Usefulness of Electron Beam Tomography in Adolescents and Young Adults With Heterozygous Familial Hypercholesterolemia

Samuel S. Gidding, MD; Lisa C. Bookstein, MS, RD; Eva V. Chomka, MD

Background—Because of the success of secondary prevention of coronary events by intense risk factor modification, a more precise measure of atherosclerosis in youth would have great clinical value both in the design of clinical trials for the demonstration of the usefulness of coronary disease prevention early in life and in guiding therapy. Identification of calcium in coronary arteries by electron beam tomography has been associated with severity of atherosclerosis in adults.

Methods and Results—Twenty-nine youths 11 to 23 years old with familial hypercholesterolemia (average LDL cholesterol, 5.95 mmol/L) underwent electron beam tomography as well as comprehensive risk factor assessment with measurement of total cholesterol, triglycerides, HDL cholesterol, lipoprotein (a), apolipoprotein E phenotype, blood pressure, body mass index, and history of tobacco use. Significant coronary calcium was identified in 7 of 29 subjects. Increased body mass index was significantly associated with the presence of coronary calcium (25.3 versus 20.6 kg/m², P<0.03). No other risk factors were associated with the presence of coronary calcium.

Conclusions—Coronary calcium, uncommonly identified before the fourth decade, was found in a significant percentage of adolescents and young adults with familial hypercholesterolemia. Overweight may increase the likelihood of coronary calcium being present in individuals already at high risk. (Circulation. 1998;98:2580-2583.)

Key Words: coronary disease ■ hypercholesterolemia ■ obesity ■ imaging

There is intense interest in the noninvasive diagnosis of atherosclerosis, particularly in younger individuals. Risk estimates made in youth, based on known cardiovascular risk factors in adults, are useful but imprecise, particularly when cardiovascular events may be decades in the future or may never occur. Because of the success of secondary prevention of coronary events by intense risk factor modification, a more precise measure of atherosclerosis in youth would have great clinical value both in the design of clinical trials for the demonstration of the usefulness of coronary disease prevention early in life and in guiding therapy.

Coronary calcium as detected by electron beam tomography has shown some promise in the identification of individuals at risk for severe coronary disease. Young adults with obesity and obesity-related risk factors as adolescents as well as individuals with homozygous familial hypercholesterolemia are known to have detectable coronary calcium shown by this technique. The purpose of this study was to determine the prevalence of coronary calcium in adolescents and young adults with heterozygous familial hypercholesterolemia and to determine whether other known coronary risk factors, including body mass index, HDL cholesterol, lipoprotein (a) [Lp(a)], tobacco use, apolipoprotein (apo) E phenotype, apo B level, blood pressure, family history, sex, and age, were associated with an increased likelihood of identifying coronary calcium.

Methods

Individuals 11 to 23 years old with heterozygous familial hypercholesterolemia followed up in one preventive cardiology practice were offered the opportunity to participate in a protocol that involved assessment of coronary calcium by electron beam tomography, a single blood draw, and a medical history. A strict definition of familial hypercholesterolemia was used: LDL cholesterol ≥5 mmol/L and a similarly affected parent at the last recorded cholesterol level before therapy. For a child, elevated LDL cholesterol is considered to be ≥3.36 mmol/L. Approximately half of those contacted accepted. Two young adults who were previously followed up and were currently followed in an internal medicine practice were also recruited. Individuals identified by chart review who did not participate either could not be contacted, had moved from the region since their last clinic visit, or were not interested in the study. There were no significant differences between those recruited and those not recruited with regard to LDL cholesterol level. The protocol was approved by the institutional review boards of Children’s Memorial Hospital and the University of Illinois, Chicago. There were 29 participants (15 male) with a mean age of 14.6 years.

Electron beam tomography was performed with the Imatron C150 Ultrafast CT scanner (Imatron, Inc). Scanning consisted of a maximum span of three 20-level, 3-mm, 100-ms acquisitions. Each
participant was supine, in the cephalad position (head toward the scanner), with the scanning table parallel to the ground. An initial 100-ms 3-mm single-level scan during inspiration was performed to ensure proper scanning location. This identified the top of the aortic arch, where scanning commenced. High-resolution 100-ms/scan, 3-mm contiguous slices with 80% electrocardiographic R-R interval trigger, without intravenous contrast enhancement, were then made during inspiration scanning, progressing from cephalad to caudad. Between 30 and 40 slices were necessary to encompass the aortic arch and complete coronary arterial tree. The proximal coronary arteries were rescanned with twenty 3-mm slices because the coronary calcium areas to be assessed were small, and participants occasionally do not sustain a complete breathhold for 20 seconds. This has been standard practice for the past 7 years to increase reproducibility. Each participant’s calcium study was reviewed and quantified by a single observer on 2 separate occasions to ensure score reproducibility. Intraobserver reproducibility was 100%. The scanner is routinely calibrated with the Imatron uniformity scatter phantoms to verify calibration with flatness of a water phantom within 3 Hounsfield units (HU) across the scanning field.

To be positive, a scan was required to have a lesion with a 1-mm 3 volume. Depending on the field of view, 1 mm 3 equaled 4 pixels (26-cm reconstruction circle) in 27 participants or 6 pixels (19-cm reconstruction circle) in 2. This requires a 512×512-pixel matrix. A major technical consideration with low calcium scores is to exclude artifact from scatter. The reader reviewed each scan to be certain that any level with detected calcium differed from the background by >50 HU. With the generally smaller body habitus of this group, the definition of a positive scan (4 pixels) was conservative. A coronary calcium score was calculated for each participant according to the method of Agatston et al. Any density >130 HU is quantified. The calcified area in mm 2 is multiplied by a weighted density factor. Scores are measured for the left main, left anterior descending, left circumflex, and right coronary arteries.

Blood was obtained within 2 days of tomography. Before the blood draw, participants were required to fast for at least 12 hours. Blood was obtained for total cholesterol, triglycerides, HDL cholesterol, apoA-1, apoB, Lp(a), and apoE phenotype. LDL cholesterol was calculated from the Friedewald equation (total cholesterol minus HDL cholesterol minus triglycerides/5 = LDL cholesterol). A history of recent infection was obtained. Fasting venous blood was collected in tubes with EDTA (1 mg/mL) centrifuged within 4 hours, and sent at 4°C via overnight courier to a central laboratory (Boehringer Mannheim Diagnostics) as previously described. The laboratory participated in and remained certified by the NHLBI-CDC Part III Lipid Standardization Program. HDL cholesterol was isolated by use of heparin/2 mol/L manganese chloride. Apo B was measured by immunonephelometry (BNA-100, Behring Diagnostics) calibrated against a World Health Organization traceable standard. Apo E phenotype was assessed from VDL isolated from plasma.

Age, family history of cardiovascular disease in parents or grandparents <55 years old, history of tobacco use by the participant or a family member, and use of lipid-lowering medications were obtained by interview. Height, weight, waist circumference, blood pressure, and hip circumference were measured by a single individual.

Statistical analysis included calculation of descriptive statistics for the entire cohort and comparisons between those with and without coronary calcium by either unpaired test or Fisher’s exact test. A Wilcoxon rank sum test was used for Lp(a) because of the nonnormal distribution of this variable. A value of P<0.05 was considered statistically significant.

Results

In Table 1, demographic data and risk factor data for the entire cohort are presented. One individual had isolated systolic hypertension. LDL cholesterol was significantly elevated, with a range from 3.54 to 8.28 mmol/L. HDL cholesterol <0.91 mmol/L (35 mg/dL) was present in 7, whereas 3 had HDL cholesterol ≥1.55 mmol/L (60 mg/dL). Triglycerides ≥2.26 mmol/L (200 mg/dL) were present in 2. Either the apoE 4/4 or 4/3 phenotype was present in 5, and the apoE 2/2 or 3/2 phenotype was present in 2. Tobacco use or familial exposure was present in 2. Lipid-lowering medications were currently being used by 5. A family member with a coronary event before age 55 years was present for 13.

High coronary calcium scores were present in 7 of 29 subjects, with scores ranging from 1.02 to 7.5 (median, 1.53 in these 7). Coronary calcium scores between 0.16 and 0.77 were present in 12, and no detectable coronary calcium was present in 10. In Table 2, comparisons between the 7 of 29 with and without significant coronary calcium are shown. Those with coronary calcium had significantly increased body mass index. No other continuous variable demonstrated statistical significance.

### Table 1. Characteristics of the 29 Adolescents and Young Adults With Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.7 (5.1)</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.80 (0.05)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>113 (11)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>7.73 (1.19)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>5.95 (1.24)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.19 (0.31)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.37 (0.55)</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>195 (41)</td>
</tr>
<tr>
<td>Lp(a),* mg/dL</td>
<td>28 (1–113)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or *median and range. Unit conversions: cholesterol values, 38.67 mg/dL = 1 mmol/L; triglycerides, 88.57 mg/dL = 1 mmol/L.

### Table 2. Comparison of Subjects With and Without Coronary Calcium Scores >1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coronary Calcium Score &gt;1</th>
<th>Coronary Calcium Score &lt;1</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>16 (4)</td>
<td>14 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3 (6.9)</td>
<td>20.6 (4.0)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.81 (0.04)</td>
<td>0.80 (0.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>116 (10)</td>
<td>112 (12)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>7.86 (1.32)</td>
<td>7.71 (1.19)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>6.15 (1.60)</td>
<td>5.87 (1.22)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.06 (0.34)</td>
<td>1.22 (0.28)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.39 (0.45)</td>
<td>1.35 (0.59)</td>
<td>NS</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>211 (41)</td>
<td>190 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a),* mg/dL</td>
<td>42 (4–113)</td>
<td>20 (1–113)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values as in Table 1.
a statistically significant difference, nor were differences demonstrated for categorical variables, including sex (5 of 15 males positive for coronary calcium), family history (2 of 13 positive), tobacco use (1 of 2 positive), and medication use (2 of 5 positive).

Discussion

This study has shown that a modest percentage of adolescents with heterozygous familial hypercholesterolemia have small amounts of coronary calcium present. The presence of calcium is associated with increased body mass index but not with the severity of hypercholesterolemia in this group already at increased risk. This suggests that the presence of increased body mass index in individuals with familial hypercholesterolemia is an additional and potent risk factor for the acceleration of atherosclerosis.

Although Agatston scores were low in this cohort, several methodological considerations were made to ensure the quality of the data. Four adjacent pixels with a threshold of 130 HU (Agatston score of >1) were necessary to be considered positive for coronary calcium. Each of these requirements increases sensitivity at the expense of specificity.8 The smaller body habitus of most of the participants in this study compared with adults increased the quality of image interpretation; none had significant signal scatter resulting in uninterpretable low scores.

Studies of otherwise normal young adults would suggest that the presence of any coronary calcium in this age group is unusual. In the most comprehensive study segregating out those <29 years old, the prevalence of any calcium was <11% for males and <6% for females.16 This compares with the prevalence of 19 of 29 (66%) for any coronary calcium in this study and demonstrates that accelerated atherosclerosis, known to occur in familial hypercholesterolemia, can be detected noninvasively.4,16 However, the relatively low scores for coronary calcium would suggest that the atherosclerosis is nonobstructive at this time.17

Autopsy studies of young adults suggest that individuals with coronary risk factors begin to develop plaque in late adolescence.18,19 Furthermore, these studies suggest that the presence of calcium in atherosclerotic plaque does not generally occur until the fourth decade of life.20 Therefore, the finding of coronary calcium in these adolescents, even in small amounts, is distinctly unusual and represents an acceleration of atherosclerosis. In the past, identification of coronary calcium has been used as an evaluation tool for the presence of coronary disease in the symptomatic adult. The amount of calcium identified would not predict coronary obstruction.21 This study expands the use of this technique to include the identification of the youth or young adult with accelerated atherosclerosis on the basis of the presence of major coronary risk factors.

Obesity and obesity-related risk factors are known to be associated with coronary calcium in slightly older cohorts.6,27 In the Muscatine Study, measurements of coronary risk made in adolescence were important in understanding the prevalence of coronary calcium at age 27 to 33 years. In particular, overweight, low HDL cholesterol, and increased blood pressure were important future determinants of coronary calcium a decade later. In the CARDIA study, which includes a biracial cohort 28 to 40 years old, coronary calcium was associated with increased body mass index. These findings and the increased prevalence of overweight and its associated dyslipidemia in adolescents currently being observed suggest that the early onset of atherosclerosis may be increasing in the population at large.28

Two limitations of this study design are the small sample size and the constraint on the range of LDL cholesterol, excluding those with normal and mildly elevated values. This did not allow sufficient statistical power to detect influences of other critical risk factors. Enrollment of 200 to 400 individuals would be necessary to determine whether unfavorable differences in LDL and HDL cholesterol observed in this study would be statistically significant as well as to detect significant interactions with age. Another limitation is the lack of an obese control group to determine whether obesity alone can account for the observed findings. Finally, limitations in the prognostic ability of calcium scores in the lower ranges with regard to future coronary disease make generalization of these findings to individual patients difficult.17

The presence of multiple cardiac risk factors in children increases the severity of asymptomatic atherosclerosis in youth.29 Obesity is associated with the presence of increased cardiovascular risk because of associations with many other risk factors.25 Further studies with larger samples will be necessary to assess the independent importance of hypertension, diabetes mellitus, tobacco use, and low HDL cholesterol toward the premature accumulation of coronary calcium. In particular, it is not known whether this finding increases the likelihood of a coronary event beyond that predicted by conventional risk assessment. However, this study has identified a subgroup of individuals who may be appropriate for clinical trials of lipid-lowering drug therapy with an end point of progression of coronary calcium score. Because of the low prevalence of positive findings in this age group, we are not
recommending the routine use of electron beam tomography as part of the evaluation of adolescents with coronary risk factors until further studies to answer the above concerns are conducted.

Acknowledgment

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References

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