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# Obesity Is Independently Associated With Coronary Endothelial Dysfunction in Patients With Normal or Mildly Diseased Coronary Arteries

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<b>OBJECTIVES</b>	This study evaluates the impact of obesity on coronary endothelial function in patients with normal or mild coronary artery disease.
<b>BACKGROUND</b>	The American Heart Association (AHA) has recently classified obesity as a modifiable risk factor for coronary heart disease.
<b>METHODS</b>	A total of 397 consecutive patients with normal or mildly diseased coronary arteries at angiography underwent coronary vascular reactivity evaluation using intracoronary adenosine, acetylcholine and nitroglycerin. Patients were divided into three groups based on the body mass index (BMI): Group 1, patients with a BMI <25 (n = 117, normal weight); Group 2, patients with a BMI 25–30 (n = 149, overweight) and Group 3, patients with a BMI >30 (n = 131, obese).
<b>RESULTS</b>	There were no significant differences among the groups in regard to other cardiovascular risk factors, except that overweight but not obese patients were significantly older than normal-weight patients ( $47 \pm 1$ years in Group 1, $53 \pm 1$ years in Group 2 and $50 \pm 1$ years in Group 3, $p < 0.001$ ). The percent change of coronary blood flow to acetylcholine (% $\Delta$ CBF Ach) was significantly lower in the obese patients than in the normal-weight group ( $85.2 \pm 12.0\%$ in Group 1, $63.7 \pm 10.0\%$ in Group 2 and $38.1 \pm 9.6\%$ in Group 3, $p = 0.009$ ). By multivariate analysis, overweight (odds ratio, 1.55; 95% confidence interval, 1.2–2.0) and obesity (odds ratio, 2.41; 95% confidence interval, 1.5–4.0) status were independently associated with impaired coronary endothelial function.
<b>CONCLUSIONS</b>	The study demonstrates that obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. (J Am Coll Cardiol 2001;37:1523–8) © 2001 by the American College of Cardiology

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Atherosclerosis is a complex chronic disease of the arteries that may be initiated early in life and becomes more common with increasing age (1,2). The Bogalusa autopsy study revealed that the extent of atherosclerotic lesions in the coronary vessels increased markedly with the presence of multiple risk factors, including obesity, hypertension and hypercholesterolemia (2). Patients with obesity have an increased risk of coronary atherosclerosis. However, until recently the role of obesity as an independent risk factor for coronary atherosclerosis remained controversial; its relationship with coronary atherosclerosis was initially viewed as indirect, because obesity often coexists with other cardiovascular risk factors including hyperlipidemia, hypertension and diabetes (3,4). In response to several long-term longitudinal studies that have indicated obesity as an independent predictor of coronary atherosclerosis (5–8), the American Heart Association (AHA) has reclassified obesity as a major, modifiable risk factor for coronary heart disease (9,10). Furthermore, Calle et al. (11) recently reported

higher total-cause and cardiovascular mortality with increasing body weight in both men and women in all age groups.

Coronary risk factors including hypercholesterolemia, hypertension, diabetes and smoking have been shown to cause impairment of endothelial vasodilator function in both the epicardial and the coronary resistance arteries (12–19). We and others have recently demonstrated an association between coronary endothelial dysfunction and the development of cardiac events in patients with normal or mild coronary artery disease, underscoring the functional significance of coronary endothelial dysfunction (20–22). However, to date the association between obesity and coronary endothelial function in humans with early coronary atherosclerosis has not been defined. Thus, the present study was designed to assess the association between obesity and coronary endothelial function in patients with normal or mild coronary artery disease.

## METHODS

**Study population.** A total of 397 consecutive patients who had been referred for cardiac catheterization to exclude coronary artery disease were considered for enrollment in the study. The decision to refer the patient for cardiac catheterization was made at the discretion of the referring

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**Abbreviations and Acronyms**

AHA	= American Heart Association
BMI	= body mass index
CAD	= coronary artery diameter
CBF	= coronary blood flow
%Δ CBF Ach	= % change of coronary blood flow in response to acetylcholine
%Δ CBF NTG	= % change of coronary blood flow in response to nitroglycerin
CI	= confidence intervals
HDL	= high density lipoprotein
LDL	= low density lipoprotein
OR	= odds ratio

cardiologist. In our institution, the protocol of assessing coronary endothelial dysfunction and coronary flow reserve is used as a clinical practice protocol that is usually performed in patients with normal or mild coronary artery disease in consultation with the referring cardiologist (20). Patients were included in this study if they had the following: 1) angiographically smooth arteries; 2) mild irregularities, <30% lumen diameter stenosis by visual assessment in any major epicardial vessel and 3) proximal coronary arteries >2.0 mm in diameter. Patients with a history of variant angina, documented previous myocardial infarction, acute coronary syndromes, previous coronary artery bypass graft or coronary intervention were excluded from this study (20). Long-acting nitrates and calcium channel blocking agents were both withheld for 36 to 48 h before the study to allow for the assessment of coronary physiology in the baseline state. The study was approved by the Mayo Clinic Institutional Review Board and informed consent was obtained.

The 397 patients in this study were divided into three groups according to their body mass index (BMI) at the time of the study. Group 1 consisted of 117 patients who had a BMI of <25 (normal weight group), Group 2 consisted of 149 patients who had a BMI between 25 and 30 (overweight group) and Group 3 consisted of 131 patients who had a BMI of >30 (obese group).

**Definitions.** The definition of obesity is based on the BMI, which is defined as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). This index is independent of height ( $r = -0.03$ ) and strongly related to weight ( $r = 0.86$ ) (23). Recently the AHA has defined obesity as a BMI >30. A BMI between 25 and 30 is considered overweight and normal BMI <25 (10). Patients were considered to have systemic hypertension if they had a history of elevated blood pressure requiring medical therapy (17).

**Study protocol.** Diagnostic coronary angiography was performed using a 6F Judkins catheter with a standard femoral percutaneous approach. Two thousand five hundred units of intravenous heparin were administered at the beginning of the procedure. Nonionic contrast material was used for all patients. Nitroglycerin was not given before the diagnostic procedure.

Coronary vascular reactivity responses to acetylcholine and adenosine were studied according to a previously reported protocol (16,17,20). After control coronary angiograms had been obtained, a 0.014-inch Doppler guidewire (Endosonics, Santa Ana, California) was introduced within a 2.2F coronary infusion catheter into the left anterior descending coronary artery (16). After stable baseline flow velocities were obtained, a bolus of intracoronary adenosine (18–42  $\mu\text{g}$ ) was administered for measurement of coronary flow reserve. Time was allowed for coronary blood flow to return to baseline, then selective intracoronary infusion of increasing concentrations of acetylcholine ( $10^{-6}$ ,  $10^{-5}$  and  $10^{-4}$  mol/l) was performed for a total of 3 min at each dose. At the end of each infusion, the following data were obtained: electrocardiogram, Doppler velocities and coronary angiography, heart rate and blood pressure. After infusions of acetylcholine, 200 to 300  $\mu\text{g}$  of intracoronary nitroglycerin was given and all data were repeated within 2 min using the same projection as the baseline.

**Quantitative coronary angiography.** Analysis of artery diameter from the cine films was done with a modification of the technique previously described (16,17,20). An end-diastolic still frame at each infusion (baseline, acetylcholine  $\times 3$  and nitroglycerin) was selected from the angiographic sequence. The absolute diameter of the vessel lumen perpendicular to the long axis of the artery was measured by using the 8F guide catheter as the calibration standard. These measurements were made by experienced observers unaware of the results of the coronary vascular reactivity tests or BMI.

**Assessment of coronary blood flow.** Doppler flow velocity spectra were analyzed online to determine time-averaged peak velocity. Coronary flow reserve was calculated as the ratio of hyperemic to basal average peak velocity following adenosine administration. Volumetric coronary blood flow (CBF) was determined from the relation:  $\text{CBF} = \text{cross-sectional area} \times \text{average peak velocity} \times 0.5$  (24,25).

**Statistical analysis.** Continuous variables are summarized as mean  $\pm$  standard error, unless otherwise indicated. Discrete variables are presented as frequencies and percentages of available data. Differences between groups were tested using one-way analysis of variance or Pearson chi-squared test. Pairwise comparisons were conducted using Tukey's Studentized range. Odds ratios adjusted for conventional risk factors (age, gender, lipid levels, hypertension, smoking status and menopausal status) were estimated by ordinal logistic regression. A continuous relation between BMI and percent change of coronary blood flow to acetylcholine was evaluated using Spearman correlation coefficient. A linear regression model between BMI and percent change of coronary blood flow to acetylcholine with age, glucose, high density lipoprotein, hypertension and triglycerides as covariates was also assessed.

**Table 1.** Patient Characteristics and Fasting Serum Lipids and Glucose

Characteristics	BMI < 25 (n = 117)	25 ≤ BMI < 30 (n = 149)	BMI > 30 (n = 131)
Age, yrs, mean (range)	47 (17–78)	53 (23–80)*	50 (26–82)
Male, no. (%)	37 (32)	68 (46)	47 (36)
Hypertension, no. (%)	32 (28)	49 (33)	40 (31)
Ejection fraction (mean ± SD)	0.64 ± 0.08	0.64 ± 0.09	0.65 ± 0.09
Diabetes, no. (%)	5 (4)	7 (5)	11 (8)
Family history, no. (%)	58 (52)	76 (52)	69 (54)
Ever smoked, no. (%)	57 (51)	75 (51)	57 (45)
Postmenopause, no. (%)	39 (52)	61 (84)*	50 (63)*
Mean arterial pressure (mm Hg)	102 ± 17	105 ± 15	105 ± 14
Total Cholesterol, mg/dl	203 ± 5	218 ± 4	209 ± 4
Triglycerides, mg/dl	127 ± 9	159 ± 8*	184 ± 10*
HDL cholesterol, mg/dl	59 ± 2	52 ± 2	49 ± 1*
LDL cholesterol, mg/dl	118 ± 4	133 ± 4	123 ± 4
Fasting blood glucose, mg %	91 ± 1	99 ± 2†	102 ± 2†
Medications (%)			
Angiotensin-converting enzyme inhibitors	5.1	6.0	3.1
Beta-blockers	22.2	18.8	20.6
Calcium channel blockers	40.2	37.6	29.0
Lipid lowering	20.5	20.8	14.5
Antioxidants	10.2	9.4	8.6

Data presented are mean ± SE unless otherwise indicated.

\*p < 0.001 versus normal weight group; †p = 0.005 versus normal weight group.

BMI = body mass index; HDL = high density lipoprotein; LDL = low density lipoprotein; SD = standard deviation.

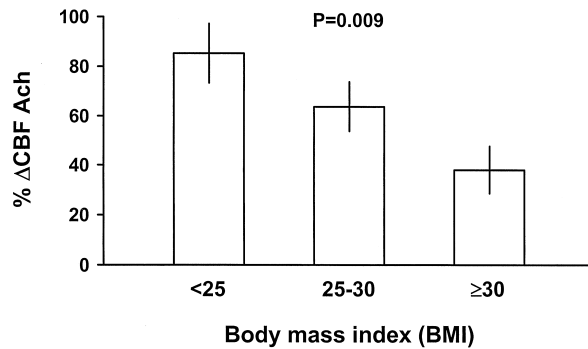
## RESULTS

**Patient characteristics.** Patients with normal weight were significantly younger than those in the overweight group (47 ± 14 yrs in Group 1, 53 ± 12 yrs in Group 2 and 50 ± 10 yrs in Group 3) (Table 1). This significant difference in age is primarily between the overweight and normal-weight groups, whereas there were no significant differences between the obese and normal-weight groups. Women in the normal-weight group were less likely to be postmenopausal (52%, 84% and 63% respectively, p < 0.001). There was no significant difference among the study groups with regard to coronary risk factors, mean arterial pressure or the use of medications (Table 1).

**BMI, fasting blood glucose and serum lipids.** Group 1 consisted of patients with a BMI <25; the mean BMI was 22.2 ± 0.18 kg/m<sup>2</sup>. Group 2 consisted of patients with BMI between 25 and 30; the mean BMI was 27.4 ± 0.12 kg/m<sup>2</sup>. Group 3 consisted of patients with BMI >30; the mean BMI was 34.7 ± 0.39 kg/m<sup>2</sup>. Compared with the normal-weight group, both the overweight and obese groups had significantly higher levels of fasting blood glucose (91.4 ± 1.3 mg%, 98.8 ± 2.5 mg% and 101.8 ± 2.4 mg%, respectively, p < 0.05) and triglycerides (126.6 ± 8.7 mg/dl, 159.1 ± 7.7 mg/dl and 184.1 ± 10.0 mg/dl, respectively, p < 0.05). There was no statistical difference, however, between the overweight and obese groups with regard to these two variables. There was no difference among all three groups with regard to fasting total cholesterol level (203 ± 5 mg/dl, 218 ± 4 mg/dl and 209 ± 4 mg/dl). However, compared with the normal-weight group, both the overweight and obese groups had slightly significantly lower

levels of HDL (59 ± 2 mg/dl, 52 ± 2 mg/dl and 49 ± 1 mg/dl, both p < 0.001). Furthermore, there was a significant correlation between BMI and elevated triglyceride levels, low high density lipoprotein and fasting blood glucose levels (p < 0.001). However, there was no evidence of interaction between gender and BMI.

**Changes in coronary blood flow.** Baseline coronary blood flow did not differ among the study groups (48.3 ± 2.5 ml/min in Group 1, 52.4 ± 2.9 ml/min in Group 2 and 50.4 ± 3.0 ml/min in Group 3, p = 0.61). Baseline coronary artery diameter also did not differ among the three groups (2.2 ± 0.06 mm in Group 1, 2.25 ± 0.05 mm in Group 2 and 2.20 ± 0.05 mm in Group 3, p = 0.72). Coronary endothelial function assessment using the percent change in coronary blood flow in response to acetylcholine (%Δ CBF Ach) demonstrated significant reduction in coronary blood flow changes in the obese group compared with the normal-weight group (85.2 ± 12.0% in Group 1, 63.7 ± 10.0% in Group 2 and 38.1 ± 9.6% in Group 3, p = 0.009) (Fig. 1). This difference remained significant even after adjustment for age (p = 0.01). However, the percent change coronary artery diameter in response to acetylcholine was not significantly different among the three groups (–14.2% ± 2.6% in Group 1, –13.5 ± 2.4% in Group 2 and –15.9 ± 2.5% in Group 3, p = 0.79). Furthermore, the coronary flow reserve to adenosine was within the normal range among the three groups (2.88 ± 0.07 in Group 1, 2.81 ± 0.06 in Group 2 and 3.06 ± 0.07 in Group 3). There was no difference in percent change of coronary blood flow in response to nitroglycerin (%Δ CBF NTG) among the three groups (53 ± 9.0% in Group 1, 38 ± 11% in Group



**Figure 1.** Mean ( $\pm$  SE) of the percent change of coronary blood flow in response to acetylcholine in the study groups. %  $\Delta$ CBF Ach = % change of coronary blood flow in response to acetylcholine.

2 and  $54 \pm 10\%$  in Group 3). There was no correlation between % $\Delta$  CBF NTG and BMI (Spearman  $r = -0.007$ ,  $p = 0.90$ ). By multivariate ordinal logistic regression analysis, overweight (odds ratio, 1.55; 95% confidence interval, 1.2–2.0) and obesity (odds ratio, 2.41; 95% confidence interval, 1.5–4.0) status were independent predictors of impaired coronary endothelial function. Similarly, a significant association between obesity and coronary endothelial dysfunction was observed when BMI was analyzed as a continuous variable univariately (Spearman  $r = -0.167$ ,  $p = 0.0012$ ) and in a multivariable analysis ( $p = 0.03$ ). There were no significant differences in the angiographic degrees of coronary atherosclerosis among the three groups.

## DISCUSSION

The current study demonstrates for the first time that obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries and that it is a risk factor for the progression of coronary atherosclerosis in humans. The current study underscores the need to address obesity as a risk factor for the development of coronary atherosclerosis. The role of obesity as an independent risk factor for coronary atherosclerosis continues to emerge. The Nurses' Health Study of women 30 to 55 years of age who were free of cardiovascular disease at entry revealed that the rate of cardiac mortality among the obese women was more than twice that among the leanest women (5). Moreover, the Health Professionals Follow-up Study revealed BMI to be a strong predictor of coronary heart disease. Men with BMI  $\geq 33$  had a relative risk of 3.44 for coronary heart disease (8).

Coronary endothelial dysfunction is considered an early stage of coronary atherosclerosis and may occur at the epicardial vessels, resistance vessels or both (12–18,25). In the current study there was no difference between the groups in the epicardial coronary response to acetylcholine. Moreover, there was no attenuation in the response to the nonendothelial vasodilators, including adenosine and nitroglycerin. Thus, our study suggests that the primary effect of obesity on coronary endothelial function appears to occur at the resistance vessels. This observation is in accord with

other studies that demonstrated that coronary endothelial dysfunction occurs at the resistance vessels before the development of epicardial coronary artery disease (13,14). Another possibility for this differential effect at the resistance vessels may be related to the coexistence of insulin resistance syndrome, which is associated with obesity, in our patients (26). This possible mechanism is supported by the correlation between BMI and other metabolic factors that was obtained in the current study.

The current study extends recent observation of an association between obesity and peripheral endothelial function (26–29). This association may occur through the development of insulin resistance syndrome that is commonly present in obese patients and as was demonstrated by Steinberg et al. (26). Our study also indirectly suggests an association between obesity, insulin resistance syndrome and coronary endothelial dysfunction, as evidenced by the presence of elevated fasting blood glucose and triglycerides when compared with normal-weight groups. Several other investigators reported an association between endothelial dysfunction and insulin resistance syndrome (30). Furthermore, Yudkin et al. (30) suggested that adipose tissue is an important determinant of a low-level, chronic inflammatory state reflected by increased levels of interleukin-6, tumor necrosis factor- $\alpha$  and C-reactive protein inducing insulin resistance and endothelial dysfunction. Other possible underlying mechanisms may include the activation of the sympathetic nervous system, activation of vasoconstrictive peptides such as endothelin-1 and angiotensin and decreased insulin-mediated vasodilation, all of which were found to be associated with obesity (31). This link between obesity and coronary endothelial dysfunction suggests a major independent role of obesity in the progression of coronary artery disease, as evidenced by the association between severe endothelial dysfunction and cardiac events at follow-up in patients with mild coronary artery disease (20–22).

**Clinical implications.** The current in vivo study extends the previous epidemiologic (5–8) and autopsy (2) observations that obesity is an important independent risk factor for the development of coronary atherosclerosis. Furthermore, in contrast to these previous studies that have only adjusted for limited numbers of cardiovascular risk factors, thus making the issue of “independence” unresolved (5–8), our study demonstrates an independent effect of obesity on coronary endothelial function even after analysis of all conventional cardiovascular risk factors. These data support the recent AHA recommendations for classifying obesity as a major modifiable risk factor for coronary atherosclerosis.

The worldwide epidemic of obesity is reaching critical proportions. An estimated 250 million people in the world are obese, and this number is predicted to reach 300 million by 2050 (32). Obesity has joined the ranks of chronic diseases that have displaced undernutrition and infectious diseases as the major causes of death (32,33). In the developing countries, the emerging epidemic of cardiovascular disease may in part be explained by recent lifestyle changes resulting in

increased body weight (34). The increasing prevalence of obesity will have a major effect on health care costs (35).

Obesity is a chronic disease that is present in both the adult and the pediatric population (36), and compared to other cardiovascular risk factors such as hypertension and diabetes, the presence of obesity is evident to obese people as well as to casual observers. Preventive measures are the primary tools to slow or reverse the worldwide explosion of obesity (32). Unfortunately, research on primary and secondary prevention of obesity is in its infancy and more efforts are needed (10). Furthermore, no matter how effective preventive strategies may be, there will still be a large pool of people who are already at risk of obesity and who need treatment. Simple prevention techniques may have major impact. The importance of modifying this risk factor is underscored by the recent observation that exercise training may improve coronary endothelial function (37). Other management strategies for treatment and secondary prevention of obesity must be appropriate and safe enough for use by all obese people, even those who may be without clear medical indications for intensive interventions such as drug treatment (38).

**Study limitations.** Although all traditional risk factors have been analyzed, other nontraditional risk factors including homocysteine levels have not been adjusted for. Second, this is a cross-sectional study and its findings may warrant confirmation through a prospective study. Third, because this study was conducted in patients undergoing coronary angiography, selection bias cannot be ruled out in that physicians might be reluctant to refer these patients for coronary angiography until their symptoms are advanced. Fourth, other measures of adiposity such as waist-hip ratios were not measured.

**Conclusions.** This *in vivo* study demonstrates for the first time that obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. This study supports a role for obesity as an independent risk factor for the development of coronary atherosclerosis in humans.

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