Progression of Subclinical Coronary Atherosclerosis
Does Obesity Make a Difference?

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Background—Obesity is associated with coronary artery calcification (CAC), a marker of the presence and extent of subclinical coronary atherosclerosis. Obesity adds incremental information in identifying those at higher risk of coronary heart disease to traditional risk factor assessment. The present study examined associations between obesity measures and progression of CAC in those at higher (≥10%) and lower (<10%) 10-year coronary heart disease risk according to the Framingham risk equation.

Methods and Results—In this study, 443 asymptomatic white individuals >30 years of age (243 men) had baseline and follow-up CAC measurements an average of 8.9 years apart. Multivariable linear regression models were fit to determine associations of obesity measures at baseline with progression of CAC defined as loge of the difference between follow-up and baseline CAC area plus 1 divided by time (in years) between examinations, adjusting for baseline CAC quantity, age, sex, baseline hypertension status, and baseline cholesterol level. Among 329 participants (74.3%) in the lower-risk group, waist circumference (P = 0.024), waist-to-hip ratio (P < 0.001), body mass index (P = 0.036), and being overweight compared with being underweight or of normal weight (P = 0.008) were each significantly positively associated with progression of CAC. Among those at higher coronary heart disease risk, no baseline obesity measures were associated with CAC progression.

Conclusions—Various measures of obesity were associated with increased progression of CAC in those at lower risk of coronary heart disease. Future studies examining the effectiveness of weight reduction strategies in reducing CAC progression among those with an otherwise favorable risk factor profile may be warranted. (Circulation. 2005;111:1877-1882.)

Key Words: atherosclerosis ■ calcium ■ imaging ■ obesity ■ population

More than half of US adults are overweight or obese, placing them at increased risk for morbidity and mortality from chronic diseases, including coronary heart disease (CHD).1,2 Coronary artery calcification (CAC), a marker of subclinical coronary atherosclerosis,3 progresses over time4 and predicts CHD events.5 Although CAC is associated with measures of obesity obtained at the same time as the CAC measurement,6 only one study has investigated the association between obesity and progression of CAC, and that study included only those with type I diabetes.7 Thus, little is known about the role of obesity in the progression of CAC in asymptomatic individuals free of diabetes.

The present study examined associations between various measures of obesity and the presence, quantity, and progression of CAC over time in asymptomatic men and women >30 years of age without diabetes from a community-based study. Recently, having a body mass index (BMI) ≥30 kg/m² added information in predicting increased CAC quantity among those with CHD risk ≥20% according to traditional risk factor assessment.8 Therefore, we examined associations in subgroups of individuals identified as having higher or lower CHD risk on the basis of the Framingham risk equation. A better understanding of whether obesity is an independent predictor of progression in CAC quantity may identify which individuals to target for interventions to slow the progression of subclinical coronary atherosclerosis.

Methods

Study Participants
The Rochester Family Heart Study (RFHS), a community-based study of 3974 individuals 5 to 90 years of age, was conducted between 1984 and 1991.9,10 The Epidemiology of Coronary Artery Calcification (ECAC) study, conducted between 1991 and 1998, examined 1240 participants from the RFHS and 496 individuals living in the vicinity of Rochester (Minn) who were ≥20 years of age at the time of recruitment for the ECAC study; who were not pregnant or lactating, and who never had coronary or noncoronary
heart surgery. Participants in the present study were recruited for a follow-up examination between December 2000 and July 2004. In general, participants were invited to return for a second examination on the basis of age (older age first) and longer time since baseline examination. Eligible family members of these individuals who also participated in the baseline study were invited to return at the same time. The Mayo Clinic and University of Michigan Institutional Review boards approved the study protocols, and participants gave written informed consent.

A total of 553 individuals >30 years of age at baseline without a previous report of myocardial infarction or stroke at baseline or follow-up had baseline and follow-up examinations available. Seven individuals with history of diabetes at baseline, 69 reporting a previous cancer diagnosis (excluding nonmelanoma skin cancer), 21 with missing data, and 13 with extreme measures of body size based on graphic inspection of the data values were excluded from analysis. The final sample size consisted of 443 white individuals (243 men).

**Risk Factor Assessment**

During the baseline and follow-up interviews, participants reported current medication use and history of smoking, physician-diagnosed hypertension, myocardial infarction, stroke, or diabetes. Height was measured by a wall stadiometer; weight was measured by electronic balance; and BMI was calculated (in kg/m²). Participants were categorized as overweight or obese if their BMI was ≥25 or ≥30 kg/m², respectively. Waist circumference was measured at the umbilicus; hips were measured at the level of maximal circumference; and waist-to-hip ratio was calculated. Abdominal obesity was defined from National Cholesterol Education Program/Adult Treatment Panel III criteria as waist circumference >102 cm in men and >88 cm in women.

Standard enzymatic methods were used to measure plasma glucose, total cholesterol, HDL cholesterol, and triglycerides after overnight fasting. Systolic and diastolic blood pressure levels were measured in the right arm with a random-zero sphygmomanometer (Hawksley and Sons). Three measures 2 minutes apart were taken, and the average of the second and third measurements was used. Individuals were considered hypertensive if they reported a prior diagnosis of hypertension and use of prescription antihypertensive medication or if the average systolic or diastolic blood pressure was ≥140 or ≥90 mm Hg, respectively. Participants were considered diabetic if they reported using insulin or oral hypoglycemic agents or if they reported a physician diagnosis of diabetes but were not currently taking a pharmacological agent to control their high glucose levels.

The Framingham risk equation was used to estimate the 10-year probability of CHD (10-year CHD risk) on the basis of the participant’s sex, systolic blood pressure, ratio of total cholesterol to HDL cholesterol, history of cigarette smoking in the past year, and diabetes status at baseline. National Cholesterol Education Program/Adult Treatment Panel III considers 3 categories for 10-year CHD risk: <10%, 10% to 20%, and >20%; similar cutoffs were used in a recent article demonstrating incremental prediction benefits when obesity status is used in addition to traditional risk factor assessment. The present study participants were at relatively low to intermediate risk; only 17 individuals (3.8%) had 10-year CHD risk >20%. Thus, we defined lower or higher risk of a CHD event on the basis of 10-year risk of CHD <10% or ≥10%, respectively.

**Electron-Beam CT Measures of CAC**

CAC was measured with an Imatron C-150 electron-beam CT scanner (Imatron Inc). Protocols at baseline and follow-up were written informed consent. Review boards approved the study protocols, and participants gave written informed consent.

Several CAC progression studies calculated a measure for annual change as follows: exponentiated difference of the log-transformed CAC scores divided by time minus 1. This study excluded those with detectable CAC. In the present study, progression of CAC was defined as the log annual change in CAC quantity, calculated as follows: log of the difference between follow-up and baseline CAC area plus 1 divided by time (in years) between baseline and follow-up examinations. Advantages of our measure are inclusion of those without detectable CAC and a log transformation of annual change to reduce the nonnormality of the distribution. If the difference between follow-up and baseline CAC quantity was <0 in our study, the difference was set to 0 (to avoid taking the log of a negative number); this included 25 participants with a negative difference.

Multivariable linear regression models were fit to determine associations between baseline obesity measures and log annual change in CAC quantity. Models were adjusted for log(baseline CAC quantity+1), baseline age, male sex, baseline hypertension status, and baseline total cholesterol level. Interactions between male sex and baseline obesity measures were considered. Model fit was evaluated with residual plots, and potentially influential observations were investigated.

Parameter estimates from linear regression models with log-transformed outcome variables were exponentiated and interpreted as the estimated relative increase in the outcome variable associated with a 1-SD increase in a continuous predictor variable or a change in category for a dichotomous predictor variable.
Higher-risk participants had significantly worse risk factor distributions compared with lower-risk participants ($P<0.001$ for all comparisons); however, there were no significant differences between the higher- and lower-risk groups in prevalence of cigarette smoking or mean hip circumference.

Prevalence of detectable CAC increased over time in both higher- and lower-risk groups. At baseline and follow-up, higher-risk individuals had significantly larger CAC quantity ($P<0.001$ for both) compared with lower-risk individuals. The average annual change in CAC area in the higher-risk group was significantly higher than in the lower-risk group (10.2 versus 2.6 mm$^2$/y, respectively; $P<0.001$; Table 1).

### Association of Baseline 10-Year CHD Risk With Presence, Quantity, and Progression of CAC

Mean 10-year CHD risk in the 443 participants was $7.5\pm5.8\%$. In the entire sample of 443 participants, a 1-unit-SD increase in the 10-year CHD risk was associated with a 3.3-times-greater odds of having detectable CAC at baseline ($P<0.001$). Similarly, a 1-unit-SD increase in 10-year CHD risk was associated with an 80% higher CAC quantity at baseline ($P<0.001$) in those with CAC $>0$ mm$^2$ at baseline. Finally, a 1-unit-SD increase in 10-year CHD risk was associated with a 60% increase in annual change in CAC quantity, adjusted for baseline CAC quantity ($P<0.001$) (data not shown).

### Association of Obesity Measures With Presence and Quantity of CAC Area at Baseline

As shown in Table 2, in the higher-risk group, those with abdominal obesity at baseline had 3.4-times-greater adjusted odds of having CAC compared with those without abdominal obesity ($P=0.046$). A 1-unit-SD increase in BMI resulted in a 2.1-times-greater adjusted odds of having CAC at baseline in the higher-risk group ($P=0.041$). In the higher-risk group, obese individuals had a 2.2-times-greater adjusted odds of having baseline CAC than underweight and normal-weight individuals ($P=0.046$).

In those at lower risk of CHD, a 1-unit increase in SD in baseline waist circumference, baseline waist-to-hip ratio, and baseline BMI was associated with a 1.7-, 2.1-, and 1.5-times-greater adjusted odds of having detectable CAC at baseline compared with those without abdominal obesity at baseline ($P=0.010$). Obese individuals had a 1.8-times-greater adjusted odds of having baseline CAC compared with those who were underweight or of normal weight ($P=0.002$).

In those at higher risk for CHD, the maximum CAC quantity was 756.7 mm$^2$; among those with detectable CAC at baseline, a 1-unit-SD increase in baseline waist circumference was associated with a 50% increase in CAC quantity at baseline ($P=0.041$). In those at lower risk for CHD, the maximum CAC quantity was 534.0 mm$^2$, and a 1-unit-SD increase in baseline hip circumference was associated with a 20% decrease in CAC quantity at baseline ($P=0.047$).

Inferences remained the same after additionally adjusting for baseline hypertension status and baseline cholesterol level. No influential observations were detected in any model in Table 2.

### Results

At baseline, the mean age was 51.1 years (range, 30.1 to 74.9 years), and 243 (54.9%) were male. The mean time between baseline and follow-up examinations was 8.9 years (range, 3.3 to 13.4 years). Baseline characteristics of participants by risk classification are presented in Table 1. One quarter of participants (114 of 443, 25.7%) were classified as higher risk. Overall, higher-risk participants had significantly worse risk factor distributions compared with lower-risk participants ($P<0.001$ for all comparisons); however, there were no significant differences between the higher- and lower-risk groups in prevalence of cigarette smoking or mean hip circumference.

Prevalence of detectable CAC increased over time in both higher- and lower-risk groups. At baseline and follow-up, higher-risk individuals had significantly larger CAC quantity ($P<0.001$ for both) compared with lower-risk individuals. The average annual change in CAC area in the higher-risk group was significantly higher than in the lower-risk group (10.2 versus 2.6 mm$^2$/y, respectively; $P<0.001$; Table 1).
Association of Obesity Measures at Baseline and Progression of CAC Quantity

After adjustment for baseline CAC quantity, baseline age, male sex, baseline hypertension status, and baseline cholesterol level, no baseline obesity measure was significantly associated with progression of CAC quantity among those at higher risk for CHD (Table 3). Only log baseline CAC quantity (P<0.001) predicted CAC progression in the higher-risk group.

After adjustment for log baseline CAC quantity, baseline age, male sex, baseline hypertension status, and baseline cholesterol level in those at lower risk for CHD, waist circumference (P=0.024), waist-to-hip ratio (P<0.001), BMI (P=0.036), and being overweight (P=0.008) compared with being underweight or normal weight were each positively and significantly associated with progression in CAC quantity (Table 3). A 1-unit increase in the SD of baseline waist circumference, waist-to-hip ratio, and BMI was associated with an estimated 19%, 49%, and 15% increase in annual change in CAC area, respectively. Overweight individuals are expected to have a 51% increase in annual change in CAC compared with underweight and normal-weight individuals.

A small number of participants in the present study were members of the same family. In the lower-risk group, 228 individuals were from unique families, and there were 39 sibships of 2, 4 sibships of 3, 1 sibship of 5, and 1 sibship of 6; in the higher-risk group, 99 participants were from unique families, and there were 5 sibships of 2 and 1 sibship of 5. When we refit the models in Table 3 using generalized estimating equations to account for the potential correlation between observations taken from the same family, all inferences were identical to the model results ignoring genetic relationships.24

Participants with diabetes were excluded a priori from the present analyses. Waist circumference and fasting glucose at baseline were significantly correlated (correlation coefficient, 0.33; P<0.001) in the total sample (n=443). When we refit the model from Table 3 that included waist circumference in those at lower risk of CHD and included fasting glucose, neither waist circumference (P=0.102) nor fasting glucose (P=0.167) was significantly associated with progression of CAC quantity. However, fasting glucose (P=0.040) was positively associated with CAC progression when waist circumference was not included in the model.

Follow-up times were similar in obese and nonobese participants. In the 57 obese individuals in the lower-risk group, the mean follow-up time was 9.4 years compared with 9.3 years in the nonobese participants (P=0.802); in the 36 obese participants in the higher-risk group, the mean follow-up time was 8.1 years compared with 8.0 years in the nonobese participants (P=0.818). Additionally, incorporation of follow-up time into the multivariable models in Table 3 did not alter the associations.

There was no evidence for sex-specific differences in the relationship between baseline obesity measures and progression of CAC. No influential observations were detected in any modeling procedures for CAC progression.

**Discussion**

Our findings add evidence that obesity adds valuable clinical information, independent of traditional CHD risk factors, for identifying individuals at risk for CHD who otherwise may be
considered to be at low to intermediate risk. Participants in the present study who were classified as at lower risk on the basis of traditional risk factors had a 10-year CHD risk <10%. Among these participants, measures of obesity were associated with the future progression of CAC over time.

Although other studies have shown associations between obesity measures and CAC measured at the same time, this is the first study to provide evidence that obesity measures are associated with CAC progression among nondiabetic individuals. Associations between different obesity measures and CAC varied in the present study. This is not unexpected, given that waist circumference and BMI capture different aspects of adiposity. Waist circumference measures central adiposity and is associated with insulin resistance and glucose abnormalities, whereas BMI measures overall adiposity and may be associated with different pathogenic mechanisms. Increased hip circumference, independent of increased waist circumference, may be an indicator of a benign adiposity that does not affect the abdominal organs and has been shown to be protective against cardiovascular morbidity and mortality in women.

In the present study, obesity measures were associated with baseline CAC in both risk groups. However, baseline obesity measures were associated with CAC progression only in the lower-risk group. Against this background of fewer traditional risk factors, associations with other risk factors such as obesity may be more readily identified. In addition, every other risk factor considered predicted CAC progression in the lower-risk group. In contrast, in the higher-risk group, it was interesting that baseline CAC quantity was the only predictor of CAC progression. Against a background of more traditional risk factors, as in the higher-risk group, other factors for CAC progression may be more difficult to identify.

Measures of abdominal obesity are associated with glucose abnormalities; in the present study, when we refit the multivariable model of CAC progression in the lower-risk group including waist circumference and fasting glucose, neither was statistically significantly associated with progression of CAC quantity. Individually, however, fasting glucose and baseline waist circumference each were significantly associated with increased progression. These findings suggest that the increased progression of CAC resulting from increased waist circumference or fasting glucose may occur through similar mechanisms. Thus, easily obtained abdominal size measurement during regular physical examinations or screenings may be a useful clinical tool for identifying individuals at risk for accelerated atherosclerosis progression.

Obesity is associated with an increased inflammatory response, and inflammatory processes are involved in the pathogenesis of atherosclerosis. Weight reduction has been shown to reduce the presence of inflammatory markers and to reduce carotid intima-media thickness in obese premenopausal women. Lifestyle interventions, including energy restriction and vigorous exercise, were shown to reduce both glucose and insulin concentrations in response to an oral glucose tolerance test among overweight, sedentary men. Obesity measures in this study may be surrogates for unmeasured but important factors for atherosclerosis.

Overweight/obesity is an important public health concern, and the prevention and treatment of overweight and obesity is a goal of the US Department of Health and Human Services Healthy People 2010 initiative. Approximately 16% of US children 6 to 19 years of age are obese, and there is evidence that childhood obesity predicts adult obesity. Furthermore, the effects of obesity on atherosclerosis may begin in childhood. Mahoney et al previously showed that childhood weight and BMI in male subjects were significantly associated with the presence of CAC detected 15 to 20 years later in young adults. In the present study, lower-risk participants who were obese were estimated to have significantly greater progression of CAC than underweight and normal-weight participants. Thus, public health interventions targeted at prevention of obesity may aid in slowing the progressive nature of atherosclerosis.

This study has several limitations. The study population is limited to white individuals, and the associations found in the present study may not be generalizable to other study populations. Obesity is related to genetic susceptibility and a variety of underlying lifestyle factors, including diet and physical inactivity. The present study was not designed to assess the relationships between these factors and CAC. Finally, we used obesity measures taken at a single time point to predict the presence, quantity, and progression of CAC; these measures may be only a proxy for the level of obesity for any given individual over his or her lifetime.

Participants (n=25) in the present study whose CAC area at follow-up was less than the CAC area at baseline were treated as having no change as part of the progression definition. The mean change in this group was −0.3 mm²/y. The median CAC area at baseline among these participants was 2.4 mm², with a maximum baseline CAC area of 18.9 mm². The negative differences between

### TABLE 3. Association of Baseline Obesity Measures And Log Annual Change in CAC Quantity Adjusted for Log Baseline CAC Quantity, Baseline Age, Male Sex, Baseline Hypertension, and Baseline Cholesterol Level Among Those at Higher or Lower 10-Year Risk of CHD

<table>
<thead>
<tr>
<th>Baseline body size measure</th>
<th>Higher Risk, Relative Increase* (95% CI)</th>
<th>Lower Risk, Relative Increase* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, cm</td>
<td>0.76 (0.57–1.00)</td>
<td>1.19§ (1.01–1.39)</td>
</tr>
<tr>
<td>Abdominal obesity†</td>
<td>0.88 (0.55–1.41)</td>
<td>1.27 (0.88–1.84)</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>0.81 (0.63–1.05)</td>
<td>1.01 (0.88–1.16)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.78 (0.53–1.15)</td>
<td>1.49¶ (1.23–1.81)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.97 (0.75–1.25)</td>
<td>1.15§ (1.00–1.32)</td>
</tr>
<tr>
<td>BMI category‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under/normal weight</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.91 (0.50–1.68)</td>
<td>1.51¶ (1.12–2.02)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.05 (0.75–1.47)</td>
<td>1.16 (0.96–1.41)</td>
</tr>
</tbody>
</table>

*Relative increase refers to exponentiated parameter estimates and are for a 1-unit-SD increase in obesity measure or change in category.
†Abdominal obesity defined as waist circumference >102 cm in men and >88 cm in women.
‡BMI categories defined as follows: underweight/normal weight, BMI <25 kg/m²; overweight, BMI ≥25 and <30 kg/m²; obese, BMI ≥30 kg/m².
§P<0.05.
¶P<0.001.

The present study may not be generalizable to other study populations. Obesity is related to genetic susceptibility and a variety of underlying lifestyle factors, including diet and physical inactivity.
baseline and follow-up are most likely attributable to measurement errors rather than being true negative changes; thus, the treatment of these participants as having no change between baseline and follow-up is reasonable.

The present study was conducted among asymptomatic community-based research participants without diabetes who were neither selected nor self-referred on the basis of any risk factor or disease. All obesity measures were clinically obtained, minimizing potential bias associated with self-reported obesity.

In summary, obesity measures were associated with the presence and quantity of CAC. Importantly, obesity measures were associated with the progression of CAC quantity among individuals considered to be at lower risk for CHD. Interventions aimed at the primary prevention of obesity may help to retard the development and progression of CAC. Future studies examining the effectiveness of weight reduction strategies in reducing CAC progression among those with an otherwise favorable risk factor profile may be warranted.

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