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ARTICLE

Obesity without metabolic disorder and silent brain infarcts in aneurologically healthy population

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Abstract

Objective Obesity without metabolic disorder [Ob(+)MD(−)] is a unique subcategory of obesity where individuals are protected from the obesity-related complications. Although conflicting clinical outcomes have been reported, there has been no study of the effects of Ob(+)MD(−) on cerebrovascular disease. In this study, we evaluated the association between the Ob(+)MD(−) phenotype and silent brain infarcts (SBI) in a neurologically healthy population.

Subjects/methods We evaluated a consecutive series of healthy volunteers recruited between January 2006 and December 2013. MD(−) status was assessed using five clinical markers: blood pressure, triglycerides, high-density lipoprotein, fasting plasma glucose, and waist circumference. Obesity was defined when body mass index ≥ 25 kg/m^2. SBI was defined as asymptomatic, well-defined lesions with a diameter ≥ 3 mm with the same signal characteristics as the cerebrospinal fluid on T1- or T2-weighted images.

Results A total of 3165 subjects were assessed, and 262 (8%) SBI cases were identified. In multivariate analyses, non-obesity with metabolic disorder [Ob(−)MD(+)] (adjusted odds ratio [aOR] = 1.65, 95% confidence interval [CI] = 1.07–2.56, $P = 0.025$) and obesity with metabolic disorder [Ob(+)MD(+)] (aOR = 1.75, 95% CI = 1.12–2.75, $P = 0.014$) were closely associated with SBI after adjustment for confounders. Meanwhile, Ob(+)MD(−) did not show any significant association with SBI (aOR = 0.85, 95% CI = 0.20–3.72, $P = 0.832$). These findings may indicate that metabolic abnormality, irrespective of obesity status, is a main risk factor of SBI. When we compared SBI burdens between the four metabolic phenotypes, the Ob(+)MD(+) and Ob(−)MD(+) groups had higher rates of multiple lesions than the Ob(+)MD(−) and non-obesity without metabolic disorder groups.

Conclusions The presence of metabolic abnormality, and not obesity per se, is independently associated with the prevalence of SBI in a healthy population.

Introduction

Contemporary obesity rates have increased epidemically worldwide [1]. It has become a major public health problem, and is related to various metabolic and cardio/cerebrovascular diseases [1–3]. However, these obesity-related complications seem to have substantial heterogeneity between individuals [4, 5]. The disparity could result from limitations of the traditional definition of obesity based on body mass index (BMI), because BMI has low sensitivity in distinguishing between fat and lean mass [6].

From these backgrounds, a unique subgroup of obese individuals has recently become the focus of attention. Despite their high adiposity, this so-called obesity without metabolic disorder [Ob(+)MD(−)] group exhibit normal metabolic features, including high insulin sensitivity and favorable lipid and inflammatory profiles [1, 5, 7, 8].

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However, it is still unclear whether the Ob(+)MD(−) phenotype is "harmless" or "at intermediate risk" relative to the non-obesity without metabolic disorder [Ob(−)MD(−)] phenotype [7, 8]. Many studies have reported conflicting results regarding the effects of the Ob(+)MD(−) phenotype on the subsequent prevalence of diabetes, atherosclerosis, and cardiovascular diseases [5, 7–9]. Nonetheless, no studies have examined its effects on cerebrovascular disease.

Silent brain infarct (SBI) is a preclinical pathology, which is commonly found in the elderly prior to symptomatic ischemic stroke [10, 11]. As an intermediate stage of ischemic stroke [11], assessment of modifiable risk factors, such as metabolic status and obesity, and their early control is important. In this study, we conducted cross-sectional analyses to evaluate the relationship between Ob(+)MD(−)-related phenotypes and the prevalence of SBI in a neurologically healthy population. Although the causal relationship is hard to be proven owing to the limitation of cross-sectional design, these analyses would give us insights whether obesity itself or metabolic disorder is more closely related to cerebrovascular disease development.

Methods

Patients and population

As a part of a consecutive registry of health check-ups in a large center in Korea (Seoul National University Hospital Health Promotion Center) between January 2006 and December 2013, 3257 subjects were initially evaluated. Among them, 64 subjects who had a history of stroke or severe neurological deficit were excluded. According to the exclusion criteria, we then excluded participants who were younger than 30 years ($n = 4$) and had missing data regarding covariates ($n = 24$). Finally, a total of 3165 neurologically healthy subjects were included in the final analyses (Fig. 1). All participants underwent wide-ranging evaluations, including brain magnetic resonance imaging (MRI), magnetic resonance angiography, and laboratory examinations as a part of health check-ups. The current study was approved by the Institutional Review Board at the Seoul National University Hospital (IRB number: H-1502-026-647). Any data not published within the article are available from the corresponding author upon reasonable request.

Clinical assessment

We evaluated demographic and clinical factors, including age, sex, BMI, current smoking, current alcohol use, and use of anti-platelet agents, anti-hypertensives, and lipid-lowering agents [12]. Systolic and diastolic blood pressures were measured after 5 min rest in the sitting position [12].

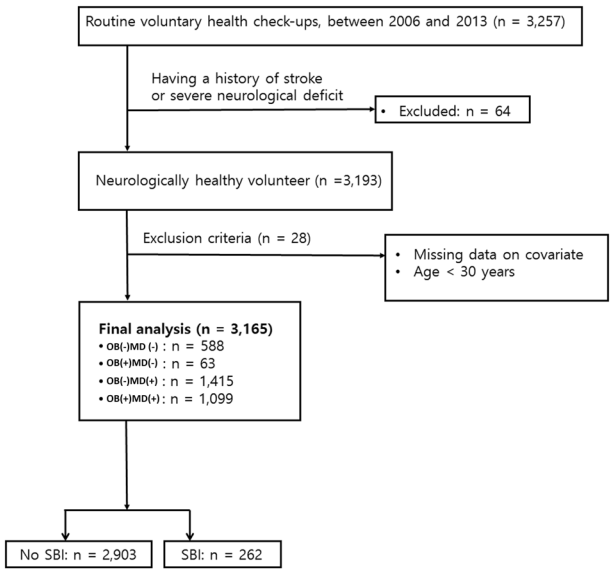

Fig. 1 Patients inclusion flow-chart of the cohort

Laboratory examinations were performed after 12 h of overnight fasting, and included glucose profiles, lipid profiles, high-sensitivity C-reactive protein (hs-CRP) levels, and white blood cell counts. Insulin resistance was calculated according to the homeostatic model assessment of insulin resistance (HOMA-IR) equation, and impaired insulin sensitivity was defined as HOMA-IR <2.5 [13].

We defined the "without metabolic disorder" [MD(−)] status as when participants did not meet any of the following criteria: (1) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of anti-hypertensives; (2) decreased high-density lipoprotein (HDL) levels (< 40 mg/dL in men and < 50 mg/dL in women); (3) elevated triglyceride (TG) levels (≥ 150 mg/dL) or use of lipid-lowering agents; (4) elevated fasting plasma glucose (≥ 100 mg/dL) or use of glucose-lowering agents; (5) enlarged waist circumference (WC) (> 90 cm in men and > 85 cm in women) for Asian according to the National Cholesterol Education Program-Adult Treatment Panel III criteria for the definition of metabolic syndrome [14]. Obesity was defined as BMI ≥ 25.0 kg/m^2, which has been proposed as the cutoff value for Asian populations [8]. According to the contribution of metabolic disorder status and obesity, we classified the cohort into four phenotypes: (1) Ob(−)MD(−), (2) Ob(+)MD(−), (3) non-obesity with metabolic disorder [Ob(−)MD(+)], and (4) obesity with metabolic disorder [Ob(+)MD(+)] [8].

Radiological assessment

All participants underwent brain magnetic resonance imaging (MRI) and magnetic resonance angiography using 1.5-T MR scanners (Signa, GE Healthcare, Milwaukee, WI, USA or

Magnetom SONATA, Siemens, Munich, Germany). The detailed MRI acquisitions were as follows: T1-weighted images (repetition time (TR)/echo time (TE) = 500/11 ms); T2-weighted images (TR/TE = 5000/127 ms); T2 fluid-attenuated inversion recovery images (TR/TE = 8800/127 ms); T2-gradient echo images (TR/TE = 57/20 ms); and basic slice thickness = 5 mm.

We defined SBI as asymptomatic, well-defined ≥ 3-mm lesions with the same signal characteristics as the cerebrospinal fluid on T1- or T2- weighted images [5]. We also categorized SBI lesion burdens as either absent, single, or multiple. The presence and burden of SBI lesions were rated by two neurologists (K.-W.N. and H.-Y.J.), and disagreements were resolved by discussion with a third rater (H.-M.K.).

Statistical analysis

Univariate analyses to compare baseline characteristics between groups with and without SBI were conducted using Student's *t* test, Mann–Whitney *U* test, chi-squared test, or Fisher's exact test. We then performed binary logistic regression analyses to assess the relationship between metabolic phenotypes and SBI, adjusting for age, sex, current smoking, current alcohol use, anti-platelet agents, hs-CRP, and white blood cell counts as confounders. We also conducted sensitivity analyses to confirm our results using "impaired insulin sensitivity" as a component of metabolic healthy status instead of WC [13].

To evaluate the individual and synergistic effects of MD(−) status and obesity on the development of SBI, we also compared SBI burden between four metabolic phenotypes using the chi-squared test and linear-by-linear association analyses. All statistical analyses in the current study were conducted using SPSS 23 (IBM SPSS, Chicago, IL, USA), and statistical significance was considered $P < 0.05$.

Results

A total of 3165 healthy participants were evaluated (median age: 56 years, male: 54%, median BMI: 24.04 kg/m^2). SBI was found in 262 (8%) subjects (single lesion: 193 cases; multiple lesions: 69 cases). According to the metabolic phenotypes, our cohort was divided into 588 (19%) Ob(−)MD(−), 63 (2%) Ob(+)MD(−), 1,415 (45%) Ob(−)MD(+), and 1099 (35%) Ob(+)MD(+) groups. Baseline characteristics according to the metabolic phenotypes are presented in Supplementary Table 1.

In univariate analyses, SBI was significantly related to age, anti-platelet agents, systolic/diastolic blood pressure, fasting glucose, HbA1c, total cholesterol, TG, low-density lipoprotein, HDL cholesterol, HOMA-IR, hs-CRP, and white blood cell counts (Table 1). When we performed multivariate analyses to evaluate the relationship between metabolic phenotypes and SBI, Ob(−)MD(+) (adjusted odds ratio (aOR) = 1.65, 95% confidence interval (CI) = 1.07 to 2.56, $P = 0.025$) and Ob(+)MD(+) (aOR = 1.75, 95% CI = 1.12 to 2.75, $P = 0.014$) were closely associated with SBI after adjustment for confounders (Table 2). We obtained similar results when we conducted an additional sensitivity analysis with another definition of metabolic phenotypes using insulin resistance instead of WC (Supplementary Table 2). Meanwhile, Ob(+)MD(−) did not show any significant association with SBI (Table 2 and Supplementary Table 2).

In line with previous studies, our cohort also showed significant correlation between MD(−) status and obesity ($P < 0.001$ in Pearson correlation analysis). To evaluate both the individual and synergistic effects of MD(−) status and obesity on SBI development, we compared the SBI lesion burden between the four metabolic phenotypes. The Ob(+)MD(+) group had the highest SBI burden with more multiple lesions than the other groups, showing synergistic effects of both MD(−) status and obesity (P for trend = 0.001) (Fig. 2). The Ob(+)MD(−) group was not different from the Ob(−)MD(−) groups ($P = 0.151$). When we compared between the two groups respectively, the presence of a MD(−) status had more significant influence (Ob(−)MD(−) vs. Ob(−)MD(+), $P = 0.003$; Ob(+)MD(−) vs. Ob(+)MD(+), $P = 0.087$), whereas obesity itself did not have much effect (Ob(−)MD(−) vs. Ob(+)MD(−), $P = 0.151$; Ob(−)MD(+) vs. Ob(+)MD(+), $P = 0.093$).

Discussion

In this study, we found that the Ob(+)MD(−) phenotype was not associated with the prevalence of SBI in a neurologically healthy population. On the contrary, all phenotypes with a metabolically unhealthy status (i.e., Ob(−)MD(+) and Ob(+)MD(+)) had significantly higher SBI frequency and lesion burdens. Thus, the presence of metabolic disorder, and not obesity alone, seems to be associated with SBI development.

The importance of MD(−) status was prominent in the current study, consistent with previous studies [8, 15]. However, obesity itself did not show harmful effects, according to the previous "benign obesity" concept [6, 8]. The prevalence of SBI did not differ between Ob(+)MD(−) and Ob(−)MD(−) groups, although the difference in BMI was almost 4 kg/m^2. This phenomenon was similar when we compared Ob(−)MD(+) and Ob(+)MD(+) phenotypes. The exact mechanisms by which Ob(+)MD(−) "protective" or "less harmful" are unclear. However, findings from previous histological studies may provide hints [16, 17]. According to

Table 1 Difference in characteristics between patients with and without SBI

	No SBI ($n = 2903$)	SBI ($n = 262$)	*P*-value
Age, y (IQR)	56 (50–62)	64 (57–69)	<0.001
Sex, male, *n* (%)	1563 (54)	146 (56)	0.558
BMI, kg/m^2 (IQR)	24.02 (22.11–25.96)	24.24 (22.05–26.18)	0.369
Current smoking, *n* (%)	455 (16)	34 (13)	0.247
Current alcohol, *n* (%)	1415 (49)	120 (46)	0.362
Anti-platelet agent, *n* (%)	285 (10)	41 (16)	0.003
Anti-hypertensives, *n* (%)	635 (22)	63 (24)	0.417
Statin, *n* (%)	233 (8)	22 (8)	0.833
Metabolic phenotypes, *n* (%)			0.001
Ob(−)MD(−)	561 (19)	27 (10)	<0.001
Ob(+)MD(−)	61 (2)	2 (1)	
Ob(−)MD(+)	1286 (44)	129 (49)	
Ob(+)MD(+)	995 (34)	104 (40)	
Systolic BP, mmHg (IQR)	125 (115–136)	130 (119–140)	<0.001
Diastolic BP, mmHg (IQR)	75 (69–83)	77 (70–85)	0.005
FBS, mg/dL (IQR)	91 (85–101)	94 (85–109)	0.003
HbA1c, % (IQR)	5.7 (5.5–6.0)	5.9 (5.6–6.2)	<0.001
HOMRA-IR (IQR)	1.49 (0.93–2.17)	1.69 (1.10–2.61)	0.002
Total cholesterol, mg/dL (IQR)	198 (175–223)	191 (166–217)	0.002
Triglyceride, mg/dL (IQR)	99 (72–144)	108 (77–148)	0.029
LDL cholesterol, mg/dL (IQR)	125 (102–148)	115 (90–147)	0.007
HDL cholesterol, mg/dL (IQR)	53 (45–63)	51 (43–61)	0.025
hs-CRP, mg/dL (IQR)	0.04 (0.01–0.15)	0.07 (0.01–0.17)	0.035
White blood cell counts, × 10^3/μL (IQR)	5.30 (4.40–6.36)	5.49 (4.47–6.77)	0.045

BMI = body mass index, Ob(−)MD(−) = non-obesity without metabolic disorder, Ob(+)MD(−) = obesity without metabolic disorder, Ob(−)MD(+) = non-obesity with metabolic disorder, Ob(+)MD(+) = obesity with metabolic disorder, BP = blood pressure, FBS = fasting blood sugar, IR = insulin resistance, LDL = low-density lipoprotein, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, WBC = white blood cell

Table 2 Odds ratio for SBI according to metabolic phenotypes

	Ob(−)MD(−)	Ob(+)MD(−)	Ob(−)MD(+)	Ob(+)MD(+)	*P* for trend
No. of SBI	27/588	2/63	129/1,415	104/1,099	
Model 1[a]	1.00 (Ref.)	0.68 (0.16–2.94)	2.08 (1.36–3.19)	2.17 (1.41–3.36)	0.002
Model 2[b]	1.00 (Ref.)	0.82 (0.19–3.60)	1.69 (1.09–2.61)	1.79 (1.15–2.80)	0.052
Model 3[c]	1.00 (Ref.)	0.85 (0.19–3.69)	1.71 (1.10–2.64)	1.81 (1.16–2.83)	0.048
Model 4[d]	1.00 (Ref.)	0.85 (0.20–3.72)	1.65 (1.07–2.56)	1.75 (1.12–2.75)	0.074

SBI = silent brain infarct, Ob(−)MD(−) = non-obesity without metabolic disorder, Ob(+)MD(−) = obesity without metabolic disorder, Ob(−)MD(+) = non-obesity with metabolic disorder, Ob(+)MD(+) = obesity with metabolic disorder

Odds ratio was calculated using binary logistic regression analysis after adjusting for confounders

Unless otherwise noted, values are expressed as odds ratio (95% confidence interval)

[a]Model 1 was unadjusted

[b]Model 2 adjusted for age and sex

[c]Model 3 adjusted for model 2 plus current smoking and current alcohol use

[d]Model 4 adjusted for model 3 plus anti-platelet agent, hs-CRP levels, and white blood cell counts

the previous studies, individuals with Ob(+)MD(−) phenotype had lower visceral adipose tissue (VAT) proportions and higher subcutaneous adipose tissue (SAT)/lean mass [4, 17–19]. SAT has higher deposing capacity with smaller adipocytes and can trap circulating TG and glucose, referred to as the "metabolic sink" effect [1, 16, 19]. Consequently, the Ob(+)MD(−) group may be less likely to develop insulin resistance and various metabolic diseases that are also risk factors for SBI. On the contrary, subjects with the Ob(−)MD(+) phenotype had higher distributions of VAT and liver fat accumulation, leading to a metabolically unhealthy status [19, 20]. In addition, Ob(+)MD(−) had a more favorable inflammatory status than the Ob(+)MD(+) phenotype. Previous studies reported that the Ob(+)MD(−) group had

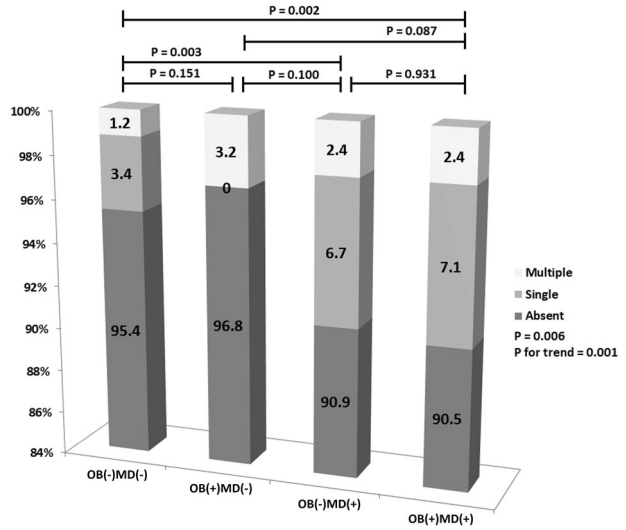

Fig. 2 Distribution of the amount of SBI lesions according to metabolic phenotypes. The Ob(+)MD(+) group had the highest SBI burden with a greater proportion of individuals having multiple lesions than other groups (P for trend = 0.001). The Ob(+)MD(−) group was not significantly different from the Ob(−)MD(−) groups ($P = 0.151$). When we compared between the two groups, the presence of a MD(−) status had a significant influence [Ob(−)MD(−) vs. Ob(−)MD(+), $P = 0.003$; Ob(+)MD(−) vs. Ob(+)MD(+), $P = 0.087$), whereas obesity itself did not have much effect (Ob(−)MD(−) vs. Ob(+)MD(−), $P = 0.151$; Ob(−)MD(+) vs. Ob(+)MD(+), $P = 0.931$)

higher levels of anti-inflammatory adiponectin and lower levels of pro-inflammatory adipokines (e.g., IL-6, TNF-a, PAI-1), showing weaker subclinical inflammation states (e.g., hs-CRP) [4, 13, 16, 19, 21]. Chronic inflammation and endothelial dysfunction have been focused in the development of SBI lesions because they could lead to occlusion of perforating arterioles and leakage of toxic metabolites into the perivascular neural spaces [22]. Thus, we thought that the less harmful inflammatory state in Ob(+)MD(−) may also result in the lack of difference between Ob(+)MD(−) and Ob(−)MD(−).

Interestingly, our messages concerning "benign obesity" could change over time. Owing to cross-sectional nature of the study, we could only suggest the lack of association between baseline MD(−) status and prevalence of SBI. However, numerous investigators have argued that the Ob(+)MD(−) phenotype is not a "steady healthy" state but a "transient at risk" intermediate [19]. A previous study in a Japanese American population showed that two thirds of Ob(+)MD(−) individuals changed into Ob(+)MD(+) phenotype during 10-year follow-up [23]. In addition, various systematic meta-analyses indicated a tendency for Ob(+)MD(−) phenotype to show no harmful effects compared with Ob(−)MD(−) only in studies with a < 10-year follow-up, whereas longer studies consistently found that Ob(+)MD(−) had a higher risk of diabetes, metabolic syndrome, and cardiovascular disease [2, 3, 7, 9, 24, 25]. Supporting these ideas, Ob(+)MD(−) presented with intermediate levels of metabolic profiles (e.g., blood pressure, lipid profiles, glucose profiles, and inflammatory profiles) between Ob(−)MD(−) and Ob(−)MD(+)/Ob(+)MD(+) phenotypes. Obesity itself also could affect the long-term development of SBI (e.g., via obstructive sleep apnea, elevated sympathetic tone through renin–angiotensin–aldosterone system activation) [18, 26]. Further prospective studies that deal with baseline and change in MD(−) status and risk of SBI could solve these questions.

Although we have reported several novel findings and confirmed previous ones, there are several caveats for the current study. First, this study was designed as a retrospective, single-center study. Although we assessed a relatively large number of participants with extensive evaluations, the possibility of selection bias remains. Second, owing to the limitations of cross-sectional analyses, we could not identify a causal relationship between metabolic phenotypes and SBI. Further large prospective studies are needed to prove underlying pathophysiologic mechanisms between the two. Third, since the current study included only Asian population, we defined the obesity using BMI values of ≥ 25 kg/m^2. Our results should be confirmed in other ethnic groups, which have different genetic traits and lifestyles. Fourth, because some brain areas are involved in peripheral metabolic homeostasis (i.e., hypothalamus, basal ganglia), the possibility of metabolic disorder development owing to infarcted lesions should also be considered. Last, using a very strict definition of metabolically healthy status, we had only small Ob(+)MD(−) group (5% of obese individuals). As metabolic phenotypes vary according to their definition, our results may not be reproducible in other studies with different definitions. However, our strict definition may provide a very specific test of the effects of MD(−) status and obesity on SBI. We also confirmed our results in a sensitivity analyses using another definition of metabolic phenotypes, which had a higher proportion of Ob(+)MD(−) phenotype (15%) Thus, we thought that our main conclusions could be acceptable.

In conclusion, we showed that Ob(+)MD(+) or Ob(−)MD(+) phenotypes, not the Ob(+)MD(−) phenotype, were associated with a higher prevalence of SBI in a neurologically healthy population. Because SBI is thought to be both an intermediate stage and independent risk factor for ischemic stroke, screening metabolic disorder and early intervention should be performed regardless of whether a patient is obese. However, our findings should be confirmed with further large prospective studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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