Obesity Accelerates the Progression of Coronary Atherosclerosis in Young Men

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Background—Obesity is a risk factor for adult coronary heart disease and is increasing in prevalence among youths as well as adults. Results regarding the association of obesity with atherosclerosis are conflicting, particularly when analyses account for other risk factors.

Methods and Results—The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study collected arteries, blood, and other tissue from ≈3000 persons aged 15 to 34 years dying of external causes and autopsied in forensic laboratories. We measured gross atherosclerotic lesions in the right coronary artery (RCA), American Heart Association (AHA) lesion grade in the left anterior descending coronary artery (LAD), serum lipid concentrations, serum thiocyanate (for smoking), intimal thickness of renal arteries (for hypertension), glycohemoglobin (for hyperglycemia), and adiposity by body mass index (BMI) and thickness of the panniculus adiposus. BMI in young men was associated with both fatty streaks and raised lesions in the RCA and with AHA grade and stenosis in the LAD. The effect of obesity (BMI ≥30 kg/m²) on RCA raised lesions was greater in young men with a thick panniculus adiposus. Obesity was associated with non-HDL and HDL (inversely) cholesterol concentrations, smoking (inversely), hypertension, and glycohemoglobin concentration, and these variables accounted for ≈15% of the effect of obesity on coronary atherosclerosis in young men. BMI was not associated with coronary atherosclerosis in young women although there was trend among those with a thick panniculus adiposus.

Conclusions—Obesity is associated with accelerated coronary atherosclerosis in adolescent and young adult men. These observations support the current emphasis on controlling obesity to prevent adult coronary heart disease. (Circulation. 2002;105:2712-2718.)

Key Words: coronary heart disease ■ atherosclerosis ■ obesity ■ risk factors ■ youth

For many years, there were inconsistent results regarding the association of obesity with atherosclerosis and coronary heart disease (CHD), despite overwhelming evidence of its association with CHD risk factors (reviewed by Alexander1). The relationship became clearer as long-term follow-up studies found obesity to be associated with CHD independently of other risk factors.2 The increasing prevalence of obesity among adults3 and youths,4 and recognition of the role of central adiposity,5 have directed renewed attention to the relation of obesity to atherosclerosis and CHD.

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The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study was organized in 1985 to examine the effects of risk factors for adult CHD on atherosclerosis in autopsied persons aged 15 to 34 years dying of external causes.6 Previous reports have described the association of dyslipidemia, smoking, hypertension, hyperglycemia, and obesity with atherosclerosis in the coronary arteries and aorta.7-10 A previous analysis7 indicated little association of obesity with aortic atherosclerosis and a strong association with coronary atherosclerosis in men. The present report focuses on the effects of obesity on coronary atherosclerosis, consolidates previously reported results, adds ≈1300 cases (including over 300 women) to the analyses, examines the effects of fat distribution, and presents topographic maps of lesion prevalence in the right coronary artery. The results strongly support control of obesity in youth as important in the long-range primary prevention of atherosclerosis and its sequelae.

Methods

Study Design
Fifteen cooperating centers followed standardized procedures to collect specimens and information and to submit them to central laboratories for analysis. A statistical center received all data.
Study subjects were persons aged 15 through 34 years who died of external causes (accident, homicide, or suicide) within 72 hours after injury and were autopsied within 48 hours after death in a forensic laboratory. The analyses in this report are based on 2133 men and 688 women accessioned between June 1, 1987 and August 31, 1994. The Institutional Review Board of each participating center approved this study.

Preparation of Arteries
The PDAY team dissected the right coronary artery (RCA) from the heart, opened it longitudinally, and fixed it in 10% neutral buffered formalin. The team perfused the left main coronary artery and the left anterior descending coronary artery (LAD) with formalin at a pressure of ~100 mm Hg. A central laboratory stained the fixed RCAs with Sudan IV. Another central laboratory excised a block from the LAD just distal to the origin of the circumflex artery. Paraffin sections from half of this block were stained with Gomori’s trichrome acid fuchsin (GTAF), and frozen sections from the other half were stained with Oil Red O. RCAs were available for 2736 cases, and LAD sections for 760 cases.

Body Mass Index
The body was weighed to the nearest 0.5 kg or 1 lb before tissue or fluids were removed from the body. Cadaver length, from the vertex of the cranium to the base of the heel, was measured to the nearest 1 cm or 0.5 in. We computed the body mass index (BMI) as weight (kilograms) divided by height (meters) squared. Cases were grouped into categories of BMI <25, 25 ≤ BMI <30, and BMI ≥ 30 kg/m².

Panniculus Adiposus
The PDAY team measured subcutaneous abdominal fat, including the subcutaneous tissue from the inner edge of the rectus sheath, at a point halfway between the xiphoid process and the umbilicus, to the nearest millimeter. Cases were classified as ≤ or > the median value for their sex and BMI classification (men: 12, 20, and 30 mm; women: 20, 28, and 37 mm for BMI ≤25, 25 ≤BMI 30, BMI >30, respectively) in order to reflect fat distribution rather than overall fat mass and to offset the known sex difference.

Other Risk Factors
Methods for postmortem assessment of the other risk factors are described in previous publications. Briefly, we measured total serum cholesterol and HDL cholesterol (after precipitation of other lipoproteins) by a cholesterol oxidase method and calculated non-HDL cholesterol by subtraction. Because some trauma victims receive large quantities of fluids, we excluded all serum data if the serum cholesterol concentration was >100 mg/dL. Smokers were identified by serum thiocyanate concentration ≥90 μmol/L. Hypertension was identified when the intimal thickness of small renal arteries indicated a mean blood pressure ≥110 mm Hg. Chronic hyperglycemia was indicated by a red blood cell glycohemoglobin concentration ≥8%.

Gross RCA Lesions
Three pathologists independently estimated the percentage of intimal surface involved by fatty streaks (flat intimal lesions stained by Sudan IV) and by raised lesions (fibrous plaques and other complicated lesions). The mean of the 3 grades was used in the statistical analyses.

Microscopic LAD Lesions
As described in a previous publication, 2 pathologists reached a consensus grade according to the American Heart Association (AHA) system. In GTAF sections, the morphometry laboratory measured the intimal area and the potential lumen area as the maximum area that could occur within the measured length of the internal elastic lamina. We defined an intimal area ≥40% of the potential lumen area combined with an AHA grade ≥3 as atherosclerotic stenosis ≥40%.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Race</th>
<th>Age</th>
<th>n</th>
<th>BMI, kg/m²</th>
<th>Panniculus Thickness, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>White</td>
<td>15 to 19</td>
<td>207</td>
<td>24.3 ± 0.3</td>
<td>17.5 ± 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 to 24</td>
<td>248</td>
<td>25.0 ± 0.3</td>
<td>19.3 ± 0.9</td>
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<tr>
<td></td>
<td></td>
<td>25 to 29</td>
<td>294</td>
<td>26.1 ± 0.3</td>
<td>22.5 ± 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 to 34</td>
<td>242</td>
<td>26.7 ± 0.4</td>
<td>24.5 ± 1.0</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>15 to 19</td>
<td>253</td>
<td>24.1 ± 0.3</td>
<td>14.6 ± 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 to 24</td>
<td>333</td>
<td>24.5 ± 0.3</td>
<td>15.9 ± 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 to 29</td>
<td>328</td>
<td>25.3 ± 0.3</td>
<td>17.2 ± 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 to 34</td>
<td>228</td>
<td>25.0 ± 0.3</td>
<td>18.6 ± 0.8</td>
</tr>
<tr>
<td>Women</td>
<td>White</td>
<td>15 to 19</td>
<td>74</td>
<td>23.1 ± 0.5</td>
<td>20.5 ± 1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 to 24</td>
<td>98</td>
<td>24.1 ± 0.5</td>
<td>21.3 ± 1.2</td>
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<td></td>
<td></td>
<td>25 to 29</td>
<td>104</td>
<td>24.2 ± 0.5</td>
<td>25.7 ± 1.4</td>
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<tr>
<td></td>
<td></td>
<td>30 to 34</td>
<td>87</td>
<td>25.9 ± 0.7</td>
<td>28.3 ± 1.8</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>15 to 19</td>
<td>67</td>
<td>24.2 ± 0.7</td>
<td>22.8 ± 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 to 24</td>
<td>76</td>
<td>25.9 ± 0.8</td>
<td>24.5 ± 1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 to 29</td>
<td>97</td>
<td>25.3 ± 0.6</td>
<td>25.2 ± 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 to 34</td>
<td>85</td>
<td>26.0 ± 0.6</td>
<td>25.8 ± 1.6</td>
</tr>
</tbody>
</table>

*Mean±SE.

Topographic RCA Maps
The morphometry laboratory digitized the image of each Sudan IV–stained RCA and an outline of raised lesions on a black-and-white print and converted the images to a standard template. Composite images were assembled to indicate prevalence of each type of lesion at each location in the image of the artery.

Statistical Analysis
The associations of intimal surface involved by atherosclerosis, lipid risk factors, and glycohemoglobin with adiposity were analyzed by multiple regression analysis. A logit transformation, with a small constant added to avoid the logarithm of zero, was applied to the extent of surface area involved. We analyzed the prevalence of AHA grades using polytomous logistic regression. The associations of obesity with stenosis ≥40%, hypertension, and smoking were analyzed by binary logistic regression.

Results
Adiposity
Table 1 shows the mean BMI and panniculus thickness by sex, race, and age. Among whites, men had a greater BMI than women (P=0.0001); among blacks, men had a slightly lower BMI than women (P=0.1733). White men had a greater BMI than black men (P=0.0080), whereas black women had a greater BMI than white women (P=0.0062). In whites, BMI increased linearly with age (P=0.0001). In blacks, BMI increased from age 15 to 19 to 20 to 24 (P=0.0004) and did not change in subsequent ages (P=0.2446).

Women of both races had a thicker panniculus than men (P≤0.0003). White men had a thicker panniculus than black men (P=0.0001), whereas white and black women were not significantly different (P=0.5456). The panniculus increased linearly with age in whites (P=0.0001) and blacks (P=0.0008) although the rate of increase was greater in whites (P=0.0079).
The partial correlation coefficient between BMI and panniculus, adjusted for sex, race, and age, was 0.52 ($P=0.0001$).

**Relation of Adiposity to Other Risk Factors**
Table 2 shows that non-HDL cholesterol concentration was directly associated with both BMI ($P=0.0001$) and panniculus thickness ($P=0.0444$). HDL cholesterol concentration was inversely associated with BMI ($P=0.0577$), but not with panniculus thickness ($P=0.2462$). Glycohemoglobin was directly associated with BMI ($P=0.0001$), but not with panniculus thickness ($P=0.1458$). Smoking prevalence decreased with increasing BMI ($P=0.0001$), but not with panniculus thickness ($P=0.6116$), and smokers had a lower BMI than nonsmokers (nonsmokers, 25.5±0.2; smokers, 24.2±0.2 kg/m²; $P=0.0001$). Prevalence of hypertension did not differ between BMI<25 and BMI≥30 ($P=0.3318$), but was greater with BMI>30 than with BMI≤30 ($P=0.0408$). Prevalence of hypertension was not associated with panniculus thickness ($P=0.5384$).

**Relation of Adiposity to Lesions of the RCA**
The mean extent of lesions by BMI, panniculus thickness, and sex, adjusted for race and 5-year age group, is shown in Figure 1. In men, extent of fatty streaks increased with increasing BMI ($P=0.0001$) but was not affected by panniculus thickness ($P=0.1734$). There was a nonsignificant trend for extent of fatty streaks to increase with increasing BMI in women with a thick panniculus ($P=0.1449$), whereas there was no association in women with a thin panniculus ($P=0.3454$). Over all categories of BMI, women with a thick panniculus had an increased extent of fatty streaks ($P=0.0225$).

Extant of raised lesions increased with increasing BMI in men regardless of panniculus thickness ($P=0.0001$). In men, there was no effect of panniculus thickness for BMI≤30, whereas for BMI>30, those with a thick panniculus had more extensive raised lesions ($P=0.0244$). Neither BMI nor panniculus thickness was associated with extent of raised lesions in women.

There were no significant interactions of age with obesity ($P>0.6981$) or race with obesity ($P>0.4617$) for fatty streaks or raised lesions.

Topographic maps of lesion prevalence in the RCA of men (Figure 2) and women (Figure 3) show that adiposity did not change the pattern of lesion distribution. Adiposity increased the prevalence of both fatty streaks and raised lesions in men although it had little effect on prevalence of lesions in women. These relationships were similar to that shown by analyses of extent of intimal surface (Figure 1). Lesion prevalence was greatest in the first 2 to 3 cm of the RCA, and in men, the effects of adiposity on raised lesions in this region were evident even before age 25.

**Adiposity and RCA Lesions After Adjusting for Other Risk Factors**
We compared the effects of adiposity with and without adjusting for the other risk factors in 1080 men having measurements for all risk factors. The mean extent of lesions in these men with and without adjusting for other risk factors is shown in Figure 4. Adjusting for the other risk factors diminished but did not eliminate the effects of adiposity (fatty streaks, $P=0.0001$; raised lesions, $P=0.0642$) and did not change the observed associations. The effects of adiposity on the prevalence of both fatty streaks and raised lesions in men although it had little effect on prevalence of lesions in women. These relationships were similar to that shown by analyses of extent of intimal surface (Figure 1). Lesion prevalence was greatest in the first 2 to 3 cm of the RCA, and in men, the effects of adiposity on raised lesions in this region were evident even before age 25.

**Figure 1.** Mean ($±$SE) extent of RCA lesions by BMI, panniculus thickness, and sex, adjusted for race and 5-year age group. Light gray bars indicate panniculus thickness =median for sex and BMI; Black bars, panniculus thickness >median for sex and BMI.
lesions, expressed as the ratio of mean extent of lesions relative to the mean extent in the category of BMI < 25 kg/m² and panniculus thickness ≤ median, were reduced an average of 15% for fatty streaks and 12% for raised lesions due to adjustment for other risk factors.

Adiposity and LAD Lesions
Preliminary analyses indicated no difference in prevalence of AHA grades or stenosis ≥ 40% between BMI 25 to 30 and BMI < 25, but there were differences between BMI ≥ 30 and BMI > 30. Table 3 shows odds ratios before and after adjusting for other risk factors. Men with BMI > 30 had a greater prevalence of AHA grades 2 to 3, AHA grades 4 to 5, and stenosis ≥ 40% than those with BMI ≤ 30. There was no association of BMI with AHA grade or stenosis in women. Panniculus thickness was not associated with AHA grade or stenosis in men or women. Other risk factors did not account for the association of BMI with AHA grade or stenosis in men.

Discussion
Summary of Results
Obesity in young men, as defined by BMI, is associated with both fatty streaks and raised lesions in the RCA and with the microscopic grade of atherosclerosis and stenosis in the LAD. The effect of BMI on RCA raised lesions is greater among men with a thick panniculus adiposus, that is, men with a central pattern of adiposity. There is little association of adiposity with coronary atherosclerosis in young women, although there is a slight but nonsignificant trend for an association of BMI with fatty streaks in women who have a thick panniculus adiposus. Obesity is associated with non-HDL and HDL cholesterol concentration, hypertension, smoking, and glycohemoglobin concentration, but these risk factors account for only about 15% of its effects on atherosclerosis.

Comparison With Other Studies
Alexander reviewed the predominantly negative results regarding the relationship of obesity to atherosclerosis in both

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Figure 2. Prevalence map of RCA lesions in men by BMI, panniculus thickness, and 10-year age group.
autopsy and angiographic studies. Positive findings may be more frequent among the more recent studies, possibly because the increasing prevalence of obesity makes the association easier to detect. The association of obesity with other cardiovascular risk factors in youth is consistent with the results of many other studies.15,16

Mechanism of Effects of Obesity on Atherosclerosis and CHD

Obesity may affect atherosclerosis through unrecognized intervening variables.1 Emerging risk factors for CHD also associated with obesity are C-reactive protein in adults17 and children,18,19 insulin resistance,20–22 and fibrinogen.23 As other physiological variables related to obesity are identified, they may explain a larger proportion of the association of obesity with atherosclerosis through plausible physiological mechanisms.

Lack of Association of Obesity With Atherosclerosis in Young Women

The association of obesity with clinical CHD in middle-aged and older women is firmly established, but the relative risks for women are slightly lower than those for men.24 However, we find only a weak and nonsignificant trend of an association of BMI with fatty streaks in the RCA of young women who also had a thick panniculus (Figure 1). Serum lipids, smoking, blood pressure, or elevated glycohemoglobin did not account for the differences in the effects of obesity in men compared with women.

At an equivalent BMI, women at all ages, even as children, have a larger percentage of body fat than men.25 However, men are more likely to have a central (visceral) distribution of fat than women,26 and most reports indicate that the adverse consequences of obesity are more strongly associated with central obesity27–29 than non-central obesity.
Another possible explanation is the slower progression of atherosclerosis with age in young women compared with that in young men. Coronary raised lesions in young women lag behind those in young men by about 10 years independently of risk factor status, and obesity may accelerate the process in women only after 35 years of age. In older women, obesity may affect susceptibility to plaque rupture and thrombosis rather than affecting atherosclerosis.1

Fat Distribution

The potential importance of central obesity compared with peripheral obesity was not appreciated when this study began in 1985, and we do not have any of the usual measurements of this variable. Subcutaneous abdominal fat is associated with visceral fat (r = 0.6),30 and therefore, the thickness of the panniculus may also provide information on visceral fat. Despite the numerous reports similar to those cited regarding the contribution of visceral obesity to CHD, 2 studies report that subcutaneous abdominal fat is more closely associated with insulin resistance than visceral fat;21,22 and 2 others find that BMI is a stronger predictor of other major risk factors than waist-hip ratio.31,32 Apparently, excess adipose tissue in any depot adversely affects health-related variables.

Implications

Our results show that obesity in adolescent and young adult men is associated with extent and severity of early atherosclerotic lesions. This conclusion is consistent with results of long-term follow-up studies, which show that obesity in youth not only predicts obesity in adulthood,20,33 but also predicts CHD morbidity and mortality.34,35 These results indicate that obesity in adolescents and young adults, through mechanisms yet to be identified, accelerates the progression of atherosclerosis decades before clinical manifestations appear. Obesity is an important modifiable contributor to coronary atherosclerosis, particularly in young adult men, and efforts to control childhood obesity are justified for the long-range prevention of CHD as well as other chronic diseases. The increasing prevalence of obesity among young persons4 emphasizes the need for obesity control efforts.

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**TABLE 3. Odds Ratios (OR) for Effects of BMI and Panniculus Thickness on LAD Lesions by Sex, Adjusted for Race and Age (n=760)**

<table>
<thead>
<tr>
<th>Other Risk Factors</th>
<th>Sex</th>
<th>Adiposity Index</th>
<th>AHA Grade (2–3 vs 0–1)</th>
<th>AHA Grade (4–5 vs 0–1)</th>
<th>Stenosis &gt;40%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>BMI*</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Not adjusted</td>
<td></td>
<td>2.09</td>
<td>1.15–3.79</td>
<td>5.81</td>
<td>2.53–13.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panniculus†</td>
<td>1.00 0.66–1.50</td>
<td>0.99 0.46–2.11</td>
<td>0.97 0.56–1.69</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>BMI</td>
<td>0.62 0.20–1.92</td>
<td>0.33 0.04–2.84</td>
<td>0.44 0.05–3.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panniculus</td>
<td>0.74 0.33–1.66</td>
<td>0.98 0.21–4.55</td>
<td>0.78 0.19–3.15</td>
</tr>
<tr>
<td>Adjusted</td>
<td>Men</td>
<td>BMI</td>
<td>2.02 1.08–3.78</td>
<td>5.25 2.12–12.98</td>
<td>2.35 1.16–4.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panniculus</td>
<td>0.93 0.61–1.43</td>
<td>0.92 0.42–2.04</td>
<td>0.90 0.51–1.59</td>
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<tr>
<td></td>
<td>Women</td>
<td>BMI</td>
<td>0.67 0.22–2.04</td>
<td>0.37 0.04–3.67</td>
<td>0.46 0.05–3.91</td>
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<tr>
<td></td>
<td></td>
<td>Panniculus</td>
<td>0.64 0.28–1.48</td>
<td>0.82 0.15–4.41</td>
<td>0.66 0.16–2.73</td>
</tr>
</tbody>
</table>

Bold typeface indicates associations where confidence intervals (CIs) do not include 1.00.
*BMI >30 vs BMI ≤30.
†Panniculus thickness >median vs ≤median.
References


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