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Association between obesity type and obstructive coronary artery disease in stable symptomatic postmenopausal women: data from the KoRean wOmen'S chest pain rEgistry (KoROSE)

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Abstract

Objectives: This study investigated the association between obesity type and obstructive coronary artery disease (CAD) in postmenopausal women.

Methods: Study data were obtained from a nation-wide registry, composed of 659 women older than 55 years with chest pain undergoing elective invasive coronary angiography in the suspicion of CAD. Obstructive CAD was defined as angiographic findings of $\geq$50% diameter stenosis with any major epicardial coronary artery. Overall obesity was defined as a body mass index of $\geq$25 kg/m^2, and central obesity was defined as a waist circumference of $\geq$85 cm.

Results: A total of 311 women (47.2%) had obstructive CAD. The incidence of overall obesity was not different between participants with and without obstructive CAD ($P = 0.340$), but the prevalence of obstructive CAD was significantly higher in participants with central obesity than those without (55.5% vs 41.0%, $P < 0.001$). There was no significant difference in body mass index between participants with and without obstructive CAD ($P = 0.373$). Multivariable analysis showed that central obesity was associated with obstructive CAD even after controlling for potential confounders (odds ratio, 1.61; 95% confidence interval, 1.10-2.34; $P = 0.013$). However, overall obesity was not associated with obstructive CAD in the same multivariable analysis ($P = 0.228$).

Conclusions: Central obesity but not overall obesity is associated with obstructive CAD in postmenopausal women with stable chest pain undergoing invasive coronary angiography.

Key Words: Central obesity – Coronary artery disease – Overall obesity – Postmenopausal women.

Video Summary: Supplemental Digital Content 1, http://links.lww.com/MENO/A440.

Coronary artery disease (CAD) is the leading cause of death worldwide.[1] Obesity has been advocated as one of the major risk factors for CAD. Obesity is associated with endothelial cell dysfunction, systemic inflammation, insulin resistance, and coronary atherosclerosis,[2] and obesity is usually accompanied by other cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus.[3] In general, obesity is classified into overall obesity assessed by body mass index (BMI) and central obesity assessed by waist circumference (WC) and/or waist-to-hip ratio. It has, however, not yet been fully determined which type of obesity is more influential to the development of CAD. Some studies showed that overall obesity predicts the development of CAD,[4,5] but others showed that central obesity is more important to developing CAD.[6,7]

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Estrogen has the effect of protecting the cardiovascular system by various mechanisms that inhibit the development and progression of atherosclerosis through anti-inflammatory and antioxidative effects.[8] As estrogen withdrawal has a detrimental effect on the cardiovascular system, CAD prevalence is rapidly increasing after menopause.[9,10] The incidence of CAD is lower in premenopausal women than in men, but the incidence of CAD in postmenopausal women rapidly increases, which is similar to that of men, and the trend of prevalence of CAD reverses after 75 years.[10] Menopause is also associated with changes in body fat distribution from a gynecoid to an android pattern.[11-13] Several studies have demonstrated that there was no change in total fat mass after menopause, but the central distribution of body fat increased, which can be considered one of the causes of increased CAD risk in postmenopausal women.[11-13]

Considering the rapidly increased CAD risk in postmenopausal women, it is very important to identify modifiable risk factors for CAD and to control them. Although two types of obesity (overall and central obesity) with different pathophysiological relevance to the cardiovascular system have been introduced, which obesity type is more influential in the development of CAD in postmenopausal women has not been well studied. Therefore, this study was performed to investigate the association between obesity type and obstructive CAD in postmenopausal women.

MATERIALS AND METHODS

Study population

Data were extracted from a prospective and nationwide registry database, the Korean Women's Chest Pain Registry.[14,15] The registry was established to assess the clinical characteristics and outcomes of CAD in Korean women. Twenty-nine qualified cardiac centers in Korea participated in the registry. At the participating sites, consecutive outpatient women (age $\geq$20 years) with chest pain undergoing elective invasive coronary angiography (CAG) for the evaluation of CAD were asked to register into the database. Participants with end-stage renal disease, chronic obstructive lung disease, primary pulmonary hypertension, malignancy, or autoimmune disease were excluded. Between February 2011 and June 2015, a total of 1,630 participants were identified from the database. Among them, 659 postmenopausal women older than 55 years with full information on study parameters were analyzed in this study. All data were entered into an electronic Web-based computerized database. This study protocol was reviewed and approved by the institutional review board of each center, and written informed consent was obtained from each study participant.

Data collections

Information on traditional risk factors, including hypertension, diabetes mellitus, dyslipidemia, and smoking status, were identified. Hypertension was defined as a previous history of hypertension or use of antihypertensive medications or blood pressure $\geq$140/90 mmHg. Diabetes mellitus was defined as a previous history of diabetes mellitus or use of antidiabetic medications or fasting plasma glucose >126 mg/dL. Dyslipidemia was defined as a previous history of dyslipidemia, use of antidyslipidemic medications, or low-density lipoprotein cholesterol >160 mg/dL. Blood pressure measurements were made by a trained nurse after sufficient rest in a stable environment. Before invasive CAG, blood samples were collected after overnight fasting for complete blood count, lipid profile, creatinine, and glycated hemoglobin. Information on concomitant cardiovascular medications at study enrollment was also recorded in detail.

Anthropometric measurements and obesity definition

Variables used to calculate baseline BMI and WC were measured during the index hospitalization. Physical measurements, with participants in light clothing and without shoes, included height to the nearest centimeter and weight to the nearest 1/10 of a kilogram. BMI was calculated by weight (kg)/height (m^2). WC was measured at the natural waist midpoint between the lowest edge of the rib cage and the highest point of the iliac crest at the end of normal expiration using a nonstrechable tape. Overall obesity was defined as a BMI $\geq$25 kg/m^2,[16] and central obesity was defined as a WC of $\geq$85 cm.[17]

Definition of obstructive coronary artery disease

The degree of epicardial coronary artery stenosis was assessed by invasive CAG. Obstructive CAD was defined as a $\geq$50% stenosis of 1 or more major epicardial coronary arteries. All management strategies for CAD, including coronary revascularization and medications, were chosen at the attending physician's discretion, based on current guidelines.[18]

Statistical analysis

Data are expressed as mean $\pm$ standard deviation for continuous variable and percentages for categorical variables. The clinical characteristics of participants with and without obstructive CAD were compared with Pearson chi-square tests for categorical variables or Student *t* tests for continuous variables. Multivariable binary logistic regression analysis was performed to determine independent variables associated with obstructive CAD. Age, hypertension, diabetes mellitus, dyslipidemia, and current smoking were adjusted in this multivariable model. These independent variables are well-known classical cardiovascular risk factors that are highly related to obstructive CAD. Logistic analysis was performed using the ''enter'' method. Hosmer-Lemeshow goodness-of-fit test was also performed to confirm the model fit ($P = 0.208$). Analysis of variance with Tukey post-hoc analysis was performed to investigate the associations of BMI and WC with CAD extent (insignificant, 1, 2, or 3 vessel disease). A two-tailed P value of <0.05 was considered statistically significant. All data were analyzed using SPSS for Windows 20.0 (IBM Co., Armonk, NY).

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RESULTS

Clinical characteristics of study participants

Of 659 study women, 311 (47.2%) had obstructive CAD. Baseline characteristics with comparisons between participants with and without obstructive CAD are shown in Table 1.

Participants with obstructive CAD were older and had more traditional risk factors, including hypertension, diabetes mellitus, and current smoking, than those without. Participants with obstructive CAD took more cardioprotective medications, including beta-blockers, renin-angiotensin system blockers, and statins, than those without. In baseline laboratory examinations, high white blood cell count, low hemoglobin, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, and high triglyceride were associated with obstructive CAD.

Association between obesity type and the prevalence of obstructive coronary artery disease

The association between obesity type and the prevalence of obstructive CAD is demonstrated in Figure 1. The prevalence of obstructive CAD was not different between participants with and without overall obesity (44.6% vs 48.5%, $P = 0.340$). The prevalence of obstructive CAD was significantly higher in participants with central obesity than in those without (55.5% vs 41.0%, $P < 0.001$). BMI was not different between participants with and without CAD (24.6 ± 3.9 vs 24.8 ± 3.3 kg/m^2, $P = 0.373$). WC was, however, significantly higher in participants with obstructive CAD than in those without (84.7 ± 9.2 vs 82.4 ± 8.8 cm, $P = 0.001$) (Fig. 2). We also analyzed the association between obesity type and CAD extent (insignificant, 1, 2, or 3 vessel disease). As a result, CAD extent was more closely associated with WC ($P = 0.004$) than with BMI ($P = 0.124$). In post-hoc analysis, there was a significant difference between insignificant versus 1 vessel disease ($P = 0.002$) but not among other groups ($P > 0.05$ for each). Multivariable analysis showed that central obesity was associated with obstructive CAD even after controlling for potential confounders including age, hypertension, diabetes mellitus, dyslipidemia, and current smoking (odds ratio, 1.61; 95% confidence interval [CI], 1.10-2.34; $P = 0.013$) (Table 2).

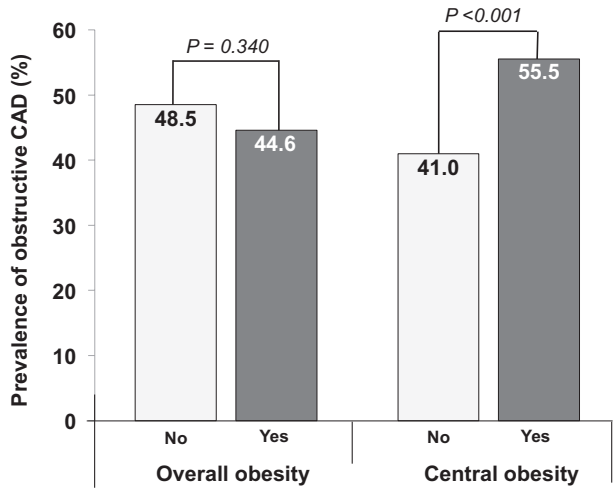

FIG. 1. Association between obesity type and prevalence of obstructive CAD. CAD, coronary artery disease.

TABLE 1. *Baseline characteristics of study participants*

Characteristic	CAD (−) (n = 348)	CAD (+) (n = 311)	*P*
Age, y	66.8 ± 7.9	69.5 ± 7.2	<0.001
Occupation, %	18.2	21.5	0.347
Risk factors, %			
Hypertension	55.3	69.5	<0.001
Diabetes mellitus	16.8	34.6	<0.001
Dyslipidemia	24.3	19.2	0.155
Current smoking	2.1	5.4	0.038
Systolic blood pressure, mmHg	127 ± 16	128 ± 21	0.590
Diastolic blood pressure, mmHg	77 ± 10	76 ± 13	0.224
Laboratory findings			
WBC, per μL	6,537 ± 2,245	8,009 ± 3,007	<0.001
Hemoglobin, g/dL	12.9 ± 1.3	12.2 ± 1.5	<0.001
Total cholesterol, mg/dL	178 ± 39	182 ± 51	0.330
HDL cholesterol, mg/dL	51.8 ± 14.5	45.2 ± 11.4	<0.001
LDL cholesterol, mg/dL	105 ± 35	132 ± 119	0.027
Triglyceride, mg/dL	114 ± 62	132 ± 119	0.035
Creatinine, mg/dL	0.8 ± 0.4	0.9 ± 0.9	0.079
HbA1c, %	6.3 ± 1.2	6.6 ± 1.3	0.140
Medications, %			
Beta-blocker	18.4	43.7	<0.001
RAS blocker	27.0	51.4	<0.001
Statin	39.9	60.8	<0.001

CAD, coronary artery disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system; WBC, white blood cell.

DISCUSSION

Using the nation-wide registry database of postmenopausal women with stable chest pain and undergoing elective CAG, this study showed that BMI was not different between participants with and without CAD; however, WC was significantly higher in those with CAD than in those without. The association between WC and obstructive CAD remained significant even after controlling for potential confounders. This result suggests that central obesity, but not overall obesity, may be an independent risk factor for obstructive CAD in postmenopausal women undergoing elective invasive CAG.

Association between central obesity and coronary artery disease risk in postmenopausal women

Our result supports the previous finding that central obesity was an independent factor for CAD in postmenopausal women. In a 4-year follow-up cohort study of 32,898 postmenopausal women aged 55 to 69 years, women having WC of 31.4 to 36.0 inches had a 1.7 times higher CAD mortality rate than those with a WC of <31.4 inches.[19] Another study showed that higher levels of WC (≥88 cm) were associated with a 22% increased risk of mortality, but BMI showed no independent association with coronary death.[20] In the Iowa Women's Health Study, the relative risk ratio of waist-to-hip ratio and BMI for CAD-related mortality were 1.8 (95% CI,

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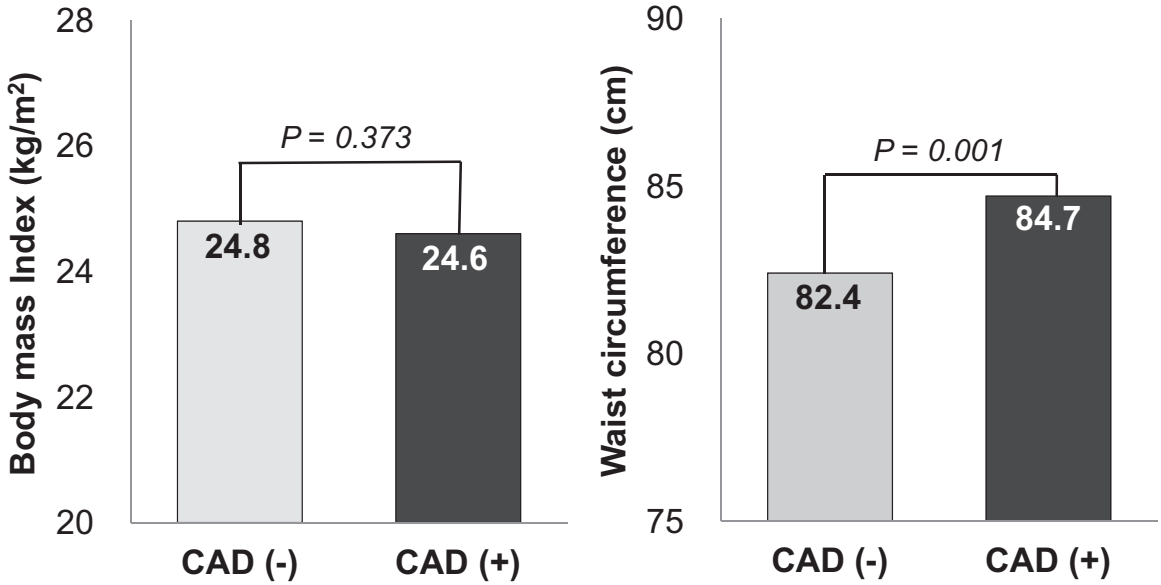

FIG. 2. Comparison of body mass index and waist circumference according to CAD status. CAD, coronary artery disease.

1.2-2.7) and 1.3 (95% CI, 0.9-1.9), respectively.[21] As demonstrated in these clinical studies, the prognostic value of central obesity in the prediction of future cardiovascular events is evident; however, there has been lack of studies focusing on the association between central obesity and the prevalence of obstructive CAD. Therefore, the results of our study using invasive CAG deserve clinical attention and would be helpful in understanding the increased CAD risk in postmenopausal women.

Association between body mass index and obstructive coronary artery disease in postmenopausal women

There was no significant association between BMI and obstructive CAD in our study. This result corresponds well with those found in the earlier studies. Also in the two previous studies as mentioned above,[19,20] BMI was not associated with CAD. It has been suggested that BMI has a poor sensitivity to detect obesity, especially in older women.[16,22] Hwu et al[23] also reported that BMI is an insufficient measure of cardiovascular risks in postmenopausal women. Although BMI is the most widely used anthropometric index, the use of BMI to determine obesity or body composition seems to be limited. Because BMI is associated with both body fat and lean mass, postmenopausal women with very low muscle mass and moderate amounts of body fat will still be in the normal range of BMI, and may be considered a ''normal.'' This misclassification is more prominent especially in older women with decreased muscle mass and increased body fat.[22]

TABLE 2. *Independent associations between central obesity and obstructive coronary artery disease*

Variable	OR (95% CI)	*P*
Age	1.04 (1.02-1.07)	0.001
Waist circumference	1.61 (1.10-2.34)	0.013
Hypertension	1.24 (0.85-1.83)	0.263
Diabetes mellitus	2.16 (1.39-3.37)	0.001
Dyslipidemia	0.75 (0.48-1.17)	0.203
Current smoking	3.16 (1.04-9.60)	0.043

CAD, coronary artery disease; CI, confidence interval; OR, odd ratio.

Possible mechanisms

The change of body composition may be one of the reasons for the increased CAD risk in postmenopausal women. After menopause, a decline in estrogen level is associated with body fat distribution shifting from gluteofemoral subcutaneous to abdominal visceral area.[24] Visceral adipose tissue is a major site of cytokine production that contributes to atherosclerotic progression, vascular dysfunction, sympathetic, and renin-angiotensin-aldosterone system activation.[25,26] In addition, visceral adipose tissue plays a major role in insulin resistance and dyslipidemia and in the induction of prothrombotic and chronic inflammatory states.[27] Moreover, visceral fat may be more sensitive to lipolysis than subcutaneous fat, thereby preferentially increasing circulating free fatty acid levels.[28]

Clinical implications

WC is a closer surrogate marker for visceral adiposity, and WC has been advocated as a single measure to assess the need for weight reduction, because it reflects both total adiposity and central fat deposition.[29,30] BMI is, however, more widely used in the diagnosis of obesity in clinical practice. Considering the more pronounced association of CAD with WC rather than BMI, additional WC measurements should be suggested especially in elderly women, even though they have normal BMI.

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STUDY LIMITATIONS

In addition to the retrospective study design, there are several limitations of this study. First, cross-sectional analysis could not confirm a causal relationship between obesity and CAD. Second, we considered that women aged >55 years were postmenopausal; however, there is a possibility that some women were premenopausal even if they were >55 years. It has, however, been reported that the average age of menopause in Korean women was 49.2 years, and only 2.4% of women experienced menopause over the age of 56 years.[31] By this report, only a few were premenopausal in our study. Lastly, our study population was constricted to postmenopausal Korean women, and thus, this result could not be applied to other populations.

CONCLUSIONS

WC, but not BMI, was associated with the presence of obstructive CAD in postmenopausal women. This suggests the importance of the assessment of central obesity rather than overall obesity in postmenopausal women for better risk stratification and therapeutic considerations of CAD.

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