Metabolically Healthy Obesity and Risk of Incident CKD

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Abstract

Background and objectives Metabolically healthy obesity (MHO) is a unique obesity phenotype that apparently protects people from the metabolic complications of obesity. The association between MHO phenotype and incident CKD is unclear. Thus, this study investigated the association between MHO phenotype and incident CKD.

Design, setting, participants, & measurements A total of 3136 Japanese participants were enrolled in an 8-year follow-up cohort study in 2001. Metabolically healthy status was assessed by common clinical markers: BP, triglycerides, HDL cholesterol, and fasting plasma glucose concentrations. Body mass index ≥25.0 kg/m^2 was defined as obesity. CKD was defined by proteinuria or eGFR of <60 ml/min per 1.73 m^2. To calculate the odds ratio for incident CKD, logistic regression analyses were performed.

Results The crude incidence proportions of CKD were 2.6% (56 of 2122 participants) in participants with the metabolically healthy nonobesity phenotype, 2.6% (8 of 302) in those with the MHO phenotype, 6.7% (30 of 445) in those with the metabolically abnormal nonobesity phenotype, and 10.9% (29 of 267) in those with the metabolically abnormal obesity phenotype. Compared with metabolically healthy nonobesity phenotype, the odds ratios for incident CKD were 0.83 (95% confidence interval [95% CI], 0.36 to 1.72; *P*=0.64) for MHO, 1.44 (95% CI, 0.80 to 2.57; *P*=0.22) for metabolically abnormal nonobesity, and 2.80 (95% CI, 1.45 to 5.35; *P*=0.02) for metabolically abnormal obesity phenotype after adjustment for confounders, including age, sex, smoking statues, alcohol use, creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes.

Conclusion MHO phenotype was not associated with higher risk of incident CKD.

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Introduction

Obesity (1) and metabolic syndrome (2) are major public health problems worldwide that frequently coexist and define obese people who are at risk for adverse health outcomes. Recent studies have identified a subset of obese people who have a low burden of adiposity-related metabolic abnormalities compared with at-risk obese people, the so-called metabolically healthy obesity (MHO) phenotype (3–5). MHO phenotype is characterized by high levels of insulin sensitivity, low prevalence of hypertension, and a favorable fasting glucose, lipid, and inflammation profile (6,7).

CKD is an important and increasingly prevalent health concern worldwide (8,9). It is associated with ESRD, as well as cardiovascular morbidity and mortality (10–12).

Recent studies reported that metabolic syndrome (13,14) and obesity (15–18) were risk factors for incident CKD, but the association between MHO phenotype and incident CKD remains to be elucidated. Therefore, we aimed to investigate whether MHO phenotype was associated with higher risk of incident CKD in this cohort study.

Materials and Methods

Study Participants and Study Design

The Oike Health Survey is an ongoing cohort investigation of risk factors for chronic diseases, including hypertension, diabetes, and CKD. The Oike Clinic (Kyoto, Japan) provides regular health checkups for the employees of various companies. In Japan, yearly routine examination for employees is legally mandated, and all or most of the costs for the health checkup are usually paid by their employers.

In this retrospective cohort study, we enrolled 4127 participants without malignant disease, liver cirrhosis, or hematologic disease who had health checkup examinations at the Oike Clinic in 2001 and 2009. We excluded 709 participants who had CKD at the baseline examination, which was performed in 2001. Furthermore, we excluded 282 participants with missing data on covariates. Thus, 3136 participants were eligible for this analysis.

The Ethical Committee of the Oike Clinic approved this study, and the study was conducted in accordance with the Declaration of Helsinki. Each participant provided informed consent.

Date Collection and Measurements

All participants provided demographic details. Smoking was defined as current tobacco use. Alcohol use was defined as daily alcohol consumption. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After a brief period of rest, sitting BP was measured in either arm. BP was

measured once in most participants, but up to three measurements at 1- to 2-minute intervals were made in participants who had hypertensive or prehypertensive BP values. The lowest reading was used in the analysis that assessed the incidence of hypertension. After an overnight fast, venous blood was collected for the measurement of the levels of various factors, including fasting plasma glucose, total cholesterol, triglycerides, HDL cholesterol, creatinine, and uric acid. Serum creatinine was measured using an enzymatic assay (Akyurasu-auto; Shino-test Corp., Kanagawa, Japan) in an autoanalyzer; the coefficient of variation was 2.0%.

Definition of CKD

GFR was estimated using the Japanese Society of Nephrology equation (19):

$$(\text{eGFR}) = 194 \times \text{Cre}^{-1.094} \times \text{age}^{-0.287} (\text{ml/min per 1.73 m}^2)$$

For women, the eGFR was multiplied by a correction factor of 0.739. Proteinuria was determined using dipstick testing (Yurifuret-S; Arkray, Kyoto, Japan) in fasting morning urine (positive: ≥1+) (20). CKD was defined as proteinuria or an eGFR<60 ml/min per 1.73 m^2.

Definitions of Metabolic Phenotypes

BMI≥25.0 kg/m^2, which has been proposed as a cutoff for the diagnosis of obesity in Asian people (21), was defined as obesity; BMI<25.0 kg/m^2 was defined as nonobesity. The validity of this definition was confirmed previously (22,23). We used four metabolic factors (impaired fasting glucose or diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol concentration), defined by International Diabetes Federation (24), to determine whether the participant was metabolically healthy or metabolically abnormal. Data on waist circumference, visceral fat, fasting insulin, and C-reactive protein concentrations were not available for study participants, although we acknowledge that these markers can be used to define metabolic phenotypes (7,25). Participants with a systolic BP≥130 mmHg and/or a diastolic BP≥85 mmHg or who were under medical treatment were considered to have hypertension. Elevated triglyceride level was indicated by ≥150 mg/dl or treatment of hyperlipidemia, and reduced HDL cholesterol level was indicated by <40 mg/dl in men and <50 mg/dl in women. Participants with fasting plasma glucose ≥100 mg/dl or who were under medical treatment were considered to have impaired fasting glucose or diabetes. A metabolically healthy state was considered if none or one of the metabolic factors based on the International Diabetes Federation definition was present, and a metabolically abnormal state was declared if two or more metabolic factors were present (24). Then, participants were categorized at the baseline examination into four phenotypes: (*1*) metabolically healthy nonobesity (MHNO), (2) MHO, (*3*) metabolically abnormal nonobesity (MANO), or (*4*) metabolically abnormal obesity (MAO). This definition of metabolic phenotypes has often been used in a Japanese population (26). We also analyzed data with obesity defined as BMI≥27.5 kg/m^2, which has also been proposed as a cutoff for the diagnosis of obesity in Asian people (27).

Statistical Analyses

Continuous variables were expressed as mean±SD, and categorical variables were expressed as percentage (number). The analyses of continuous and categorical variables to assess differences among four phenotypes were determined by one-way ANOVA or the chi-squared test. We performed logistic regression analyses to assess the association of metabolic phenotypes with incident CKD, adjusting for covariates that included age, sex, smoking statues, alcohol use, creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes. In addition, we performed logistic regression analyses to assess the association of metabolic phenotypes with incident proteinuria adjusting for covariates, including age, sex, smoking statues, alcohol use, creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes. The variance inflation factor was used for detecting the co-linearity; a variance inflation factor ≥10 indicates a colinearity problem. In addition, we conducted a second analysis when we defined obesity as a BMI≥27.5 kg/m^2. The statistical analyses were performed using JMP software, version 10.0 (SAS Institute Inc., Cary, NC). A P value <0.05 was considered to represent a statistically significant difference.

Results

The baseline characteristics are shown in Table 1. The prevalence of MHNO, MHO, MANO, and MAO was 67.7% (n=2122), 9.6% (n=302), 14.2% (n=445), and 8.5% (n=267), respectively. At the follow-up examination, which was performed 8 years after baseline examination, 123 participants had developed CKD. The crude incidence proportions of CKD were 2.6% (56 of 2122) for the MHNO phenotype, 2.6% (eight of 302) for the MHO phenotype, 6.7% (30 of 445) for the MANO phenotype, and 10.9% (29 of 267) for the MAO phenotype. The crude incidence proportions of proteinuria were 0.5% (11 of 2122) for the MHNO phenotype, 1.0% (three of 302) for the MHO phenotype, 1.6% (seven of 445) for the MANO phenotype, and 5.6% (15 of 267) for the MAO phenotype.

Logistic regression analyses were performed to investigate the association between each metabolic phenotype and incident CKD (Table 2). No colinearity was found between variables. The MHO phenotype was not associated with higher risk of incident CKD. On the other hand, MAO phenotype was associated with significantly higher risk of incident CKD (multivariate-adjusted odds ratio [OR], 2.80; 95% confidence interval [95% CI], 1.45 to 5.35; P=0.02).

Logistic regression analyses were also performed to investigate the association between each metabolic phenotype and incident proteinuria (Table 3). The MHO phenotype was not associated with higher risk of incident proteinuria. On the other hand, MAO phenotype was associated with a significantly higher risk of incident proteinuria (multivariate-adjusted OR, 6.29; 95% CI, 2.05 to 19.6; P<0.01).

Results of the Second Analyses

The prevalence of MHNO, MHO, MANO or MAO in the analysis that defined obesity as a BMI≥27.5 kg/m^2 (and in

Table 1. Characteristics of study participants at the baseline examination

Characteristic	MHNO	MHO	MANO	MAO	*P* Value
Participants (*n*)	2122	302	445	267	–
Age (yr)	45.3±9.3	45.0±9.4	52.2±9.0	49.2±9.0	<0.001
Men, % (*n*)	50.4 (1070)	72.2 (218)	73.5 (327)	81.6 (218)	<0.001
Body mass index (kg/m^2)	21.1±2.1	26.8±1.7	22.4±1.7	27.2±2.0	<0.001
Systolic BP (mmHg)	111.9±14.2	120.1±15.5	130.3±16.8	132.0±15.7	<0.001
Diastolic BP (mmHg)	67.2±9.5	72.4±10.4	78.8±11.0	79.7±9.9	<0.001
Fasting plasma glucose (mg/dl)	88.9±8.9	91.6±10.3	100.4±20.0	108.5±29.4	<0.001
Total cholesterol (mg/dl)	203.4±32.0	212.2±34.6	219.3±35.4	217.3±36.5	<0.001
Triglycerides (mg/dl)	86.3±54.9	122.9±78.1	175.4±132.5	202.7±134.1	<0.001
HDL cholesterol (mg/dl)	65.9±15.3	55.6±11.9	54.8±16.4	48.1±12.1	<0.001
eGFR (ml/min per 1.73 m^2)	76.6±11.6	75.0±9.9	73.5±9.8	75.1±10.7	<0.001
Uric acid (mg/dl)	4.9±1.3	5.7±1.4	5.7±1.3	6.0±1.4	<0.001
Smoking, % (*n*)	15.0 (319)	18.9 (57)	16.9 (75)	19.5 (52)	0.11
Alcohol use, % (*n*)	33.7 (715)	33.4 (101)	39.8 (177)	37.5 (100)	0.07

Data are expressed as percentage (number) or mean±SD. The analyses of continuous and categorical variables to assess differences among the four groups were determined by one-way ANOVA or the chi-square test. Smoking was defined as current tobacco use. Alcohol use was defined as daily alcohol consumption. MHNO, metabolically healthy nonobesity; MHO, metabolically healthy obesity; MANO, metabolically abnormal nonobesity; MAO, metabolically abnormal obesity.

which participants were considered as being in a metabolically healthy or abnormal state) was 74.7% (*n*=2344), 2.6% (*n*=80), 19.8% (*n*=622), and 2.9% (*n*=90). Crude incidence proportions of CKD were 2.6% (61 of 2344) for the MHNO phenotype, 3.8% (three of 80) for the MHO phenotype, 7.2% (45 of 622) for the MANO phenotype, and 15.6% (14 of 90) for the MAO phenotype. Crude incidence proportions of proteinuria were 0.5% (12 of 2344) for the MHNO phenotype, 2.5% (two of 80) for the MHO phenotype, 2.1% (13 of 622) for the MANO phenotype, and 10.0% (nine of 90) for the MAO phenotype. The MHO phenotype was not associated with a higher risk of incident CKD (multivariate-adjusted OR, 1.35; 95% CI, 0.32 to 3.93; *P*=0.64). On the other hand, MAO phenotype was associated with a significantly higher risk of incident CKD (multivariate-adjusted OR, 5.34; 95% CI, 2.35 to 11.7; *P*<0.001). In addition, the MHO phenotype was not associated with a higher risk of incident proteinuria (multivariate-adjusted OR, 5.06; 95% CI, 0.85 to 6.53; *P*=0.09). On the other hand, MAO phenotype was associated with a significantly higher risk of incident proteinuria (multivariate-adjusted OR, 14.0; 95% CI, 4.01 to 48.5; *P*<0.001).

Discussion

The major finding of our study is that MHO phenotype was not associated with higher risk of incident CKD. On the other hand, MAO phenotype was associated with significantly higher risk of incident CKD. In addition, we also showed that MHO phenotype was not associated with higher risk of incident proteinuria. On the other hand, MAO phenotype was associated with a significantly higher risk of incident proteinuria.

People with the MHO phenotype are apparently protected from the metabolic complications of obesity; at least, the risk appears to be considerably lower than expected for the given level of obesity (4,5). To our knowledge, ours is

Table 2. Odds ratios for incident CKD at 8 years after the baseline examination according to metabolic phenotypes

Variable	MHNO	MHO	MANO	MAO
Incidence of CKD (*n*/*n*)	56/2122	8/302	30/445	29/267
Model 1[a]	1.00 (Reference)	1.00 (0.44 to 2.01)	2.67 (1.67 to 4.18)[b]	4.50 (2.78 to 7.12)[b]
Model 2[c]	1.00 (Reference)	0.97 (0.42 to 1.95)	1.83 (1.12 to 2.93)[d]	3.52 (2.14 to 5.69)[b]
Model 3[e]	1.00 (Reference)	0.97 (0.42 to 1.95)	1.83 (1.12 to 2.93)[d]	3.51 (2.13 to 5.68)[b]
Model 4[f]	1.00 (Reference)	0.83 (0.36 to 1.72)	1.44 (0.80 to 2.57)	2.80 (1.45 to 5.35)[d]

Unless otherwise noted, values are expressed as odds ratio (95% confidence interval).
[a]Model 1 was unadjusted.
[b]*P*<0.001 versus MHNO phenotype.
[c]Model 2 adjusted for age and sex.
[d]*P*<0.05 versus MHNO phenotype.
[e]Model 3 adjusted for model 2 plus smoking status and alcohol use.
[f]Model 4 adjusted for model 3 plus creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes.

Table 3. Odds ratios for incident proteinuria at 8 years after the baseline examination according to metabolic phenotypes

Variable	MHNO	MHO	MANO	MAO
Incidence of proteinuria (*n*/*n*)	11/2122	3/302	7/445	15/267
Model 1[a]	1.00 (Reference)	1.93 (0.43 to 6.21)	3.07 (1.12 to 7.83)[b]	11.4 (5.22 to 25.8)[c]
Model 2[d]	1.00 (Reference)	1.84 (0.41 to 5.99)	2.05 (0.73 to 5.43)	8.68 (3.83 to 20.3)[c]
Model 3[e]	1.00 (Reference)	1.88 (0.42 to 6.13)	2.06 (0.73 to 5.47)	8.85 (3.89 to 20.8)[c]
Model 4[f]	1.00 (Reference)	1.65 (0.36 to 5.57)	1.62 (0.50 to 5.00)	6.29 (2.05 to 19.6)[g]

Unless otherwise noted, values are expressed as odds ratio (95% confidence interval).
[a]Model 1 was unadjusted.
[b]$P<0.05$ versus MHNO phenotype.
[c]$P<0.001$ versus MHNO phenotype.
[d]Model 2 adjusted for age and sex.
[e]Model 3 adjusted for model 2 plus smoking status and alcohol use.
[f]Model 4 adjusted for model 3 plus creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes.
[g]$P<0.01$ versus MHNO phenotype.

the first study to investigate the association between MHO phenotype and incident CKD.

Most studies reported that obesity is a risk factor for incident CKD (15–18) and proteinuria (28); however, a study showed that obesity was not associated with higher risk of incident CKD after adjusting for known cardiovascular risk factors, including diabetes, systolic BP, and HDL cholesterol (29). Our study also suggested that MAO phenotype, not MHO phenotype, was associated with higher risk of incident CKD in the obese people. Thus, we demonstrated that the association between obesity and CKD may be mediated by metabolic abnormalities. The association between obesity and CKD might be mediated through multiple biologic mechanisms, including hormonal factors, inflammation, oxidative stress, and endothelial dysfunction (30,31). The expansion of visceral adipose tissue (*i.e.*, a target for infiltration by immune cells) is involved in these mechanisms (32). Excess visceral adipose tissue can lead to the activation of the sympathetic nervous and renin-angiotensin systems, as well as lipid deposition, hyperfiltration, and increased sodium absorption in the kidneys, resulting in a feedback loop where obesity-induced declines in kidney function lead to the development of hypertension, which results in further damage to the kidneys (33). Previous studies have demonstrated that hypertension mediates the association between obesity and incident CKD (34,35). Moreover, the decrease in adiponectin concentration is relevant: It is associated with reduced whole body insulin sensitivity and possibly causes increased proinflammatory signaling in the kidney as well (36). On this point, studies of obese people suggested that the MHO phenotype had a more favorable distribution of low visceral fat, although the total fat mass was similar between MHO phenotype and MAO phenotype (3,37). Taking these findings together, not MHO phenotype but MAO phenotype is associated with higher risk of incident CKD.

Strengths of our study include the large number of participants both at baseline and at follow-up. However, this study has some limitations that require consideration. First, because we could not assess changes in waist circumference, insulin resistance, or insulin secretion, some metabolically healthy participants might have isolated insulin resistance or visceral adiposity without the major common metabolic abnormalities. Thus, we cannot deny the possibility of misclassification of participants. However, the four metabolic factors (impaired fasting glucose or diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol concentration) used in this study are commonly available in clinical settings, and the validity of this definition was confirmed previously (26,38).

Second, this is a relatively long follow-up study, but duration of follow-up may have been insufficient to allow us to evaluate the risk of incident CKD. Recent studies revealed the possibility that MHO phenotype was also a risk factor for different clinical characteristics, including diabetes (26,38,39), cardiovascular diseases (40–42), and hypertension (43). On this point, some clinical outcomes occurred only after a long-term follow-up (40,43). Thus, further long-term follow-up study is needed.

Third, the study population consisted of Japanese men and women; therefore, it is uncertain whether these findings can be generalized to other ethnic groups.

Fourth, we defined proteinuria by dipstick testing and thus did not quantitate the proteinuria. However, a dipstick test is a useful tool. Most patients with a 1+ or 2+ dipstick test result have microalbuminuria instead of macroalbuminuria, whereas patients with 3+ proteinuria mostly have macroalbuminuria (20). In addition, proteinuria by dipstick testing was also useful to determine development of ESRD (44,45).

Finally, our study participants underwent a health examination; thus, some participants might have made lifestyle changes based on results of the health examination to prevent the development of metabolic abnormalities.

In conclusion, our study showed that MAO phenotype, not MHO phenotype, was associated with higher risk of incident CKD.

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Disclosures
None.

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