Coronary Calcification and Its Relation to Extracoronary Atherosclerosis in Asymptomatic Hypercholesterolemic Men

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Background. The prevalence of coronary calcifications and extracoronary plaques was studied in patients with asymptomatic hypercholesterolemia.

Methods and Results. Ultrafast computed tomography for coronary calcification (presence or absence: calcium score) and echographic assessment of carotid, aortic, and femoral plaques were performed in 111 hypercholesterolemic men: 65% had coronary calcification, 72% had extracoronary plaque. The two lesions were associated as: 1) compared with subjects without coronary calcification, those with calcification had a higher prevalence of aortic (p<0.05) and femoral (p<0.01) plaque and of two diseased sites (p<0.05); 2) the prevalence of coronary calcification was higher in the presence than in the absence of aortic (p<0.05) or femoral (p<0.01) plaque and higher in two (p<0.01) and three diseased (p<0.05) sites than in no diseased site; 3) the calcium score was higher in the presence than in the absence of carotid (p<0.05), aortic (p<0.05), or femoral (p<0.001) plaque, higher in two (p<0.001) and three diseased (p<0.05) sites than in no diseased sites, and higher in two (p<0.01) than in one diseased site; and 4) the calcium score correlated with femoral plaque (p<0.001). Overall, the presence of two or three diseased extracoronary sites versus no or one diseased site showed a power of 78% for predicting coronary calcification. Coronary calcium score correlated with age (p<0.01) and triglycerides (p<0.05).

Conclusions. The close relation between coronary calcium and extracoronary plaques suggests that echography of extracoronary vessels could aid in the screening of coronary atherosclerosis in high-risk, asymptomatic individuals. (Circulation 1992;85:1799–1807)

Key Words • atherosclerosis • tomography, ultrafast computed • ultrasonography • calcium • plaques • hypercholesterolemia • triglycerides

The noninvasive detection of early atherosclerosis long before the onset of clinical symptoms underlying more severe and complicated lesions may help to improve the efficiency of cardiovascular disease prevention by individualizing the vascular status of high-risk subjects. This point is particularly crucial for coronary arteries because the relation of symptoms with atherosclerosis in this arterial bed is notoriously poor.1 Very early extracoronary atherosclerotic lesions are easily detectable by ultrasonography,2–5 which is not possible for coronary lesions because of the limitations of the resolution and depth penetration of ultrasound, and to a lesser degree because of cardiac motion. Therefore, an interesting issue to help in screening for coronary artery disease is to determine whether the presence of extracardiac atherosclerosis may be predictive of coronary lesions, assuming the generalized nature of atherosclerosis.1 To solve this question, we used ultrafast computed tomography (CT), which was recently proposed for the noninvasive quantification of coronary calcium.6,7 It surpasses ultrasound for two reasons: its spatial resolution is higher, and calcium selectively attenuates x-radiations, whereas it does not specifically reflect sound waves. Moreover, ultrafast CT allows rapid acquisition times that freeze coronary motion and result in sharp images.6,7 As angiographic and necropsy studies have shown that coronary calcification was invariably associated with coronary atheroma,8–10 ultrafast CT offers a new, noninvasive, reliable methodology to detect coronary atherosclerosis.11 Thus, the simultaneous use of extracoronary echography and coronary ultrafast CT in symptom-free hypercholesterolemic men allowed us to test for the distribution of atherosclerosis and for associations between extracardiac lesions and coronary calcium in this high-risk population. A secondary objective of the study was to analyze whether serum lipid levels and other risk factors were related to coronary calcium.
Methods

Study Subjects

The 111 hypercholesterolemic men included in the study were selected by means of a cholesterol screening program conducted at the work site for employees of several companies within the Paris area by a group of occupational health physicians (PCV METRA group [groupe de prevention cardiovasculaire en medecine du travail]). Total cholesterol levels were measured in biochemistry laboratories close to the work site of all employees. Only those having serum total cholesterol concentrations above 240 mg/dl (or 6.2 mmol/l) were referred to the hospital for complete investigation, including ultrasonic detection of extracoronary arterial plaques, detection of coronary calcium by ultrafast CT, and evaluation of traditional risk factors. All of these investigations were performed during 1 day of hospitalization.

Risk Factor Evaluation

Lipid measurements were performed in the biochemistry laboratory after subjects had fasted for 14 hours. Venous blood samples were withdrawn from each subject, who had rested in the supine position for at least 10 minutes. Serum total cholesterol and triglycerides were measured by enzymatic methods. High density lipoprotein cholesterol was measured by an enzymatic method after the precipitation of low density lipoprotein (LDL) and very low density lipoprotein by phosphotungstic acid magnesium chloride. The level of LDL cholesterol was calculated from total cholesterol, high density lipoprotein cholesterol, and triglyceride values according to the classic Friedewald formula. Subjects whose cholesterol level in the hospital was less than 200 mg/dl (or 5.2 mmol/l) were excluded from the study. We selected only hypercholesterolemic subjects to make the group homogeneous on this risk factor. We also excluded subjects with triglyceride levels higher than 400 mg/dl (or 4.50 mmol/l) to calculate accurately the LDL cholesterol by the Friedewald formula, which is valid for triglyceride values below 400 mg/dl (or 4.50 mmol/l). The excluded subjects represented about 10% of the men screened at the work site by the PCV METRA group and referred to the hospital. Subjects with diseases or factors causing secondary hypercholesterolemia were also excluded from the study. None had ever been treated with any lipid-lowering drug. Subjects were classified into three subtypes of dyslipidemia: borderline hypercholesterolemia, with total cholesterol level from 200 mg/dl (or 5.2 mmol/l) to 239 mg/dl (or 6.19 mmol/l); type IIA hypercholesterolemia, with total cholesterol level of 240 mg/dl (or 6.2 mmol/l) or above and triglyceride level less than 175 mg/dl (or 2 mmol/l); and type IIB hypercholesterolemia, with cholesterol level of 240 mg/dl (or 6.2 mmol/l) or above and triglyceride level of 175 mg/dl (or 2 mmol/l) or above. In all cases, lipid electrophoresis was performed to exclude hyperchylomicronemia. Systemic blood pressure was determined in the arm as the mean of at least three measurements by standard sphygmomanometric procedure with the patient in supine position after 10 minutes of rest. Hypertension was characterized by a diastolic blood pressure of 90 mm Hg or above (Korotkoff phase V). Essential hypertension was established on the basis of appropriate laboratory tests, and no subject had ever taken any antihypertensive treatment. Patients with secondary hypertension were excluded from the study. The body mass index (weight/height2) was used to measure excess of weight. Smoking was defined by the following criteria, carefully assessed by questioning the subjects: 1) a current daily smoker was defined as someone who had regularly smoked at least five cigarettes per day for the previous 3 months, and 2) lifelong smoking dose was calculated by multiplying the mean number of cigarettes smoked daily by the number of years of smoking and was expressed in pack-years (i.e., smoking of one pack each day during a year). Blood glucose level was measured after an overnight fast; patients with diabetes mellitus were excluded from the study to make the study group as homogeneous as possible on a main risk factor and to avoid possible interactions between lipid abnormalities and glycemia elevation on atherosclerotic process in the analysis. Serum calcium concentration was also determined in all subjects. A complete clinical examination verified the absence of cardiovascular complications such as carotid artery disease, coronary heart disease, and arteritis of the legs. In each subject, careful interrogation verified the absence of any history of cardiovascular disease and of its symptoms such as transient ischemic attacks, chest pain compatible with angina, or intermittent claudication. A complete clinical examination also verified the absence of murmur in the cervical arteries, in the abdominal aorta and its main branches, in the iliofemoral arteries, and in the precordial area. All peripheral pulses including posterior tibial and dorsalis pedis pulses were also examined and found present. The presence of any history, symptom, or clinical abnormality constituted an exclusion criterion from our study. No subject had ever undergone coronary investigations such as exercise testing, thallium scanning, or coronary angiography.

Detection of Coronary Artery Calcium

Coronary calcifications were detected by using an ultrafast CT scanner (Imatron, San Francisco, Calif.) in conjunction with a 100-msec scan time, a 3-mm slice thickness, and an ECG triggering. Subjects were examined in supine position during a single full inspiratory breath hold. The examination did not require any injection of contrast substance. ECG monitoring electrodes were applied, and four localization slices were made to determine the first level of image triggering; 20 contiguous slices (60 mm) were then acquired caudally to the bifurcation of the main pulmonary artery. Each image slice was triggered at 80% of the RR interval (that is, at the same point in diastole). The total procedure time averaged 10 minutes, and radiation exposure was always less than 500 mrem. Each of the 20 slices was analyzed automatically to determine the presence of calcium and to quantify it in each of the major coronary arteries: the left trunk main artery, the left anterior descending artery, the left circumflex artery, and the right coronary artery. The threshold for a calcific lesion was set at a computed tomographic density of 130 Hounsfield units, with an area above or equal to 1 mm2. The choice of the number of these Hounsfield units in accordance with previous clinical studies on coronary arteries with ultrafast CT is arbitrary and raises the possibility that this
threshold for calcium may be set too high.\textsuperscript{17} This was
done to eliminate as much as possible false-positive data
caused by noise and to make the identification of calcium
more certain. The area of each calcification was mea-
sured and expressed in square millimeters. The maximal
computed tomographic density of each lesion was trans-
formed into four classes in the following manner: 1, 130–199; 2, 200–299; 3, 300–399, and 4, ≥400 Hounsfield
units.\textsuperscript{7} A lesion score was then calculated by multiplying
the density number by the area of the lesions. A total
calcium score was defined as the sum of the lesion scores
for all 20 slices.\textsuperscript{7} Although this method of calcium
evaluation, based on 130 Hounsfield units for calcium
threshold and on a total score calculation, was previously
described and used in clinical studies, it has not yet been
validated as an accurate reflection of the actual amount
of calcium in pathological specimens and probably over-
simplifies the quantification of calcium by ultrafast CT.
However, its simplicity of use and its applicability to a
wide number of subjects in clinical preventive medicine
represent its major justification in the present work.

Detection of Extracoronary Plaques

Studies were performed with a real-time, B-mode
ultrasound imager (Radius CG, General Electric, CGR
France, Issy les Moulineaux, France). The extracranial
carotid arteries, the abdominal aorta, and the femoral
arteries in the upper part of the thigh were examined
according to a careful procedure previously described in
detail.\textsuperscript{4,5} Briefly, investigation of extracranial carotid
arteries was performed with a 7.5-MHz probe and
included the common carotid artery, the carotid bifi-
cration, the carotid bulb, and the internal carotid artery.
The abdominal aorta was examined by means of a
3.75-MHz probe placed just above the umbilicus to
image the upper abdominal aorta and then moved
distally along the left of the subumbilical median line to
image the lower abdominal aorta. The investigation of
femoral arteries was performed with a 7.5-MHz probe
and included the common, superficial, and profunda
femoral artery in the upper part of the thigh. The whole
examination of both sides of extracranial carotid arter-
ies, the abdominal aorta, and both sides of the femoral
arteries took approximately 60 minutes. The ultrasonic
images were magnified and projected in real time on a
video monitor. During the scanning, the sonographic
physician classified findings into two categories at each
of the three sites: absence of any atherosclerotic plaque
or presence of one or more arterial plaques, whatever
their precise location, at a given site. The same physi-
cian checked the original classification in one session
from the hard copies of real-time images made from
longitudinal and axial sections of arteries. Arterial
plaque was defined as an echogenic structure encroach-
ing into the vessel lumen with a distinct area 50%
greater than the intimal plus medial thickness of neigh-
boring sites.\textsuperscript{4,5,18} Intima plus media thickness was eval-
uated after the sound beam was adjusted perpendicu-
larly to the arterial surface as the distance from the edge
of the first echogenic bright line corresponding to the
lumen–intima interface to the edge of the second
echogenic line corresponding to the media–adventitial
interface.\textsuperscript{2} Plaque was considered present at the carotid,
aortic, or femoral site when one or more arterial
plaques were found at this site regardless of their
precise location and the number of plaques.\textsuperscript{4,5}

Data Analysis

Coronary calcification was expressed in two ways:
first, as a dichotomous variable, absence (0) or presence
(1) of calcification, the presence of calcification being
characterized by a total calcium score above 0, and its
absence corresponding to a total score equal to 0; second,
as a quantitative parameter defined by the value
of total calcium score expressed as raw data or as
logarithm transformed data: \( \log_{10} (1+\text{total score}) \) be-
cause of the skewed distribution of the score values.
Arterial extracoronary plaque was characterized as a
dichotomous variable at each site: absence (0) or pres-
ence (1), and the different sites were defined by four
classes: no diseased site; one diseased site; two diseased
sites, and three diseased sites. Quantitative risk factors
were expressed as mean±SD. Independent sample \( t \)
tests for quantitative variables and \( \chi^2 \) tests for percent-
ages of subjects were used for comparisons between
groups with or without coronary and extracoronary
lesions. Stepwise multiple regression analysis was per-
formed to confirm the results of univariate comparis-
s.\textsuperscript{19} Statistical significance was considered to be a
value of \( p<0.05 \). The statistical analysis was carried out
on a computer (Apple Macintosh, Cupertino, Calif.)
with the use of STATVIEW (Abacus Concept Corp.,
Berkeley, Calif.) and EXCEL (Microsoft, Les Ulis,
France) software. To evaluate the probability of detect-
ing coronary calcification in this population, given the
various combinations of aortic, femoral, and carotid
disease, a test of the sensitivity and specificity of
extracardiac atherosclerosis versus either the presence
or absence of calcification was used. The pretest likeli-
hood (PL) was defined as the probability of coronary
calcification in a patient to be tested\textsuperscript{20}:

\[
\text{PL} = \frac{\text{Number of patients with coronary calcification in the test population}}{\text{Total number of patients in the test population}}
\]

Sensitivity (SE) of the test was the probability of a
positive test result (extracardiac atherosclerosis) in a
patient with coronary calcification\textsuperscript{20}:

\[
\text{SE} = \frac{\text{Number of patients with coronary calcification showing extracardiac atherosclerosis}}{\text{Total number of tested patients with coronary calcification}}
\]

Specificity (SP) of the test was the probability of not having
the positive test result (absence of extracardiac atheroscle-
rosis) in a patient without coronary calcification\textsuperscript{20}:

\[
\text{SP} = \frac{\text{Number of patients without coronary calcification not showing extracardiac atherosclerosis}}{\text{Total number of tested patients without coronary calcification}}
\]

The predictive power (PP) was calculated according to
Bayes theorem\textsuperscript{20}:
TABLE 1. Levels of Risk Factors

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 ± 7</td>
<td>30–63</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 3</td>
<td>20–36</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>127 ± 14</td>
<td>100–178</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 ± 10</td>
<td>58–120</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Lipid levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>6.88 ± 0.82</td>
<td>5.24–8.83</td>
</tr>
<tr>
<td>mmol/l</td>
<td>256 ± 32</td>
<td>203–342</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.70 ± 0.75</td>
<td>0.60–4.17</td>
</tr>
<tr>
<td>mmol/l</td>
<td>149 ± 66</td>
<td>52–365</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.23 ± 0.31</td>
<td>0.70–2.40</td>
</tr>
<tr>
<td>mmol/l</td>
<td>48 ± 12</td>
<td>27–93</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>4.88 ± 0.80</td>
<td>3.25–7.04</td>
</tr>
<tr>
<td>mmol/l</td>
<td>189 ± 31</td>
<td>126–272</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Type IIA</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Type IIB</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>5.4 ± 0.49</td>
<td>4.20–6.80</td>
</tr>
<tr>
<td>mmol/l</td>
<td>97 ± 9</td>
<td>76–122</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>2.40 ± 0.08</td>
<td>2.20–2.60</td>
</tr>
<tr>
<td>mmol/l</td>
<td>9.6 ± 0.3</td>
<td>8.8–10.4</td>
</tr>
<tr>
<td>Smokers (%) current</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Lifelong smoking (pack years)</td>
<td>14 ± 14</td>
<td>0–58</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percentage of total number of subjects. HDL, high density lipoprotein; LDL, low density lipoprotein.

\[
PP = \frac{PL \times SE}{PL \times SE + (1-PL)(1-SP)}
\]

These calculations were performed by using different tests of extracardiac atherosclerosis according to the site of lesions, the number of diseased sites, and various combinations of diseased sites.

**Results**

Table 1 shows mean levels of risk factors in the study group. Nineteen percent of the population was hypertensive, and the distribution of subtypes of dyslipidemia showed 20% with borderline high cholesterol, 60% with type IIa hypercholesterolemia, and 20% with type IIb hypercholesterolemia.

Table 2 shows that 35% of the population had no coronary calcification (total calcium score, 0); in the whole population, the total calcium score had an average value of 30, with a standard deviation of 69 and a range from 0 to 440. Table 2 also shows that 28% of the population had no extracoronary plaque, whereas 32% had carotid plaque, 51% had aortic plaque, and 58% had femoral plaque. The presence of plaque at one, two, or three different sites was found in 22%, 30%, and 20%, respectively.

Table 3 shows that the percentage of subjects with extracoronary plaque was higher in the group with present than in the group with absent coronary calcification at the aortic \( p<0.05 \) and femoral \( p<0.01 \) sites; the same trend existed (insignificantly) at the carotid site. The percentage of subjects without any diseased site was lower in the group with present than in the group with absent coronary calcification \( p<0.01 \), whereas the percentage of subjects with two diseased sites was higher in the presence than in the absence of coronary calcification \( p<0.05 \); the same trend existed but did not reach statistical significance for the percentage of subjects with one and three diseased sites.

Table 4 compares the percentage of subjects with coronary calcification in different groups defined by the absence or presence of extracoronary plaque at each site and by the number of diseased sites. This percentage was higher in the presence than in the absence of aortic plaque \( p<0.05 \) and in the presence than in the absence of femoral plaque \( p<0.01 \); the same difference existed in the presence compared with in the absence of carotid plaque but did not reach statistical significance. The percentage of subjects with coronary calcification was also higher in the group with two

**Table 2. Coronary Calcium and Extracoronary Plaques**

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with absent coronary calcium</td>
<td>35%</td>
</tr>
<tr>
<td>Total calcium score (raw)</td>
<td>30 (69)</td>
</tr>
<tr>
<td>Subjects with absent extracoronary plaque</td>
<td>28%</td>
</tr>
<tr>
<td>Subjects with</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque</td>
<td>32%</td>
</tr>
<tr>
<td>Aortic plaque</td>
<td>51%</td>
</tr>
<tr>
<td>Femoral plaque</td>
<td>58%</td>
</tr>
<tr>
<td>1 Diseased site</td>
<td>22%</td>
</tr>
<tr>
<td>2 Diseased sites</td>
<td>30%</td>
</tr>
<tr>
<td>3 Diseased sites</td>
<td>20%</td>
</tr>
</tbody>
</table>

Values are mean for calcium score (SD in parentheses) or percentage of the total number of subjects.

**Table 3. Comparison of Percentages of Subjects With Extracoronary Plaque in Groups With and Without Coronary Calcification**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Carotid</th>
<th>Aortic</th>
<th>Femoral</th>
<th>0 Site</th>
<th>1 Site</th>
<th>2 Sites</th>
<th>3 Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent coronary calcification (n=39)</td>
<td>23</td>
<td>38</td>
<td>41</td>
<td>44</td>
<td>26</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Present coronary calcification (n=72)</td>
<td>37</td>
<td>58*</td>
<td>67†</td>
<td>20†</td>
<td>21</td>
<td>37*</td>
<td>22</td>
</tr>
</tbody>
</table>

* \( p<0.05 \).
† \( p<0.01 \).
TABLE 4. Percentages of Subjects With Coronary Calcification in Groups Defined by Absence or Presence of Extracoronary Plaque

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group subjects with coronary calcification (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent carotid plaque (n=75)</td>
<td>60</td>
</tr>
<tr>
<td>Present carotid plaque (n=36)</td>
<td>75</td>
</tr>
<tr>
<td>Absent aortic plaque (n=54)</td>
<td>56</td>
</tr>
<tr>
<td>Present aortic plaque (n=57)</td>
<td>74*</td>
</tr>
<tr>
<td>Absent femoral plaque (n=47)</td>
<td>51</td>
</tr>
<tr>
<td>Present femoral plaque (n=64)</td>
<td>75†</td>
</tr>
<tr>
<td>0 Site involved (n=31)</td>
<td>45</td>
</tr>
<tr>
<td>1 Site involved (n=25)</td>
<td>60</td>
</tr>
<tr>
<td>2 Sites involved (n=33)</td>
<td>82‡</td>
</tr>
<tr>
<td>3 Sites involved (n=22)</td>
<td>73§</td>
</tr>
</tbody>
</table>

*p<0.05, absent vs. present plaque at site.  
†p<0.01, absent vs. present plaque at site.  
‡p<0.01, one or several vs. zero diseased site.  
§p<0.05, one or several vs. zero diseased site.

diseased sites (p<0.01) and in the group with three diseased sites (p<0.05) than in the group with no diseased sites. The same tendency was observed in the group with one diseased site but without statistical significance.

Figures 1 and 2 compare the coronary total calcium score according to the absence or presence of extracardiac plaque at each site and the number of diseased sites. The score was higher in the presence than in the absence of carotid (p<0.05), aortic (p<0.05), and femoral (p<0.001) plaque; it was also higher in two and three diseased sites than in no diseased site (p<0.001, p<0.05) and in two diseased sites than in one diseased site (p<0.01).

Table 5 shows that in stepwise regression analysis, taking coronary total calcium score as a dependent variable and carotid, aortic, and femoral plaque as independent variables, the coronary calcium score was significantly associated with femoral plaque (p<0.001) but not with aortic and carotid plaque.

Table 6 shows the sensitivity, specificity, and the predictive power of extracardiac atherosclerosis (taken as the test) according to the site and combination of sites versus either the presence or the absence of coronary calcification (taken as the disease). Sensitivity was dependent on the defined test: It ranged from 3% when the test was the combination of carotid and aortic plaque versus its absence to 81% when the test was the presence of one, two, or three diseased sites versus no diseased site. The specificity also ranged from 44% when the test was the presence of one, two, or three diseased sites versus no diseased site to 97% when the test was the combination of carotid and aortic plaque or of carotid and femoral plaque versus their absence. The predictive power of the test ranged from 67% to 90%; it reached 90% for the combination of carotid and femoral plaque versus its absence and 80% for the combination of aortic and femoral plaque versus its absence.

Table 7 compares the risk factor levels according to the absence or the presence of coronary calcification. Only triglycerides were significantly higher (p<0.01) in

![Figure 1: Bar graph shows comparison of the logarithmic-transformed total calcium score between groups with and without plaque at the carotid, aortic, and femoral sites. Values are mean±SD.](image1)

![Figure 2: Bar graph shows comparison of the logarithmic-transformed total calcium score between groups with one, two, three, or no diseased extracoronary sites. Values are mean±SD.](image2)

TABLE 5. Stepwise Regression Analysis of Extracoronary Plaque Influencing Total Calcium Scores

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent variables LN (total calcium score)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid plaque</td>
<td></td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic plaque</td>
<td></td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Femoral plaque</td>
<td></td>
<td>18.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LN, logarithm transformed data.
the presence than in the absence of calcification. A similar tendency existed for age but did not reach statistical significance.

Table 7. Risk Factor Levels According to Absence or Presence of Coronary Calcification

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Coronary calcification</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absence (n=39)</td>
<td>Presence (n=72)</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46±8</td>
<td>47±7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25±2</td>
<td>25±3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126±13</td>
<td>128±15</td>
<td>NS</td>
<td></td>
</tr>
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<td>Diastolic</td>
<td>79±10</td>
<td>82±10</td>
<td>NS</td>
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<td>Hypertension (%)</td>
<td>18</td>
<td>21</td>
<td>NS</td>
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<tr>
<td>Lipid levels</td>
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<tr>
<td>Cholesterol</td>
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<tr>
<td>mmol/l</td>
<td>6.88±0.7</td>
<td>6.89±0.9</td>
<td>NS</td>
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<tr>
<td>mg/dl</td>
<td>266±27</td>
<td>267±35</td>
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<tr>
<td>Triglycerides</td>
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<tr>
<td>mmol/l</td>
<td>1.44±0.6</td>
<td>1.85±0.8</td>
<td>&lt;0.01</td>
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<tr>
<td>mg/dl</td>
<td>126±52</td>
<td>162±56</td>
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<td>HDL cholesterol</td>
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<tr>
<td>mmol/l</td>
<td>1.29±0.31</td>
<td>1.20±0.3</td>
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<tr>
<td>mg/dl</td>
<td>50±12</td>
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<tr>
<td>mmol/l</td>
<td>4.93±0.74</td>
<td>4.85±0.84</td>
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<tr>
<td>mg/dl</td>
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<td>188±32</td>
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<td>Dyslipidemia (%)</td>
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<td>Type IIa</td>
<td>74</td>
<td>58</td>
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<td>Type IIb</td>
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<tr>
<td>mmol/l</td>
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<td>5.5±0.45</td>
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<tr>
<td>mg/dl</td>
<td>95±106</td>
<td>99±8</td>
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<td>Serum calcium</td>
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<tr>
<td>mmol/l</td>
<td>2.4±0.1</td>
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<tr>
<td>mg/dl</td>
<td>9.6±0.4</td>
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<td>Smokers (% current)</td>
<td>41</td>
<td>42</td>
<td>NS</td>
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<tr>
<td>Lifelong smoking (pack years)</td>
<td>11±13</td>
<td>16±15</td>
<td>NS</td>
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Values are mean±SD or percentage of number of subjects in each group.

Table 8 shows that in stepwise regression analysis, taking coronary total calcium score as a dependent variable and age, triglycerides, total cholesterol, and lifelong smoking as independent variables, the calcium score was only associated significantly with age (p<0.01) and triglyceride level (p<0.05). The same analysis for extracoronary atherosclerosis showed that carotid plaque was associated with total cholesterol (p<0.05), aortic plaque with age (p<0.01), and femoral plaque with age (p<0.001) and smoking (p<0.05).

Discussion

The primary goal of our work was to determine the distribution of atherosclerosis in high-risk asymptomatic cross-individuals. To this end, we selected (at the work site) hypercholesterolemic men exempt of clinical symptoms, history, and physical signs of cardiovascular disease, and who had never been treated by lipid-lowering drugs or other cardiovascular medication. Ultrafast CT was used to evaluate the presence or absence of coronary calcification and to determine a total calcium score from the detection of calcified areas superior to 1 mm² in epicardial segments of coronary arteries.6,7 Even though the basic technology was relatively complex, the realization remained simple, short, and did not require the presence of a physician.7 Moreover, it did not cause any discomfort to the patient, and its results were easily interpretable by means of a computer-assisted procedure. Ultrafast CT has been shown to have a high degree of sensitivity and specificity for the detection of coronary calcium.6,11 In the present study, investigation by ultrafast CT revealed that hypercholesterolemic men had a noteworthy prevalence of coronary calcifications (65%) despite the absence of symptoms or signs of coronary heart disease. Such calcifications have been described as invariably associated with coronary atherosclerotic lesions.11 Anatomopathological studies have demonstrated that coronary calcium accumulates in the intima rather than in the media in atheromatous lesions.21 Furthermore, angiographic studies of symptomatic patients have shown that coronary calcium detected by ultrafast CT is a good marker of coronary atherosclerosis.6,10 However, in a previous study,10 it was shown that all patients with marked arteriographic coronary disease had coronary calcification on ultrafast CT, whereas those with zero or minimal angiographic disease were divided into two equivalent groups with...
presence and absence of ultrafast CT calcification; therefore, the negative predictive value of the absence of coronary calcification remains to be confirmed. Moreover, previous studies have been discrepant in showing that coronary calcification is a reliable indicator of significant vascular stenosis.\textsuperscript{8,22,23} Therefore, we can only conclude that in 65% of asymptomatic, hypercholesterolemic men in whom coronary calcifications were found, the presence of a coronary atheroma is highly probable. In parallel with ultrafast CT, high-resolution B-mode echography was used for detecting atherosclerotic plaque at the carotid, abdominal aortic, and femoral sites according to a technique previously described in detail and having a high intraobserver and interobserver reproducibility rate.\textsuperscript{4,5} The analysis of prevalence of plaque in the carotid, aortic, and femoral sites shows, in accordance with our previous results,\textsuperscript{4} that only 28% of our population had no extracoronary plaque at any site. Both in coronary and extracoronary vessels, atherosclerotic lesions exist in a large majority of our asymptomatic, high-risk population.

A second major issue of the work was the relation between coronary calcification and the ultrasonic findings in the extracoronary vessels. We found a close association between coronary calcifications and extracoronary plaques. Subjects with the presence of coronary calcification, whatever the calcium score, had a higher prevalence of plaque at the aortic and femoral sites and a higher prevalence of two extracoronary diseased sites than did subjects with absence of calcification. However, it is interesting to stress that even in the absence of coronary calcification, there was a significant amount of atherosclerotic disease in extracoronary vessels. This may be due to the fact that the ultrasonic plaques detected by echography are generally noncalcified\textsuperscript{8} and probably represent earlier atherosclerotic lesions rather than coronary calcifications. On the other hand, the prevalence of coronary calcification was higher in subjects with aortic or femoral plaque than in those without plaque at the corresponding site. The presence of calcification was also higher in subjects with two or three diseased extracoronary sites than in those without plaque at any site: Thus, 82% of subjects with extracoronary plaques at two different sites had coronary calcifications. Likewise, the total coronary calcium score was on average higher in the presence than in the absence of plaque and in patients with three or two diseased extracoronary sites than in those without any diseased site. Stepwise regression analysis showed a significant association between total calcium score and the presence of femoral plaque. This analysis of association between coronary and extracoronary atherosclerosis at three different sites is the first to our knowledge to have been performed in an asymptomatic high-risk population; it indicates that extracoronary vessels (particularly the femoral artery) are affected by atherosclerosis in parallel with coronary arteries. This finding led us to evaluate the probability of detecting coronary calcification in this population from the presence of extracardiac atherosclerosis assessed ultrasonographically. We took the presence of extracardiac atherosclerosis as the test and the coronary calcification as the disease. We found a relatively high sensitivity when we used as the test the presence of aortic plaque versus its absence, the presence of femoral plaque versus its absence, the presence of one, two, or three diseased sites versus no diseased site, and the presence of two or three diseased sites versus one or no diseased site. However, the sensitivity was low when the test used was the presence of carotid plaque versus its absence, the combination of two diseased sites (whatever the site) versus its absence, and the presence of three diseased sites versus one, two, or no diseased site. This low sensitivity might be due in part to the small size of subgroups corresponding to the positivity of these tests. In contrast, the specificity of extracardiac atherosclerosis for detecting coronary calcification was higher than the sensitivity: Its lowest value was 44% for the presence of one, two, or three diseased sites versus no diseased site and reached 97% for the combination of carotid and aortic and of carotid and femoral plaque. Using Bayes theorem,\textsuperscript{20} we found that the predictive power of extracardiac atherosclerosis for coronary calcification was above 67%, reaching 90% for the combination of carotid and femoral plaque, 80% for the combination of aortic and femoral plaque, and 78% for the presence of two or three diseased sites versus one or no diseased site. The latter test also had a good sensitivity (60%) and specificity (69%) and so appears to be the best in our 111 high-risk men for predicting the presence of coronary calcification. These findings are of primary importance because they reveal the major role of ultrasonic techniques for measuring peripheral atherosclerosis in identifying individuals who have coronary atherosclerosis. In this respect, they can represent an aid in the clinical diagnosis of coronary atherosclerosis in primary prevention in high-risk asymptomatic patients. Further studies are needed to find out whether vascular disease at extracoronary sites may also be of interest in patients who already have coronary heart disease, for example, as a predictor for subsequent outcome.\textsuperscript{1}

A last question raised by our study was the relation between coronary calcification and serum lipid levels.
and other risk factors. As described in a previous study, we found that lipid parameters were not strongly associated with extracoronary plaque except for the carotid site, whereas age was correlated with aortic and femoral plaque. More original in this study was the association between coronary artery calcium and age and triglycerides. Indeed, age was found to be higher (although not statistically significant) in the group with than in the group without coronary calcification, whereas stepwise regression analysis demonstrated a significant association between age and total calcium score. The difference in the role of age on coronary calcium between univariate and multivariate analysis may be explained by two reasons. First, calcium was expressed qualitatively in univariate comparison and quantitatively (score) in multiple analysis. Second, the multiple regression model, in contrast with the univariate analysis, considered the role of age independently of the other variables entered in the model. The association between age and coronary calcification has been previously observed in another study concerning a different population. Concerning the relation between elevated triglycerides and coronary calcium, this finding was unexpected. The mean value of triglycerides was higher in subjects with than in those without coronary calcification. Moreover, stepwise regression analysis showed a significant association between elevated triglycerides and the total calcium score. This association was independent of other variables and in particular of high density lipoprotein cholesterol, as defined in the stepwise regression model. These findings emphasize the importance of reevaluating the influence of plasma triglycerides on coronary atherosclerosis. In the literature, such an influence has long been controversial, particularly with respect to multivariate analysis in which the levels of triglyceride are adjusted with other lipids such as high density lipoprotein cholesterol. However, the focus on triglycerides as a risk factor on coronary calcium, whereas cholesterol was not found to be a risk factor as classically shown, may be due in part to our criteria selecting hypercholesterolemic individuals and thus making the group homogeneous on this risk factor. On the other hand, it has been reported recently in a prospective 12-year study on incidence of coronary heart disease that serum triglyceride was the only risk factor to be an independent predictor of early onset of disease. The mechanisms of the association between triglycerides and coronary atherosclerosis remain to be clarified by further investigations, in particular those concerning the genetic susceptibility of dyslipidemic subjects. Several observations suggest a familial component in the excessively high levels of serum triglyceride in individuals who would develop early coronary heart disease.

Conclusions

Our findings point out the substantial prevalence and the generalized nature of atherosclerosis in a symptom-free, high-risk population of hypercholesterolemic men. This noninvasive detection of arterial lesions adds considerable objectivity to the individual assessment of high-risk patients. Because extracoronary atherosclerosis, in particular at the femoral site or at the combination of different sites, demonstrated a strong predictive power for coronary calcification, its routine ultrasonographic detection, easy and inexpensive to perform in clinical practice, could justify, when positive, the indication of more complex investigations of coronary vessels such as ultrafast CT or other classical noninvasive coronary examinations. Overall, our work provides information on the importance of using vascular lesions rather than only risk factors to help in the treatment decision.

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Appendix

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