The Association of Differing Measures of Overweight and Obesity With Prevalent Atherosclerosis

The Dallas Heart Study

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Objectives

This study sought to evaluate the associations between different measures of obesity and prevalent atherosclerosis in a large population-based cohort.

Background

Although obesity is associated with cardiovascular mortality, it is unclear whether this relationship is mediated by increased atherosclerotic burden.

Methods

Using data from the Dallas Heart Study, we assessed the association between gender-specific obesity measures (i.e., body mass index [BMI]; waist circumference [WC]; waist-to-hip ratio [WHR]) and prevalent atherosclerosis defined as coronary artery calcium (CAC) score >10 Agatston units measured by electron-beam computed tomography and detectable aortic plaque measured by magnetic resonance imaging.

Results

In univariable analyses (n = 2,744), CAC prevalence was significantly greater only in the fifth versus first quintile of BMI, whereas it increased stepwise across quintiles of WC and WHR (p trend < 0.001 for each). After multivariable adjustment for standard risk factors, prevalent CAC was more frequent in the fifth versus first quintile of WHR (odds ratio 1.91, 95% confidence interval 1.30 to 2.80), whereas no independent positive association was observed for BMI or WC. Similar results were observed for aortic plaque in both univariable and multivariable-adjusted analyses. The c-statistic for discrimination of prevalent CAC was greater for WHR compared with BMI and WC in women and men (p < 0.001 vs. BMI; p < 0.01 vs. WC).

Conclusions

We discovered that WHR was independently associated with prevalent atherosclerosis and provided better discrimination than either BMI or WC. The associations between obesity measurements and atherosclerosis mirror those observed between obesity and cardiovascular mortality, suggesting that obesity contributes to cardiovascular mortality via increased atherosclerotic burden. (J Am Coll Cardiol 2007;50:752–9) © 2007 by the American College of Cardiology Foundation

Obesity is a major health problem within the U.S., with an estimated prevalence of one-third of all U.S. adults (1). Many significant cardiovascular risk factors have been well-established as common comorbid conditions accompanying obesity, most notably insulin resistance, hypertension, and dyslipidemia (2). Because of its association with excess total and cardiovascular mortality in the general population, obesity has been recognized by the American Heart Association and the American College of Cardiology as a modifiable risk factor (3). However, the mechanisms underlying increased cardiovascular risk among obese subjects have not been fully defined, and it is unclear whether the entirety of risk associated with obesity can be explained by well-established risk factors. Moreover, it is not known whether obese subjects have an increased burden of atherosclerosis or whether excess cardiovascular risk in this population is mediated via alternative mechanisms.

Authors of previous studies evaluating the association between obesity and cardiovascular risk have reported varied results. Population-based studies measuring clinical cardiovascular events have reported threshold effects (4), J-shaped relationships (5), and linear relationships (6). Angiographic studies have reported both direct (7) and inverse (8) relationships between increasing obesity and atherosclerotic burden. In most of these studies, body mass index (BMI)
was used as the primary measure of obesity rather than alternative measures such as waist circumference (WC) or waist-to-hip ratio (WHR), which have demonstrated stronger correlations with cardiovascular risk than BMI (9).

In the present study, we evaluated the association between different measurements of obesity and prevalent subclinical atherosclerosis as determined by detectable coronary artery calcium (CAC) and aortic plaque in the Dallas Heart Study (DHS), a population-based probability sample.

**Methods**

**Subjects and study protocol.** The DHS is a multiethnic population-based study of 6,101 adult subjects from Dallas County between the ages of 18 and 65 years (10) who were enrolled between July 2000 and January 2002. The initial cohort underwent a detailed in-home health survey visit during Visit 1, after which (mean interval 76 days) 3,398 subjects ages 30 to 65 years returned for blood and urine collection on Visit 2. Subsequently (mean interval 80 days), 2,971 subjects returned for Visit 3, which included a detailed clinical examination, abdominal magnetic resonance imaging (MRI), and 2 electron beam computed tomography (EBCT) measurements of CAC (Fig. 1).

Demographic variables, BMI, and blood pressure measurements were similar between subjects completing the initial visit and Visits 2 and 3. In addition, no significant differences in clinical or demographic variables were observed between subjects completing the phlebotomy and imaging visits (10).

Details of measurement of blood pressure, plasma lipids, and glucose and the definition of hypertension, hypercholesterolemia, and diabetes have been described previously (11). Hypertension was defined as one of the following: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined by either self-report accompanied by use of antihyperglycemic medication or by elevated serum glucose (≥126 mg/dl fasting). Hypercholesterolemia was defined by either use of lipid-lowering medication, elevated fasting low-density lipoprotein cholesterol (≥160 mg/dl fasting or ≥160 mg/dl on direct measurement), or elevated total cholesterol (≥240 mg/dl). Low high-density lipoprotein (HDL) cholesterol was defined as <40 mg/dl for men and <50 mg/dl for women. Elevated triglycerides was defined as >200 mg/dl fasting. During Visit 3, height, weight, and BMI were measured with standard methods (10). We measured WC on a horizontal plane 1 cm above the iliac crest and hip circumference (HC) at the widest circumference of the buttocks at the area of the greater trochanters. Smoking was defined as cigarette use within the previous 30 days. The present analyses include data on the cohort of subjects who participated in all 3 phases of the DHS and had complete clinical and imaging data for either EBCT or MRI (n = 2,744 who completed EBCT and n = 2,504 who completed MRI).

**Atherosclerosis imaging.** Electron beam computed tomography scans were performed twice using an Imatron C-150XP scanner (Imatron Inc., San Bruno, California), 30 cm field of view, 512 matrix, sharp reconstruction kernel, and a 3-mm slice with a table increment of 3 mm as has been previously described. Starting at the level of the carina, a single-inspiratory breath-hold from the

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**Figure 1** Characteristic Appearance of CAC and Aortic Plaque

A representative example of coronary artery calcium on electron beam computed tomography imaging (left) and aortic plaque on magnetic resonance imaging scanning (right). The arrows depict CAC and aortic plaque. CAC = coronary artery calcium.
patient allowed us to take approximately 40 slices spanning the entire heart using an electrocardiogram-gated technique for each scan (11). The CAC results were averaged and expressed in Agatston units (12). A data-derived threshold of 10 Agatston units was selected to maximize reproducibility as well as signal-to-noise ratio among obese subjects (11).

Abdominal MRI was performed using a 1.5-T whole-body MRI system (Intera, Philips Medical Systems, Cleveland, Ohio) including 6 total slices of the infrarenal abdominal aorta using a free-breathing, electrocardiogram-gated, T2-weighted turbo spin-echo (black-blood) sequence. Adventitial and luminal borders were drawn for each slice using a freehand manual contour drawing tool, and areas of increased signal intensity, luminal protrusion, and focal wall thickening were identified as atherosclerotic aortic plaque (13).

Statistical analysis. Subjects were divided into gender-specific quintiles based on BMI, WC, HC, and WHR, and female and male subjects within each gender-specific quintile were combined. Univariable logistic regression modeling was performed to determine odds ratios (ORs) for prevalent CAC for each quintile of obesity, using the first quintile as the reference group. Multivariable logistic regression models were constructed that included traditional cardiovascular risk factors (age, diabetes mellitus, current smoking, hypertension, hypercholesterolemia, low HDL, high triglycerides). The interaction of WC with HC was evaluated by nonparametric method previously described by DeLong et al. (15). The HC measurement significantly modified the association between WC and CAC in either WC stratum (p interaction <0.001) (Fig. 2). In addition, the odds of prevalent CAC were greater for each quintile of WHR and WC compared with each quintile of BMI in both women and men.

After adjustment for age, current smoking, hypertension, diabetes mellitus, hypercholesterolemia, low HDL, and high triglycerides, CAC prevalence was significantly increased in the highest quintile of WHR (OR 1.91, 95% confidence interval [CI] 1.30 to 2.80) but was not significantly increased in any quintile of BMI or WC. As was found in univariable analysis, the odds of prevalent CAC were consistently greater with WHR compared with other measures of obesity (p trend <0.001 for WHR vs. 0.16 and 0.10 for BMI and WC, respectively) (Fig. 3).

Abdominal aortic plaque. Of the 2,744 subjects undergoing EBCT, 583 (21%; 234 women, 349 men) were found to have detectable CAC. A J-shaped relationship was observed between CAC prevalence and BMI, whereas CAC prevalence increased stepwise across quintiles of WC and WHR (p trend <0.001 for WC and WHR) (Fig. 2). In addition, the odds of prevalent CAC were greater for each quintile of WHR and WC compared with each quintile of BMI in both women and men.

WC and HC interaction. The HC measurement significantly modified the association between WC and CAC in women (p interaction = 0.005), and a trend toward a significant interaction was also observed in men (p interaction = 0.07). Among women with WC ≤88 cm, HC ≤ median was associated with a greater prevalence of CAC than HC > median (14% vs. 7%, p = 0.018); in contrast, among women with WC >88 cm, no significant difference in CAC was observed according to HC (Fig. 6). Among men, HC above versus equal to or below the median value was not significantly associated with CAC in either WC stratum. The HC did not significantly modify the association between WC and aortic plaque in women or men (Fig. 6).
Beyond standard risk factor models, WHR had superior discriminatory ability compared with other obesity measures but did not increment the c-statistic. The association was strongest for WHR and weakest for BMI. This stepwise increase in the odds of prevalent coronary artery calcium (CAC) (p < 0.001 versus same-gender clinic cohort) was found among women for BMI, WC, and WHR: CAC Across Gender-Specific Obesity Quintiles. After adjustment for traditional risk factors, only WHR was associated with a measure of obesity yielded significant additional discrimination beyond the traditional model (Table 3). Analyses for aortic plaque demonstrated similar patterns for c-statistics in that WHR had superior discriminatory ability compared with other obesity measures but did not increment the c-statistic beyond standard risk factor models.

**Table 1** Baseline Characteristics of the Overall Clinic Cohort and Subjects Who Completed Imaging

<table>
<thead>
<tr>
<th>Quintile</th>
<th>BMI (kg/m²)</th>
<th>WC (cm)</th>
<th>HC (cm)</th>
<th>WHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>24.60</td>
<td>81.8</td>
<td>100.0</td>
<td>0.802</td>
</tr>
</tbody>
</table>
| 24.61–28.52 | 81.9–91.6 | 100–106.5 | 0.803–0.841
| 2nd      | 28.53–32.69 | 91.7–100.5 | 106.6–114.6 | 0.842–0.878 |
| 3rd      | 32.70–38.35 | 100.6–113.0 | 114.7–126.8 | 0.879–0.920 |
| 4th      | >38.35      | >113.0  | >126.8  | >0.920 |
| Men      |             |         |         |     |
| 1st      | 24.35       | 88.4    | 96.0    | 0.906 |
| 2nd      | 24.36–27.21 | 88.5–96.0 | 96–100.75 | 0.907–0.941 |
| 3rd      | 27.22–29.77 | 96.1–102.5 | 100.76–106.0 | 0.942–0.973 |
| 4th      | 29.78–33.35 | 102.6–111.6 | 106.1–112.5 | 0.974–1.009 |
| 5th      | >33.35      | >111.6  | >112.5  | >1.009 |

**Table 2** Quintile Ranges for Obesity Measures

**Discussion**

In this multiethnic probability-based population sample, prevalent CAC was strongly associated with BMI, WC, and WHR in univariable analysis in both men and women. This association was strongest for WHR and weakest for BMI. After adjustment for traditional risk factors, only WHR was independently associated with CAC, an observation also found with aortic plaque. Of the measures of obesity, WHR was associated with a stepwise increase in the odds of prevalent coronary artery calcium (CAC) (p < 0.001 for trend), whereas a J-shaped association was seen for body mass index (BMI).
showed superior discrimination for CAC and aortic plaque in unadjusted models but did not increase the c-statistic beyond traditional risk factors.

Although obesity has been recognized as a risk factor for adverse cardiovascular outcomes, the mechanisms underlying increased risk among obese subjects have not been clearly established. Obesity has been well-recognized as being associated with an increased prevalence and severity of traditional risk factors (2), which may contribute to excess risk. In addition, early evidence has emerged to suggest that adipose tissue may mediate a proinflammatory, prothrombotic state (16), which could contribute to cardiovascular events independent of plaque burden. Additionally, alterations in cardiac structure and function associated with obesity may lead to heart failure and arrhythmic events (17,18). The present findings suggest that the link between obesity and excess cardiovascular morbidity and mortality also may be mediated in part by an increased prevalence of atherosclerosis, as we have demonstrated a consistent and independent positive association between WHR and subclinical atherosclerosis. Because detectable CAC is a nearly 100% specific finding for atherosclerosis (19) and because prevalent disease may precede events for years, our findings suggest that obesity itself may play a role in the initiation and propagation of the atherosclerotic process.

The findings of this study examining subclinical atherosclerosis are also consistent with the J- or U-shaped relationship between BMI and mortality that has been reported previously from other population studies (20–22). In addition, similar to studies evaluating patients with established cardiovascular disease (23), we observed that a BMI within normal limits may confer additional risk compared with moderately elevated BMI. These observations with regard to BMI have created uncertainty regarding the link between obesity and atherosclerosis and highlight some of the inherent limitations of BMI to predict adverse health related outcomes. In contrast, WC and WHR may more accurately reflect the additional risk conferred by obesity as demonstrated by the current findings.

Other studies comparing obesity measures using mortality and cardiovascular events as end points have also shown WC and WHR to perform better than BMI. Rimm et al. (24) followed more than 29,000 men during a period of 3 years and reported WHR as a stronger predictor of risk compared with BMI in older individuals. More recently, Dagenais et al. (25) followed nearly 8,000 subjects over the course of 4.5 years and reported that although the upper tertiles of BMI, WC, and WHR were all associated with increased relative risk for cardiovascular events, the magni-
tude of the association was greater for WC and WHR. Finally, a recent international case-control study involving more than 12,000 cases and controls reported greater odds for myocardial infarction across increasing quintiles of WC and WHR compared with increasing quintiles of BMI (9).

An important limitation of BMI is its failure to differentiate between differing body compositions. Body mass index has poor specificity for excess adiposity (26); in addition, it does not characterize excess centrally distributed obesity, which is more consistently associated with adverse effects on metabolism, dyslipidemia, and insulin resistance (2). Body mass index also can be falsely increased in the presence of increased lean body mass (such as in trained athletes) (27), and low BMI values are associated with chronic conditions leading to loss of lean body mass. The present findings suggest that WC and WHR may be preferred measures of the cardiac risk associated with obesity. In contrast with BMI, WC and WHR specifically address abdominal obesity and correlate better with overall atherosclerotic disease prevalence.

Although WC is well-described as a measure of abdominal obesity and a marker of obesity's associated metabolic risks (28), the mechanism underlying the superior performance of WHR in estimating atherosclerotic risk is less clear. One possible explanation is that WHR, because it is an indexed value (to lower body girth), provides a more precise assessment of relative central adiposity across the spectrum of body size compared with WC. A second possibility for the superior prognostic performance of WHR is that increased HC may protect against atherosclerosis. Hip circumference has been observed to be inversely associated with cardiovascular risk factors (29); in addition, a recent investigation of the Dallas Heart Study cohort revealed that increased lower body fat, determined by dual-energy X-ray absorptometry scanning, was inversely associated with insulin resistance, dyslipidemia, C-reactive protein, and systolic blood pressure (30). There is also preliminary evidence that an inverse association exists between hip circumference and cardiovascular clinical events (9). In the present study, we found that the relationship between HC and CAC was modified by WC, that is, increasing HC was associated with less CAC in subjects with normal WC, but not among subjects with large WC.

### Figure 6 Waist and Hip Circumference Interaction

Prevalent coronary artery calcium and aortic plaque in subjects stratified by measurements of hip circumference above versus equal to or below the median and by "normal" and "large" waist circumference (>88 cm for women, >102 cm for men). Blue columns = coronary artery calcium; yellow columns = aortic plaque.

### Table 3 C-statistic Values for Univariable and Adjusted Models of Prevalent Atherosclerosis

<table>
<thead>
<tr>
<th></th>
<th>Coronary Artery Calcium</th>
<th>Aortic Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Univariable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.550</td>
<td>0.540</td>
</tr>
<tr>
<td>WC</td>
<td>0.608*</td>
<td>0.588*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.661*†</td>
<td>0.643*‡</td>
</tr>
<tr>
<td>Multivariable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td>0.864</td>
<td>0.826</td>
</tr>
<tr>
<td>+ BMI</td>
<td>0.864</td>
<td>0.827</td>
</tr>
<tr>
<td>+ WC</td>
<td>0.865</td>
<td>0.827</td>
</tr>
<tr>
<td>+ WHR</td>
<td>0.864</td>
<td>0.829</td>
</tr>
</tbody>
</table>

*p < 0.001 versus BMI, †p < 0.01 versus WC, ‡p < 0.001 versus WC. Abbreviations as in Table 1.
with a statistically significant interaction observed between WC and HC on CAC prevalence. Furthermore, increased HC was inversely associated with prevalent aortic plaque in both quintile and WC-stratified analyses. These observations suggest that lower body fat may function as a protective reservoir against ectopic (abdominal) adiposity; however, more definitive studies will be necessary to validate this hypothesis.

Few previous studies have specifically compared differing obesity measures with subclinical atherosclerosis. In a study of 443 white men without diabetes, Cassidy et al. (31) reported a positive association of prevalent CAC with increased BMI, WC, and WHR, but only in subjects with a low 10-year risk for cardiovascular events. None of these anthropometric measures were shown to be more or less predictive than the others for prevalent CAC; however, increased WHR was most associated with CAC progression in lower-risk individuals on follow-up. Snell-Bergeon et al. (32) compared BMI, WC, and WHR using CAC scoring in 762 healthy individuals without diabetes and reported BMI and WC as the only independent measures of obesity after multivariable adjustment. In contrast, the DHS involves a large cohort that closely resembles the Dallas County general population in body composition and prevalent comorbid conditions (10), which may account for some of the differences in findings between these previous studies and those of the present one.

Although WHR clearly outperformed WC and BMI in estimating subclinical atherosclerosis, it did not add significant discrimination for CAC beyond traditional risk factors, as determined by c-statistic comparisons. One possible interpretation of this finding would be that most CAC induced by obesity is mediated by the major risk factors. However, the finding that the highest quintile of WHR remained associated with CAC and aortic plaque after adjustment for these risk factors also suggests that major risk factors alone do not fully explain the influence of WHR, and that other less well-understood effects related to obesity may contribute to increased atherosclerosis in this cohort. The lack of increment in the c-statistic may be related to the fact that the association between WHR and subclinical atherosclerosis is quantitatively modest after multivariable adjustment, since large associations are needed to increase the c-statistic beyond traditional risk factors (33).

Conclusions

The present study demonstrates a stronger association of WHR with subclinical atherosclerosis as compared with BMI or WC in a large, population-based cohort. Prevalent CAC increased across increasing quintiles of both WC and WHR, whereas BMI demonstrated a J-shaped curve. In analyses adjusted for cardiovascular risk factors, WHR remained independently associated with atherosclerosis. Waist-to-hip ratio showed better discrimination of atherosclerosis than either BMI or WC.

These findings support the use of WC and WHR over BMI as clinical measures of obesity and suggest that an increased burden of atherosclerosis may explain in part the excess cardiovascular risk among persons with obesity.

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REFERENCES