Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 10, pp. 1104-1108
DOI: 10.1097/gme.0b013e31825ad66c

Relation of body mass index with carotid intima-media thickness and diameter is independent of metabolic syndrome in postmenopausal Mediterranean women

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Abstract

Objective: The aim of this study was to evaluate whether overweight and obesity are associated with arterial abnormalities in postmenopausal women and the contribution of the metabolic syndrome.

Methods: A total of 390 postmenopausal women (mean age, 63.1 ± 7.7 y) living in the metropolitan area of Naples, Southern Italy, and participating in a population-based cohort study (Progetto Atena) were offered an ultrasound examination of the carotid arteries; 370 women accepted. Blood pressure, serum high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting glucose, insulin, apolipoprotein B, and high-sensitivity C-reactive protein were measured in all participants.

Results: Women in the second and third tertiles of body mass index showed a greater common carotid intima-media thickness compared with those in the first tertile (tertile II vs I, odds ratio, 2.15; $P = 0.013$; tertile III vs I, odds ratio, 2.24; $P = 0.018$), adjusted for age and metabolic syndrome. Obese and overweight postmenopausal women showed greater common carotid lumen diameters as compared with lean postmenopausal women (mean ± SD, 6.36 ± 0.86, 6.16 ± 0.65, and 5.96 ± 0.59 mm, respectively; $P < 0.001$ [obese vs lean] and $P = 0.04$ [overweight vs lean]); no statistical difference in carotid lumen diameter was found between obese and overweight postmenopausal women. The statistical significance between obese and lean postmenopausal women was retained even after adding the components of the metabolic syndrome as covariates.

Conclusions: These findings indicate an association between overweight, obesity, and preclinical carotid artery abnormalities, independently of the metabolic syndrome, in a population of postmenopausal women.

Key Words: Atherosclerosis – Carotid arteries – Obesity – Women.

The prevalence of overweight and obesity is sharply growing in the general population and has received increasing attention in the past few years. Obesity is associated with a high risk of developing coronary heart disease, stroke, hypertension, type 2 diabetes, and dyslipidemia.[1-3]

An increased cardiovascular risk characterizes postmenopausal women.[4] Elevated oxidized low-density lipoprotein (LDL) plasma levels were found in postmenopausal women in comparison with fertile women.[5] In postmenopausal women, lipid and lipoprotein metabolism is markedly altered, as are fat mass and visceral adiposity.[6,7]

Received October 18, 2011; revised and accepted February 14, 2012.

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Funding/support: The Progetto Atena study was supported by funds from (1) Consiglio Nazionale delle Ricerche (Rome, Italy), "Progetto finalizzato Biotecnologie" and "Progetto finalizzato FATMA"; (2) Ministero dell'Università e della Ricerca Scientifica e Tecnologica-MURST 1998, grant no. 9806174392-008; and (3) Fondazione Banco di Napoli.

Financial disclosure/conflicts of interest: None reported.

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Over the last decade, high-resolution B-mode ultrasound has been used for the noninvasive assessment of carotid intima-media thickness (IMT), a marker of early atherosclerosis.[8-11] Cardiovascular risk factors relate positively to IMT of the common carotid arteries, whereas in population-based samples, the association with carotid lumen diameters is more complex, and in some cases, adverse levels of risk factors may be associated with larger lumens.[12]

In the present analysis, we evaluated whether overweight and obesity were associated with carotid abnormalities in a sample of postmenopausal women participating in a large, ongoing, prospective study (Progetto Atena).[13] Furthermore, we analyzed the contribution of the metabolic syndrome to arterial abnormalities. Our study was performed in a geographical area (southern Italy) where changes in dietary pattern (increasing calorie and animal fat intake), together with sedentary habits, have led to a high prevalence of overweight and obesity.[14]

METHODS

Study population

The main purpose of the Progetto Atena study was to investigate the causes of the chronic diseases that have a major impact

on the female population. The study population was recruited over a 6-month period by inviting the older three participants from those referred daily to the Progetto Atena to undergo an ultrasound examination of the carotid arteries, given their potentially higher risk of atherosclerotic cardiovascular disease. The same women (n = 400) were recalled after a period of 10 years of follow-up (final visit). Of these, 390 agreed to participate in the biochemical assay and clinical visit and 370 agreed to undergo a second ultrasound examination. At the final visit, all women were postmenopausal. The data from the second ultrasound examination were the object of the present study.

All women signed a written informed consent form, and the study was approved by the ethics committees of the institutions involved.

Clinical and biochemical assessment

Anthropometric measurements were made with the participant wearing indoor clothing and without shoes. Body mass index (BMI), used as a measure of general obesity, was calculated as weight (kilograms) divided by height (meters squared). Waist circumference, an index of abdominal obesity, was measured midway between the bottom of the rib cage and the top of the iliac crest. BMI changes over the adult lifetime (Δ BMI) were calculated in comparison with BMI reported at 20 years of age using the following formula: Δ BMI = BMI at the final visit − BMI at 20 years of age. Weight and height at 20 years of age were assessed on the basis of a questionnaire.[5] BMI changes between the baseline and the final visit, during the 10-year observation period, were calculated using the following formula: Δ BMI final versus baseline visit = BMI at final visit − BMI at baseline visit.

Sitting brachial blood pressure was measured two times using a random-zero sphygmomanometer, with a rest period of 5 or more minutes in between measurements. A standard questionnaire was used to collect information on smoking habits.

Blood specimens were collected after a 12- to 14-hour fast, from 8:00 to 9:30 AM, to reduce the influence of circadian variation. Total cholesterol and triglyceride concentrations were measured using standard enzymatic methods.[15,16] High-density lipoprotein (HDL) cholesterol was measured after the precipitation of very-low-density lipoproteins and LDLs with phosphotungstic acid,[17] and LDL-cholesterol was calculated according to the Friedewald formula. Fasting glucose levels were enzymatically determined by the peroxidase method. Fasting insulin levels were determined by enzyme immunoassay (Ultrasensitive Insulin Elisa, Mercodia, Sweden). The error of the method was evaluated on the two serum specimens at small and large contents of insulin and was less than 10%. Apolipoprotein B and high-sensitivity C-reactive protein were measured with a turbidimetric assay using an automated method (Cobas-Mira, Roche, Italy). The error of the method was evaluated by analyzing a plasma pool on a daily basis and was less than 5%.The homeostasis model assessment index was used to estimate insulin resistance and was calculated as fasting serum insulin (μU/mL) × fasting serum glucose (mM)/22.5, as described by Matthews et al.[18]

The American Heart Association Scientific Statement criteria[19] were used to classify women as having the metabolic syndrome on the basis of the presence of three or more of the following risk factors: (1) waist circumference greater than 88 cm, (2) fasting triglyceride level of 150 mg/dL or greater, (3) HDL-cholesterol level less than 50 mg/dL, (4) hypertension (systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg), and (5) fasting glucose level of 100 mg/dL or greater.

High-resolution carotid ultrasound

Carotid B-mode ultrasound examinations were performed by a certified sonographer using an ESAOTE AU4 instrument. The study protocol involved scanning the distal 1.0 cm of the near and far walls of the common carotid arteries. The crest at the origin of the bifurcation was used as an anatomical landmark to identify this segment. In each examination, the sonographer used different scanning angles (anterior, lateral, and posterior) to identify the greatest IMT in each wall. Scans were recorded on super 0.5-in VHS videotape for offline analysis. Readers selected the frame that contained the thickest IMT for each of the four carotid walls. The mean of the four maximum thicknesses (mean maximum) was used as the ultrasound endpoint of the study. It was possible to obtain common carotid IMT measurements in 361 of 370 women. The coefficient of reliability for the common carotid IMT was 0.85. This figure includes instrument, subject, sonographer, and reader variabilities. An additional 2 minutes of ultrasound scanning of the common carotid artery was recorded at the end of the protocol, paying attention to a perfect alignment of the walls, to allow measurement of carotid diameters. The distance between the leading edge of the echo produced by the intima-lumen interface of the near wall and the leading edge of the echo produced by the intima-lumen interface of the far wall was the lumen diameter. It was possible to obtain common carotid lumen diameters in 354 of 370 participants.

Statistical analyses

Statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). Continuous variables were described as mean and SD; the analysis of covariance was used to obtain age-adjusted means of physical and biochemical variables. Variables that were not normally distributed (homeostasis model assessment, triglycerides, and high-sensitivity C-reactive protein) were logarithmically transformed before analyses.

Univariate logistic regression analyses were used to identify predictors of an increased common carotid IMT (>1 mm)[20] or increased lumen diameter (above 90th percentile lumen diameter level). All variables that were significant at the univariate analysis were subsequently included in a multivariate model of logistic regression that excluded variables susceptible to collinearity (ie, we introduced LDL tertiles and excluded apolipoprotein B tertiles; similarly, we introduced BMI tertiles but not waist circumference tertiles). Backward stepwise logistic regression analyses were used to test the strength of association between tertiles of the single components of the metabolic syndrome and increased IMT.

A general linear model was developed to test the association of lumen diameter (dependent continuous variable) with tertiles of BMI (fixed variable) after adjustment for age. After this analysis, we added to this statistical model the single components of the metabolic syndrome as covariates.

RESULTS

The physical and biochemical characteristics of the study participants are shown in Table 1. In our cohort, there was a high prevalence of overweight and obesity: the second tertile of BMI was in the World Health Organization range of overweight (25.5-29.1 kg/m^2) and the third tertile was in the range of obesity (29.1-41.7 kg/m^2). The prevalence of overweight/obesity, following the World Health Organization classification, was 71%. Of the 390 participants included in the present study, 157 (40%) had the metabolic syndrome.

A gradual and significant increase in common carotid mean maximum IMT was present across BMI tertiles ($P = 0.013$ for linear trend), from lean (mean ± SD, 1.00 ± 0.19 mm) to overweight (1.04 ± 0.19 mm) to obese (1.07 ± 0.23 mm) women, after adjustment for age.

In univariate logistic regression analysis, an increased common carotid IMT was related to tertiles of LDL-cholesterol and apolipoprotein B concentrations, systolic blood pressure, BMI, waist circumference, presence of metabolic syndrome, and increased age. Similarly, increased lumen diameters were related to triglycerides, systolic blood pressure, diastolic blood pressure, BMI, waist circumference, metabolic syndrome, and age (Table 2).

In a multivariate model of logistic regression between increased common carotid IMT or increased lumen diameter and BMI tertiles, after controlling for age and metabolic syndrome diagnosis, women in the second and third tertile of BMI showed an increased common carotid IMT compared with those in the first tertile: tertile II versus I (odds ratio [OR], 2.15; 95% CI, 1.17-3.94; $P = 0.013$) and tertile III versus I (OR, 2.24; 95% CI, 1.15-4.37; $P = 0.018$). Similarly, after controlling for age and metabolic syndrome diagnosis, women in the third tertile of BMI showed an increased lumen diameter compared with those in the first tertile: tertile III versus I (OR, 3.61; 95% CI, 1.14-11.40; $P = 0.029$; Table 3).

In a backward conditional stepwise logistic regression analysis that included the variables that were statistically significant at univariate analyses, age, systolic blood pressure tertiles, and BMI tertiles remained significantly associated with increased IMT, whereas the association with LDL-cholesterol tertiles was no longer statistically significant (Table 4).

A significant association was present between common carotid lumen diameters (considered as a continuous variable) and BMI tertiles. Obese and overweight postmenopausal women showed increased lumen diameters as compared with lean postmenopausal women (6.36 ± 0.86, 6.16 ± 0.65, and 5.96 ± 0.59 mm, respectively; $P < 0.001$ [obese vs lean] and 0.04 [overweight vs lean]; Fig. 1); no statistical difference was found between obese and overweight postmenopausal women. In a multivariate analysis, the statistical significance between obese and lean postmenopausal women was retained even after adding as covariates all the components of the metabolic syndrome, whereas between overweight and lean postmenopausal women, it was reduced to a level that did not formally attain

TABLE 1. *Clinical and biochemical characteristics of the study population (N = 390)*

Variable	
Age, y	63.1 ± 7.7
Total cholesterol, mg/dL	225.7 ± 40
Triglycerides, mg/dL	115.9 ± 55.6
High-density lipoprotein cholesterol, mg/dL	56.8 ± 13.1
Low-density lipoprotein cholesterol, mg/dL	145.6 ± 35.7
Fasting glucose, mg/dL	102.6 ± 21.5
Apolipoprotein B, g/L	1.12 ± 0.2
High-sensitivity CRP, mg/L	2.6 ± 3.8
Insulin, mU/L	6.8 ± 4.4
Body mass index, kg/m^2	28.0 ± 4.6
Waist circumference, cm	90.3 ± 11.0
HOMA	1.7 ± 1.34
Systolic blood pressure, mm Hg	140.1 ± 19.5
Diastolic blood pressure, mm Hg	80.7 ± 8.8

Values are expressed as mean ± SD. International System conversion factors: to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586; to convert glucose to millimoles per liter, multiply by 0.05551; to convert total and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586.
CRP, C-reactive protein; HOMA, homeostasis model assessment.

TABLE 2. *Univariate predictors of an increased common carotid mean maximum IMT (>1 mm; n = 202/361) and increased lumen diameter (upper 90th percentile; n = 36/354)*

	Increased common carotid IMT		Increased lumen diameter	
Independent variables	OR	95% CI	OR	95% CI
Triglycerides tertiles[a]	1.24	0.93-1.64	1.62	1.08-2.42
Low-density lipoprotein cholesterol tertiles[a]	1.37	1.05-1.78	0.89	0.58-1.37
High-density lipoprotein cholesterol tertiles[a]	0.80	0.62-1.04	0.77	0.50-1.19
Apolipoprotein B tertiles[a]	1.33	1.02-1.73	1.14	0.74-1.75
High-sensitivity CRP tertiles[a]	0.97	0.75-1.25	1.49	0.97-2.29
HOMA tertiles[a]	1.27	0.98-1.65	1.11	0.72-1.72
Systolic blood pressure tertiles[a]	2.42	1.82-3.23	2.24	1.35-3.72
Diastolic blood pressure tertiles[a]	1.18	0.90-1.54	2.10	1.28-3.43
BMI tertiles[a]	1.50	1.15-1.96	1.98	1.21-3.21
Waist circumference tertiles[a]	1.40	1.08-1.81	1.88	1.18-2.99
Δ BMI as compared with age 20 y[a]	0.98	0.93-1.03	0.93	0.86-1.01
Δ BMI final vs baseline visit[a]	0.99	0.89-1.10	0.96	0.81-1.15
Metabolic syndrome diagnosis[b]	2.02	1.30-3.13	2.26	1.11-4.62
Age[c]	1.11	1.07-1.14	1.06	1.01-1.11

BMI changes over the adult lifetime (ΔBMI as compared with age 20 y) was calculated in comparison with BMI reported at 20 y of age using the following formula: ΔBMI = BMI at the final visit − BMI at 20 y of age. BMI changes between baseline visit and the final visit, during the observation period of 10 y, was calculated with the following formula: Δ BMI final vs baseline visit = BMI at final visit − BMI at baseline visit.
IMT, intima-media thickness; OR, odds ratio; CRP, C-reactive protein; HOMA, homeostasis model assessment; BMI, body mass index.
[a]Discrete variables (tertile 3 vs tertile 1).
[b]Yes/no.
[c]Continuous variable.

TABLE 3. *Relationships among increased common carotid mean maximum IMT, BMI tertiles, and metabolic syndrome diagnosis and among increased common carotid lumen diameter, BMI tertiles, and metabolic syndrome diagnosis*

Dependent variable: increased mean maximum IMT[a]			
Independent variables	*P*	OR	95% CI for OR
BMI tertile I	Reference	1	
BMI tertile II	0.013	2.15	1.17-3.22
BMI tertile III	0.018	2.24	1.15-4.37
Age[b]	<0.001	1.11	1.08-1.15
Metabolic syndrome diagnosis[c]	0.399	1.26	0.73-2.20
Dependent variable: lumen diameter[a]			
Independent variables	*P*	OR	95% CI for OR
BMI tertile I	Reference	1	
BMI tertile II	0.271	1.93	0.59-6.23
BMI tertile III	0.029	3.61	1.14-11.40
Age[b]	0.007	1.07	1.02-1.13
Metabolic syndrome diagnosis[c]	0.448	1.38	0.60-3.17

Multivariate logistic analyses.
IMT, intima-media thickness; BMI, body mass index; OR, odds ratio.
[a]Dichotomous variable: increased IMT greater than 1 mm; increased lumen diameter above the 90th percentile.
[b]Continuous variable.
[c]Yes/no.

statistical significance when systolic blood pressure, triglycerides, or HDL-cholesterol was added to the statistical model.

DISCUSSION

The main finding of the present study is that postmenopausal women with high BMI showed increased common carotid IMT and lumen diameters. This association persisted after adjustment for the presence of the metabolic syndrome. In a previous study, we demonstrated an association of obesity and central fat distribution with carotid artery wall thickening in middle-aged women.[21] However, the population in that study was almost 10 years younger, and almost half the participants were in the premenopause or perimenopause age.

TABLE 4. *Relationships between increased common carotid mean maximum IMT, SBP tertiles, BMI tertiles, and LDL-cholesterol tertiles*

	Dependent variable: increased mean maximum IMT[a]	
Independent variables	OR	95% CI
Model 1		
Age[b]	1.1	1.06-1.14
SBP tertiles[c]	1.77	1.31-2.40
BMI tertiles[c]	1.16	1.07-1.94
LDL tertiles[c]	1.44	0.87-1.56
Model 2		
Age[b]	1.1	1.06-1.14
SBP tertiles[c]	1.79	1.32-2.42
BMI tertiles[c]	1.45	1.08-1.95

Backward stepwise multivariate logistic analyses.
Model 1: all variables statistically significant in univariate analyses.
Model 2: all variables statistically significant in univariate analyses, except LDL tertiles.
IMT, intima-media thickness; SBP, systolic blood pressure; BMI, body mass index; LDL, low-density lipoprotein; OR, odds ratio.
[a]Dichotomous variable: increased IMT greater than 1 mm.
[b]Continuous variable.
[c]Discrete variables (tertile 3 vs tertile 1).

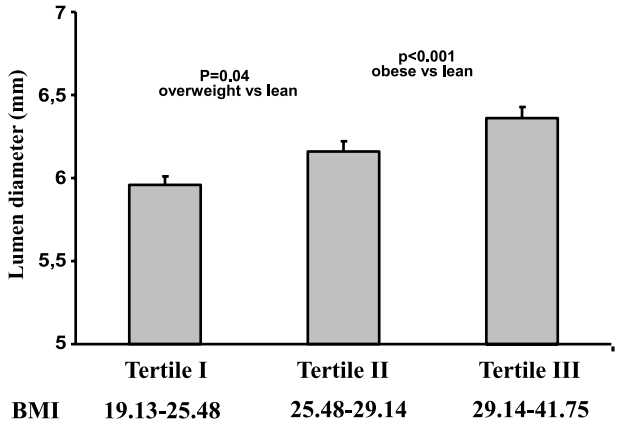

FIG. 1. Lumen diameter by BMI values (N = 390). Error bars indicate SE. BMI, body mass index.

The relationship between BMI, metabolic syndrome, and markers of atherosclerosis is controversial in women. In the Women's Ischemia Syndrome Evaluation study, the metabolic syndrome and BMI were strongly associated, but only the former was associated with a significantly increased 3-year risk of death or major adverse cardiovascular event.[22] In a sample of 313 postmenopausal women, the metabolic syndrome, but not BMI, conferred an approximate threefold adjusted odds of carotid atherosclerosis.[23] Yu et al[24] found that abdominal obesity and metabolic syndrome were both associated with carotid IMT, independently of general obesity, in asymptomatic Chinese postmenopausal women. In a recent analysis conducted in 74 postmenopausal women, multivariate analyses demonstrated that menopause and body weight were predictors of common carotid diameter, independently of atherosclerotic risk factors and metabolic variables.[25] Our study is not in line with another recent observation that brachial artery but not common carotid artery diameter correlated with obesity and waist circumference, independently of systolic blood pressure and other risk factors in postmenopausal women.[26]

Compensatory arterial enlargement is considered a common pathobiological response in early atherosclerosis.[27] In the present research, which is focused on postmenopausal Mediterranean women, obesity per se promoted carotid enlargement, whereas overweight needed the contribution of other cardiovascular risk factors (ie, blood pressure and/or HDL-cholesterol and/or triglycerides) to allow the adaptive remodeling of the carotid wall. We cannot exclude the possibility that, at least to a large extent, the association between BMI and carotid diameters in postmenopausal women could depend on body composition (particularly fat-free mass) that may modulate carotid luminal diameter through changes in stroke volume, as suggested by other authors.[28]

CONCLUSIONS

Our knowledge of the pathophysiology of cardiovascular disease comes mainly from studies in men, and therefore, more sex-specific data are required.[29] Subclinical atherosclerotic

changes in response to age and other hypertrophic stimuli may be different between women and men.[30] Furthermore, despite the fact that after menopause, women are more likely to experience cardiovascular disease than men are, physicians often underdiagnose and undertreat such women.[31] In this context (postmenopausal women), our research demonstrated an independent role of obesity in determining subclinical atherosclerosis.

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