Effects of Nonlipid Risk Factors on Atherosclerosis in Youth With a Favorable Lipoprotein Profile

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Background—The strong association between coronary heart disease and dyslipoproteinemia has often overshadowed the effects of the nonlipid risk factors—smoking, hypertension, obesity, and diabetes and impaired glucose tolerance—and even led to questioning the importance of these risk factors in the presence of a favorable lipoprotein profile.

Methods and Results—A cooperative multicenter study, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY), examined the relation of the nonlipid risk factors to atherosclerosis in 629 men and 227 women 15 to 34 years of age who died of external causes and who had a favorable lipoprotein profile (non-HDL cholesterol <4.14 mmol/L [<160 mg/dL] and HDL cholesterol ≥0.91 mmol/L [≥35 mg/dL]). In the abdominal aorta, smokers had more extensive fatty streaks and raised lesions than nonsmokers, and hypertensive blacks had more raised lesions than normotensive blacks. In the right coronary artery, hypertensive blacks had more raised lesions than normotensive blacks, obese men (body mass index ≥30 kg/m²) had more extensive fatty streaks and raised lesions than nonobese men, and individuals with impaired glucose intolerance had more extensive fatty streaks. Obese men had more severe lesions (American Heart Association grade 2 through 5) of the left anterior descending coronary artery.

Conclusions—These substantial effects of the nonlipid risk factors on the extent and severity of coronary and aortic atherosclerosis, even in the presence of a favorable lipoprotein profile, support the need to control all cardiovascular risk factors. (Circulation. 2001;103:1546-1550.)

Key Words: coronary disease • risk factors • atherosclerosis

In 50 years of attempts to control the 20th century epidemic of coronary heart disease (CHD), attention was focused primarily on hypercholesterolemia¹ because its association with CHD was strong and consistent, it was a plausible intervening variable, and lowering blood cholesterol decreased CHD risk.² Although control of hypertension, smoking, diabetes, and obesity was recommended as part of most prevention regimens,³ their importance was often overshadowed by the strength of the cholesterol effect. Sometimes even the necessity of dealing with the other risk factors in the absence of hypercholesterolemia was questioned.

We investigated the effects of the nonlipid risk factors on atherosclerosis in young persons with a favorable lipoprotein profile using data from the multicenter cooperative project Pathobiological Determinants of Atherosclerosis in Youth (PDAY), which collected material from ≈3000 15- to 34-year-old trauma victims autopsied in forensic laboratories. The results show that these nonlipid risk factors deserve attention even in the presence of a favorable lipoprotein profile.

Methods

Study Design

Fifteen cooperating centers adopted standardized methods to collect specimens and data and to analyze them in central laboratories.

Subjects

Study subjects were persons 15 through 34 years of age who died of external causes (accidents, homicides, or suicides) within 72 hours of injury and were autopsied within 48 hours of death in one of the cooperating forensic laboratories. Age and race were obtained from the death certificate. We collected 2876 acceptable cases from June 1, 1987, to August 31, 1994. Data on all risk factors were available for 1479 cases. The Institutional Review Board of each cooperating center approved this study.

Dissecting and Preserving Arteries

PDAY investigators bisected the aorta longitudinally and fixed the left half in 10% neutral buffered formalin. They opened the right coronary artery (RCA) longitudinally and fixed it in the same manner. They perfused the left main artery and left anterior descending coronary artery (LAD) with 10% buffered formalin at a pressure of ≈100 mm Hg (130 cm H₂O) and dissected them from the heart. A
central laboratory stained the aortas and RCAs with Sudan IV and packaged them in plastic bags.

In another central laboratory, a technician cut a 5-mm transverse block from the fixed LAD distal to the flow divider of the left main and left circumflex arteries. Sections from the proximal half were stained with oil red O (ORO), and sections from the distal half were stained with Gomori-trichrome aldehyde fuchsin (GTAF). Of the cases having data on all risk factors, microscopic sections of the LAD were available for 760 cases.

Grading Atherosclerosis

Three pathologists independently estimated the extent of intimal surface area of the RCA and abdominal aorta involved with fatty streaks and raised lesions by procedures described in previous publications. The consensus grade was the average of the grades of the 3 pathologists. Of the cases having data on all risk factors, assessment of extent of gross lesions was available for 1458 abdominal aortas and 1427 RCAs.

Two pathologists graded GTAF- and ORO-stained sections using the American Heart Association (AHA) classification system as described in a previous publication. Differences were resolved by discussion, and a consensus grade was reached.

Risk Factor Assessment

Methods of measuring CHD risk factors were presented in previous publications and are summarized in Table 1. We based the criterion for a favorable lipoprotein profile on the recommendation of the National Cholesterol Education Program. LDL cholesterol $<3.4$ mmol/L ($<130$ mg/dL) and HDL cholesterol $\geq 0.91$ mmol/L ($\geq 35$ mg/dL). We assumed that an LDL cholesterol concentration of 130 mg/dL was approximately equal to a non-HDL cholesterol concentration of 4.14 mmol/L (160 mg/dL). Of the PDAY cases with data on all risk factors, 856 cases (629 men and 227 women) had a favorable lipoprotein profile.

### Statistical Procedures

Extent of intimal surface area involved with atherosclerotic lesions was analyzed by multiple regression analysis. We included all effects found to be important in previous analyses. These were the effects of sex, race, 5-year age group, smoking status, hypertension, obesity, and elevated glycohemoglobin, as well as the interactions between age and the risk factors, between race and hypertension, and between sex and obesity. Because of the limited number of cases, effects higher than second order were not included. A logit transformation, with a small constant added to avoid the logarithm of zero, was applied to the extent of surface area involved.

Because the number of cases for which we had microscopic grades was small, we combined AHA grades 0 or 1 and grades 2, 3, 4, or 5 for statistical analysis using logistic regression. We included the effects of sex, race, 5-year age group, smoking, hypertension, obesity, elevated glycohemoglobin, and the sex-by-obesity interaction.

Results

Prevalence of Lipid and Nonlipid Risk Factors

Table 1 gives the prevalence of nonlipid risk factors in all PDAY subjects and the prevalence of nonlipid risk factors among subjects with a favorable lipoprotein profile. Of the individuals with a favorable lipoprotein profile, 38.8% had no nonlipid risk factors; 47.3% had 1 nonlipid risk factor, of whom 68.6% were smokers; 13.1% had 2 nonlipid risk factors (smoking and hypertension were the most prevalent combination); 0.7% had 3 nonlipid risk factors; and 0.1% had all 4 nonlipid risk factors.

Effect of Nonlipid Risk Factors on Gross Lesions

Table 2 gives the effects of nonlipid risk factors on fatty streaks and raised lesions in the presence of a favorable lipoprotein profile. The effects are presented as the ratio of extent involvement at the high level of a risk factor (as defined in Table 1) to the extent involvement at the desirable level of a risk factor. Men had less extensive fatty streaks than women (ratio $<1.0$) in the abdominal aorta, but men and women had about an equal extent of raised lesions. In contrast, although men had only slightly more extensive fatty streaks in the RCA than women (ratios slightly $>1.0$, $P=NS$), they developed considerably more extensive raised lesions in both the 15- to 24-year-old and 25- to 34-year-old age groups.

Smoking was associated with more extensive fatty streaks in the abdominal aorta in both the 15- to 24-year-old and 25- to 34-year-old age groups and with a much greater extent of raised lesions in the abdominal aorta of 25- to 34-year-old subjects. It had little effect on the extent of either type of lesion in the RCA.

Hypertension was associated with a greater extent of raised lesions in the abdominal aorta and RCA of blacks. Hypertension tended to be associated with more extensive raised lesions in whites, but the effect was smaller than in blacks of the same age. We believe that the ratio of 0.55 for raised lesions in the abdominal aorta of younger whites is due to the low prevalence of hypertension in the younger age group and does not represent a real effect of hypertension. Hypertension was not associated with fatty streaks in either whites or blacks.

Obesity was associated with more extensive fatty streaks in the RCAs of 15- to 24-year-old men and with more extensive raised lesions in both 15- to 24-year-old and 25- to 34-year-old men.
old men. Obesity was not associated with either fatty streaks or raised lesions in the RCAs or aortas of women.

Elevated glycohemoglobin was associated with more extensive fatty streaks in the RCAs of 15- to 24-year-old men and women, but the associations with raised lesions were not significant, probably because of the low prevalence of elevated glycohemoglobin.

### Effects of Nonlipid Risk Factors on Microscopic Characteristics of Lesions

Eighteen (4.2%) of 430 cases had AHA grade 4 to 5 (advanced) lesions in the LAD. One of the women with a grade 4 to 5 lesion had no risk factors, and 3 had 1 risk factor. Three of the men with a grade 4 to 5 lesion had no risk factors, 5 had 1 risk factor, and 6 had 2 risk factors. Table 3 shows the odds ratios for AHA grades 2 to 5 (fatty streaks and advanced lesions) versus AHA grades 0 to 1 (normal and isolated foam cells). All of the odds ratios (except that for smoking) were substantially different from 1.00 ($P<0.05$).

### Extent of intimal surface involved with raised lesions in RCA by nonlipid risk profile, sex, race, and age in subjects with favorable lipoprotein profile

### Table 2. Ratio of Percent Intimal Surface Area Involved for High Level of a Risk Factor to Involvement for Low Level of the Risk Factor by 10-Year Age Group, in Subjects With a Favorable Lipoprotein Profile

<table>
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<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>All</td>
<td>Fatty streaks</td>
<td>0.82±0.11*</td>
<td>0.66±0.11*</td>
<td>1.20±0.20</td>
<td>1.13±0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raised lesions</td>
<td>1.01±0.22</td>
<td>0.87±0.22</td>
<td>1.73±0.29*</td>
<td>1.89±0.31*</td>
</tr>
<tr>
<td>Smoking</td>
<td>All</td>
<td>Fatty streaks</td>
<td>1.20±0.07*</td>
<td>1.20±0.07*</td>
<td>1.04±0.14</td>
<td>0.97±0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raised lesions</td>
<td>1.17±0.18</td>
<td>2.75±0.51*</td>
<td>1.06±0.15</td>
<td>1.11±0.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Whites</td>
<td>Fatty streaks</td>
<td>0.99±0.13</td>
<td>0.94±0.12</td>
<td>1.26±0.34</td>
<td>1.32±0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raised lesions</td>
<td>0.55±0.37*</td>
<td>0.74±0.26</td>
<td>1.09±0.28</td>
<td>1.44±0.38</td>
</tr>
<tr>
<td>Obesity</td>
<td>Men</td>
<td>Fatty streaks</td>
<td>1.06±0.09</td>
<td>1.01±0.06</td>
<td>1.08±0.21</td>
<td>1.12±0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raised lesions</td>
<td>1.19±0.26</td>
<td>1.51±0.29*</td>
<td>1.51±0.32*</td>
<td>1.98±0.41*</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Fatty streaks</td>
<td>0.96±0.14</td>
<td>1.01±0.13</td>
<td>1.29±0.41</td>
<td>0.74±0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raised lesions</td>
<td>0.97±0.36</td>
<td>0.87±0.32</td>
<td>1.08±0.35</td>
<td>1.13±0.34</td>
</tr>
<tr>
<td>Elevated glycohemoglobin</td>
<td>All</td>
<td>Fatty streaks</td>
<td>0.97±0.17</td>
<td>0.91±0.12</td>
<td>2.13±0.73*</td>
<td>1.22±0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raised lesions</td>
<td>0.83±0.36</td>
<td>0.91±0.29</td>
<td>1.40±1.50</td>
<td>1.21±0.39</td>
</tr>
</tbody>
</table>

*95% CIs that do not include 1.00.

### Effect of Combined Risk Factors

The Figure compares the extent of raised lesions in the RCAs of persons who did not smoke, were normotensive, were not hypertensive, had BMI $<30$ kg/m², and had glycohemoglobin $<8%$. High-risk individuals were smokers, were hypertensive, had BMI $>30$ kg/m², and had glycohemoglobin $>8%$. T bar represents standard error.

### Table 3. OR for Risk Factor Effects on Microscopic Characteristics of Lesions (AHA Grades 2–5 vs AHA Grades 0–1) in Subjects With a Favorable Lipoprotein Profile

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number With Risk Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>311</td>
<td>4.09 (1.71–9.81)*</td>
</tr>
<tr>
<td>Smoking</td>
<td>253</td>
<td>0.99 (0.60–1.62)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78</td>
<td>1.22 (0.67–2.24)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Men 37</td>
<td>3.72 (1.73–8.04)*</td>
</tr>
<tr>
<td></td>
<td>Women 20</td>
<td>0.31 (0.06–1.52)</td>
</tr>
<tr>
<td>Elevated glycohemoglobin</td>
<td>20</td>
<td>1.78 (0.64–4.96)</td>
</tr>
</tbody>
</table>

*95% CIs that do not include 1.00.
obese, and had normal glycohemoglobin with the extent of raised lesions in persons who smoked, were hypertensive, were obese, and had elevated glycohemoglobin. All had a favorable lipoprotein profile. The differences were substantial, even in the 15- to 19-year-old age group and in both men and women. Differences became greater in succeeding age groups and were 5-fold higher in men aged 30 to 34 years. These risk factor profiles illustrate the extreme profiles of no risk factors and all risk factors. The extent of raised lesions for other profiles will be intermediate.

**Discussion**

**Summary of Results**

The nonlipid risk factors—smoking, hypertension, obesity, and impaired glucose tolerance—accelerate atherogenesis in the presence of a favorable lipoprotein profile in young people. Hence, an unfavorable lipoprotein profile is not a necessary condition for progression of atherosclerosis in young people. Control of dyslipidemia alone will undoubtedly retard the progression of atherosclerosis in young persons, but there will remain a substantial atherogenic stimulus from smoking, hypertension, obesity, and hyperglycemia.

**Male Sex**

Although male sex is not among the mutable risk factors, the results presented here emphasize the more rapid progression of coronary atherosclerosis in young men than in young women. This difference is not explained by established risk factors. The difference between young men and young women in atherosclerotic lesions precedes the difference between the sexes in clinical CHD at older ages. This observation is consistent with the concept that risk factor reduction in young people will prevent or delay the development of clinical CHD.

**Smoking**

The strongest effect of smoking is on a localized region of the dorsolateral aspect of the distal third of the abdominal aorta. The effect is evident in the late teenage years and becomes stronger in later decades. This finding is consistent with the well-established association of smoking with abdominal aortic aneurysm. Smoking is associated with a higher microscopic grade of coronary artery fatty streaks in young people, but a stronger effect on raised lesions becomes evident after age 35. Smoking is associated with increased risk of clinical CHD in the presence of low serum cholesterol levels, a finding consistent with the results reported here.

**Hypertension**

In the PDAY study, hypertension was the only risk factor that affected raised lesions but not fatty streaks. This effect remained strong in the presence of a favorable lipoprotein profile. As in previous analyses of these cases, the effect was stronger in blacks, probably due to the greater severity of hypertension in blacks.

**Obesity**

Obesity is the only risk factor in the PDAY study that affects atherosclerotic lesions in men but not in women. Its effect is not explained by other risk factors. The present results show that obesity does not depend on the presence of an unfavorable lipoprotein profile to accelerate atherogenesis.

**Impaired Glucose Tolerance**

In a previous analysis of PDAY cases, elevated glycohemoglobin was associated with a significant 3-fold excess of raised lesions in the RCAs of persons 15 to 24 years of age and a 5-fold excess in persons 25 to 34 years of age, even when adjusted for other risk factors. In this smaller number of cases with a favorable lipoprotein profile, the effect was significant only for RCA fatty streaks. The ratios (Table 2) for raised lesions were greater than 1.0 but not significantly greater, probably because the number of cases having elevated glycohemoglobin was too small.

**Limitations of Study**

Because emergency medical teams often administer large quantities of intravenous fluids to some individuals immediately before death from violent causes, we excluded serum values from cases having total cholesterol <2.59 mmol/L (100 mg/dL). The selection of desirable lipoprotein profiles having non-HDL cholesterol and HDL cholesterol concentrations at opposite ends of the distributions also minimizes the potential effects of hemodilution. Although agonal procedures may degrade associations, we do not believe that they are likely to produce spurious associations.

**Comparison With Other Studies**

The effects of the nonlipid risk factors reported here are consistent with the risk factor effects estimated from all PDAY cases. Those analyses did not indicate interactions between the lipid and nonlipid risk factors. Because those analyses used a larger number of cases, some risk factor effects were statistically significant, whereas effects of similar magnitude were not statistically significant in the smaller number of cases analyzed for the present report.

The Bogalusa Heart Study examined the effects of multiple risk factors on atherosclerosis in 93 young persons between 2 and 39 years of age (average 20 years). The severity of atherosclerosis increased as the number of risk factors increased, but the authors did not analyze the effects of nonlipid risk factors in the presence of a favorable lipoprotein profile.

**Prevalence of Nonlipid Risk Factors**

Table 1 shows a high prevalence of nonlipid risk factors among these young people having a favorable lipoprotein profile. The high prevalence of smoking in PDAY cases (44%) is consistent with recent reports of prevalence of smoking among high school students and young adults, with the prevalence being highest (28.7%) among persons 18 to 24 years old. PDAY cases showed an even higher prevalence because we used an objective marker of smoking and because there is an association of smoking with high-risk behaviors that predispose those who smoke to traumatic death.

The prevalence of hypertension among young white and black men and women observed in PDAY is consistent with prevalence of hypertension observed in a living population. Although only ~4% of PDAY cases had glycohemoglobin
Implications for Prevention of CHD

The high prevalence of nonlipid risk factors indicates considerable potential to affect early atherosclerosis and subsequent CHD by modifying these risk factors even among those young people with a favorable lipoprotein profile. Changing the behavior of young people to reduce cardiovascular risk is a serious challenge and a difficult task. Efforts to modify diet in children by intervention in school lunch programs and by family counseling have achieved only limited success.23,24 The decline in adolescent and youth smoking since 1974 slowed after 1985 and now is reversed.25 Obesity is emerging as a major health problem.26

Despite the controversy over screening for blood cholesterol, diet modification, and drug treatment at early ages, there is little or no controversy over hygienic measures to control smoking, obesity, hypertension, and hyperglycemia in young persons. As demonstrated in the results presented here, these nonlipid risk factors substantially affect the extent and severity of coronary and aortic atherosclerosis even in individuals with a favorable lipoprotein profile. The earlier all the cardiovascular risk factors are controlled, as recommended by the AHA in 1992,27 the greater the potential for deflecting the onset of CHD.

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