis [27, 28]. Secretion of adipocytokines, including TNF- α , MCP-1 and adiponectin, are increasing in adipose tissue of visceral obesity [29]. The adipokines activate the inflammatory signal of liver and skeletal muscle and induces insulin resistance [30], which is related with a mechanism of cerebral small vessel disease through endothelial dysfunction [31]. Body fat distribution, especially visceral fat, is a crucial factor in determining MUNO and MUO or MHO phenotypes. It has been reported that MHO individuals have a low adverse effect of metabolic abnormalities [3, 4, 32]. Comprehensively visceral fat obesity is associated with leukoaraiosis, therefore MHO, with low visceral fat, is the lower risk of prevalence of leukoaraiosis. In fact, a previous study reported that MHO was not the higher risk of atherosclerosis [33]. In addition, it has been reported that the relation between leukoaraiosis and obesity might be mediated by blood pressure [34]. In fact,

Table 4 Multivariate analyses of factors associated with the prevalence of leukoaraiosis

	Model 1	<i>p</i>	Model 2	<i>p</i>	Model 3	<i>p</i>
Systolic blood pressure, 1 mmHg	1.01 (1.00–1.02)	0.105	—	—		
Fasting plasma glucose, 1 mmol/L	1.11 (0.96–1.31)	0.14	—	—		
Triglycerides, 1 mmol/L	1.00 (0.92–1.42)	0.282	—	—		
HDL-cholesterol, 1 mmol/L	1.00 (0.64–1.62)	0.9309	—	—		
BMI, 1 kg/m ²	0.98 (0.93–1.03)	0.352	—	—		
Hypertension	—	—	1.56 (1.14–2.14)	0.006	—	—
Impaired fasting glucose	—	—	1.10 (0.80–1.50)	0.569	—	—
High triglycerides	—	—	1.42 (0.89–2.30)	0.141	—	—
Low HDL-cholesterol	—	—	1.16 (0.76–1.77)	0.482	—	—
Obesity	—	—	0.98 (0.70–1.37)	0.906	—	—
MHNO	—	—	—	—	1 (Reference)	—
MHO	—	—	—	—	1.19 (0.74–1.90)	0.471
MUNO	—	—	—	—	1.79 (1.22–2.62)	0.003
MUO	—	—	—	—	1.56 (1.03–2.37)	0.037
Age, 1 year	1.06 (1.04–1.08)	<0.001	1.06 (1.04–1.08)	<0.001	1.06 (1.04–1.08)	<0.001
Men	0.91 (0.60–1.38)	0.646	0.90 (0.60–1.34)	0.599	0.92 (0.62–1.36)	0.67
Regular exercise	0.99 (0.69–1.41)	0.95	0.99 (0.69–1.43)	0.978	1.01 (0.70–1.44)	0.962
Ex-smoker	1.47 (0.97–2.21)	0.066	1.42 (0.95–2.14)	0.091	1.39 (0.93–2.09)	0.111
Current smoker	0.85 (0.55–1.31)	0.462	0.84 (0.54–1.30)	0.433	1.15 (0.72–1.85)	0.557
Light alcohol	0.74 (0.49–1.12)	0.16	0.75 (0.49–1.14)	0.185	0.76 (0.50–1.15)	0.192
Moderate alcohol	0.76 (0.45–1.25)	0.282	0.78 (0.47–1.28)	0.324	0.84 (0.52–1.35)	0.465
Heavy alcohol	0.64 (0.38–1.08)	0.092	0.64 (0.38–1.07)	0.089	0.64 (0.39–1.08)	0.094

HDL, High-density lipoprotein; BMI, Body mass index; MHNO, Metabolically healthy non-obesity; MHO, Metabolically healthy obesity; MUNO, Metabolically unhealthy non-obesity; MUO, Metabolically unhealthy obesity

hypertension was the risk of prevalence of leukoaraiosis in this study. To summarize these findings, not MHO individuals but MUNO and MUO individuals are related with higher risk of the prevalence of leukoaraiosis.

In our study, there are some limitations that require consideration. Firstly, because this was a cross-sectional study, further studies should be needed to establish the effect and cause between metabolic phenotype and leukoaraiosis. Second, our study did not include the data regarding visceral obesity such as waist circumference, and visceral fat area by CT. Moreover, our study did not include the data of insulin secretion or insulin resistance. Therefore, misclassification of participants is possible. However, visceral adiposity is closely associated with the coexistence of components of metabolic syndrome, including hypertension, impaired fasting glucose, low

HDL-cholesterol concentration and hypertriglyceridemia, which were generally available in clinical settings, like our study, and the verification of this definition that the above four components were used as metabolically unhealthy status was previously confirmed [6, 35]. Additionally, in the univariate analysis, BMI did not show the correlation with the prevalence of leukoaraiosis in this study. However, previous study demonstrated that obesity was the independent risk of leukoaraiosis [36]. On the other hand, there was a report that BMI was not related with leukoaraiosis [37]. It suggests that other factors such as metabolic syndrome components other than BMI are related with the prevalence of leukoaraiosis. Therefore, we considered that not only BMI but also metabolic syndrome components were important factors to investigate the relationship with the prevalence of leukoaraiosis

and categorized the participants according to BMI and metabolic syndrome components. Third, because all the participants of this study are Japanese men and women, whether these findings in this study are applied in other ethnic groups is uncertain. Lastly, we used a binary classification for leukoaraiosis and did not use a severity scale, because at the beginning of this study a severity scale was not adopted. We should do additional research to elucidate relationship of MHO with severity of leukoaraiosis.

In conclusion, this study demonstrated that MHO individual is not related with the higher risk of the prevalence of leukoaraiosis, whereas MUNO and MUO individuals are. Future prospective study for the relation between MHO and incident leukoaraiosis would be needed.

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