Relationship of angiographically defined coronary artery disease to serum lipoproteins and apolipoproteins in young survivors of myocardial infarction

A. Hamsten, M.D., G. Walldius, M.D., A. Szamosi, M.D., G. Dahlen, M.D., and U. de Faire, M.D.

ABSTRACT The relationship of serum lipoprotein and apolipoprotein concentrations to angiographically determined coronary artery disease was investigated in 105 consecutive male survivors of myocardial infarction under the age of 45. Concentrations and composition of lipoproteins, lipid indexes, and nonlipid risk factors (tobacco consumption, hypertension, reduced glucose tolerance, and obesity) were related to a recently developed scoring system for semiquantitative estimation of diffuse coronary atheromatosis, as well as to the number and severity of significant coronary artery stenoses. The concentrations of cholesterol in very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), in combination with serum triglyceride or VLDL triglyceride level, comprised the best set of independent discriminatory lipid variables between patients and control subjects. In the patients, LDL cholesterol and apolipoprotein B levels showed strong relationships to the extent and severity of coronary atheromatosis but not to the number and severity of distinct coronary stenoses. HDL cholesterol concentration correlated inversely with the coronary atheromatosis score, whereas other variables reflecting HDL concentration and composition or VLDL lipids were not independently related to any of the coronary scores. The LDL triglyceride level, an index of intermediate-density lipoprotein (IDL) accumulation, was significantly correlated to the coronary atheromatosis score in univariate analysis. Nonlipid risk factors were correlated neither to coronary atheromatosis nor to severity of stenoses. Stepwise multiple regression analyses of data adjusted for age, cumulative tobacco consumption, and weight indicated that 18% of the variation in the coronary atheromatosis score could be accounted for by levels of apolipoprotein B. Addition of other lipoprotein variables or the nonlipid variables hypertension and glucose tolerance did not significantly increase the value of R². When ratios of lipoprotein lipids and apolipoproteins were included in the regression model, the highest multiple correlation coefficient was obtained with the LDL/HDL cholesterol ratio alone (R² = .22). The present data demonstrate the importance of elevated LDL cholesterol and apolipoprotein B concentrations for the development of coronary atheromatosis in young male survivors of myocardial infarction. The lack of correlations between the levels of lipoprotein lipids and serum apolipoproteins and the severity of coronary stenoses suggests that mechanisms other than disturbances of lipoprotein metabolism may be involved in the progression of more advanced coronary lesions.

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PROSPECTIVE epidemiologic studies have demonstrated an independent association between the concentrations of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) and the incidence of coronary heart disease in middle-aged and elderly populations, whereas results regarding very low-density lipoprotein (VLDL) have been conflicting in this respect. In cross-sectional studies the serum concentrations of the protein moieties of serum lipoproteins, the apolipoproteins, have been considered even better discriminators between patients with coronary heart
disease and healthy controls than the levels of whole serum or lipoprotein lipids.7-11

Several recent studies have related the concentrations of whole serum lipids, lipoprotein lipids, and apolipoproteins to the extent and severity of coronary artery disease (CAD) assessed by angiography.12-17 However, variation in diagnoses of coronary heart disease and ages of the patients restricts the validity of the conclusions from these studies. The coronary angiograms have been evaluated with scoring systems primarily based on the presence, number, and severity of hemodynamically significant stenoses. In most instances the presence and extent of diffuse atherosomatous lesions, i.e., sharp-edged, plaquelike or irregular indentations of the vessel wall not producing critical restriction of coronary blood flow and presumably reflecting early atherosclerosis, have not been considered in the classifications.

In middle-aged or elderly populations, myocardial infarction is almost invariably associated with some degree of diffuse coronary atherosclerosis. In contrast, young survivors of myocardial infarction do not always have definite signs of atheromatosis on the coronary angiogram.18-21 Furthermore, the confounding influence of age per se and coexisting age-dependent reactive disorders may be considered less important in young patients. Accordingly young postinfarction patients provide a suitable population for the study of predisposing metabolic disturbances in atherogenesis.

In the present study the relationship of serum lipoprotein and apolipoprotein levels to CAD was investigated in consecutive male patients who had survived a definite myocardial infarction before the age of 45 and who had subsequently been evaluated by coronary angiography. Concentrations and composition of serum lipoproteins, lipid ratios, and nonlipid risk factors were related to a recently elaborated system for semiquantitative estimation of diffuse coronary atheromatosis as well as to the number and severity of coronary artery stenoses.

Methods

Patients. Between May 1980 and September 1982, 127 male patients under the age of 45 survived a definite myocardial infarction22 in one of the 11 hospitals with a coronary care unit within Stockholm County and were subsequently referred to the cardiovascular unit at Danderyd Hospital for further metabolic and cardiologic investigations. A total of 107 patients (84%) were subjected to coronary angiography in connection with lipoprotein and apolipoprotein determinations. Of the remaining 20 patients, three died before angiography and six were excluded because of severe concomitant disease (uremia treated with diet in one and renal transplantation in three patients, severe peripheral atherosclerosis in two). One patient moved out of the study area and 10 patients declined catheterization.

Before the statistical analyses, two patients were excluded from the population, one because of coronary artery bypass surgery performed 6 years before the infarction and one because of angiographic signs indicative of coronary arteritis. Of the 105 patients included in the study, five had a history of recurrent infarctions.

Coronary. After discharge from the referring hospitals, all patients were seen by one cardiologist within 2 weeks and then at regular intervals during follow-up. All patients were invited to participate in a rehabilitation program directed by physiotherapists. Information was given on the association between smoking and coronary heart disease and smokers were advised to stop. Dietary information was not given before the metabolic evaluation. No patient had used lipid-lowering drugs 6 months before the coronary angiography. At the time of the study, 35 patients were entirely without continuous medication and 56 were treated with metoprolol and two with atenolol only. Two and three patients, respectively, were treated with isosorbide dinitrate and nifedipine in addition to metoprolol. Two had been prescribed a combination of drugs from all three groups.

Furosemide together with potassium supplementation was used in 18 patients, five of whom had no other medication. There was no clinical or laboratory evidence of thyroid dysfunction in any of the patients. Renal and liver function tests were normal.

Blood samples for determination of whole serum lipid, lipoprotein lipid, and serum apolipoprotein concentrations were drawn 3 to 6 months after the infarction (mean ± SD 3.5 ± 1.2, range 2.5 to 12 months), at which time the patients were considered to be in a stable clinical and metabolic state. The coronary angiogram was in most cases obtained within 1 month of the metabolic evaluation (0.7 ± 1.2, range 0 to 3 months).

Clinical data were abstracted from the medical records acquired during the admittance to the coronary care units. In addition, a medical history was obtained by a structured interview and questionnaires at the time of the metabolic investigation.

Subjects who smoked at least one cigarette or an equivalent amount of tobacco each day were classified as present smokers. Subjects who had never smoked or had smoked continuously for less than 1 month were defined as nonsmokers. Others were regarded as former smokers. In calculation of the average tobacco consumption, one cigarette was considered equivalent to 1 g, one cigarillo to 2 g, and one cigar to 5 g of tobacco. Tobacco consumption of pipe smokers was calculated by dividing by seven the weekly consumption in grams. As a cumulative estimate of tobacco consumption before myocardial infarction, cigarette-years was used, after transformation of data according to the relationships given above.

Weight was measured with subjects dressed in ordinary indoor clothing with jacket and shoes removed. The weight/height index was calculated (weight/(height − 100)). Blood pressure was measured in the supine position after 5 min rest. Hypertension was defined as present either if antihypertensive treatment had been instituted before infarction or in the immediate postinfarction period or if blood pressure was above 160 mm Hg systolic and/or 95 mm Hg diastolic. Manifest diabetes mellitus was defined as present with fasting hyperglycemia (whole blood) of 7.0 mmol/liter or greater. Oral glucose tolerance was assessed in all patients after ingestion of 1.75 g glucose/kg body weight. The criteria for varying degrees of glucose intolerance suggested by Efendic et al.23 were applied.

Control subjects. For each patient an age-matched randomly selected male control subject completed the metabolic investigation. The control subjects were selected from a general register kept by the Stockholm County Council including all residents within the county. Previous medical history and clinical risk factors were established in the same way among control
subjects as among the patient group. None of the controls had a
history of angina pectoris or electrocardiographic signs indica-
tive of coronary heart disease (Minnesota codes 4.1 and 4.2)
during a maximal exercise stress test. All subjects were included
in the control group, irrespective of the presence of metabolic
disturbances or additional risk indicators. For ethical reasons,
coronary angiography was not performed in the control
subjects.

Lipoprotein and apolipoprotein measurements. All sub-
jects were fasting for 12 hr before blood sampling, during which
time smokers were asked to refrain from smoking. Antecubital
vein puncture was performed between 8 and 9.30 a.m. after 10
min rest in the supine position. Serum lipoproteins were isolated
by ultracentrifugation and precipitation. The method for lip-
protein analysis has been described in detail elsewhere.24 In
principle, VLDL was separated from an aliquot of serum by
centrifugation (density 1.006 kg/liter, Beckman model L ultra-
centrifuge with a 40.3 rotor) at 40,000 rpm for 16 hr. MnCl₂-
heparin solution was then added to the infranatant quantitatively
precipitating LDL and other apolipoprotein B-containing lip-
proteins, leaving HDL in solution. Cholesterol25 and triglyc-
erides26 were determined on an Ultralab (LKB) after chloroform-
methanol extraction of whole serum, the VLDL fraction, the
infranatant after ultracentrifugation (containing LDL and
HDL), and the supernatant (HDL) after precipitation. LDL val-
ues were calculated by taking the difference between the infa-
natant and the supernatant. Only samples with a total recovery
of cholesterol and triglycerides in the three lipoprotein classes of
100 ± 10% have been used.

HDL₃ was obtained as a bottom fraction in which cholesterol
was determined after one preparative ultracentrifugal spin in a
fixed-angle rotor (Beckman model L 5-75) at a density of 1.25
kg/liter. Total HDL was obtained as described above. HDL₃
cholesterol was then calculated as the difference between total
HDL and HDL₃ cholesterol. A detailed description of this pro-
cedure has been published previously.27

Agarose gel lipoprotein electrophoresis according to Noble28
was performed on whole serum and on the top (VLDL) and the
bottom (LDL and HDL) fractions after ultracentrifugation at a
density of 1.006 kg/liter. One percent agarose (Miles-Seravac) was
used and staining was done with Sudan black (1%).

Apolipoproteins A-I and A-II were determined by electroim-
munoassay (rocket immunoelectrophoresis) as described by
Laurell29 with monospecific rabbit antisera, with the exception
that polyethylene glycol 6000 at a final concentration of 40
g/liter was included in the agarose gels used for determination
of apolipoprotein A-II to render the immunoprecipitates more
distinct. The contents of apolipoproteins A-I and A-II in standard
serum obtained from healthy blood donors were assessed by
comparison with a human HDL preparation with known
amounts of apolipoproteins A-I and A-II determined by sodium
dodecyl sulfate–polyacrylamide gel electrophoresis. The con-
centrations of apolipoproteins A-I and A-II in the standard se-
rum were 103 and 30 mg/100 ml.

Apolipoprotein B was determined by electroimmunoassay
with a monospecific rabbit antisera and an apolipoprotein B
standard solution (purified LDL with a mean protein content of
20.7% as determined by the Lowry technique30 with bovine
albumin as standard). This purified LDL was used to standard-
ize a serum sample by electroimmunoassay. The serum standard
used throughout the study was kept frozen at −70 °C in small
aliquots and regularly checked against the purified LDL
standard.

Additional lipid and apolipoprotein indexes were created by
computation of relevant ratios.

Hyperlipoproteinemias were defined according to the WHO
classification.31 The cut-off limits of the different lipoprotein
phenotypes were defined as the 90th percentiles of VLDL tri-
glyceride and LDL cholesterol values in age- and sex-matched
random controls. Type III hyperlipoproteinemia was recognized
when, in addition to an elevated VLDL triglyceride value, the
VLDL cholesterol/triglyceride molar ratio exceeded 0.77 and
an electrophoretic Lp beta band was present. Primary hypoal-
phalipoproteinemia was defined as present in normolipoprotein-
emic subjects with an HDL cholesterol value below the 10th
percentile of that of the control group.

Coronary angiography. Angiography was performed by the
percutaneous transfemoral technique and recorded on 35 mm
cine film with the aid of cesium iodide–activated image intensi-
ers (6.5 inch mode). Both coronary arteries were routinely
examined in the right anterior oblique and left anterior oblique
views. The left coronary artery was always visualized in the
posterior-anterior and lateral projections, as well as in a left
anterior oblique projection with cranio-caudal angulation. Addi-
tional views were taken for both arteries whenever necessary
for better visualization of nontangential or overlapping segments.
Coronary angiograms were routinely obtained both before and
10 min after the sublingual administration of nitroglycerin. The
left ventriculogram was obtained after completion of coronary
angiography.

Classification of the coronary angiogram. Cine films
were processed in the conventional manner and viewed by means of a
Tagarno projector. All cine angiograms were interpreted by one
of us (A. S.) without knowledge of the clinical characteristics or
lipoprotein profiles of the patients.

The presence and severity of both diffuse atheromatosis and
stenoses were determined by means of separate classification
systems in 15 proximal coronary arterial segments. The seg-
ments were defined according to the Ad Hoc Committee on
Grading of Coronary Arterial Disease of the American Heart
Association32; disease in more distal segments was not consid-
ered because of difficulties in quantifying the severity of le-
isons. Segments located distal to a total occlusion or distal to a
significant stenosis, in the absence of sufficient poststenotic
contrast filling, were not evaluated, nor were segments of a
hypoplasic coronary artery.

Grading of diffuse atheromatosis. Atheromatosis was defined
as sharp-edged, plaquelike or irregular indentations, often mul-
tiple, into the vessel lumen without features suggesting fibro-
muscular hyperplasia. A single stenosis with smooth contours,
or a single occlusion, in the absence of additional changes in
the same or any other coronary artery, was not classified as ather-
omatous, whereas multiple lesions always were. A new system
for semiquantitative estimation of diffuse atheromatosis elabo-
rated in our laboratory was used in this study. In this system

| TABLE 1 |
| Segmental grading of diffuse coronary atheromatosis |

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal vessel wall</td>
<td>0</td>
</tr>
<tr>
<td>1-2 plaques</td>
<td>1</td>
</tr>
<tr>
<td>&gt;2 plaques located in one or several groups with intervening normal vessel wall portions</td>
<td>2</td>
</tr>
<tr>
<td>&gt;2 plaques producing continuous vessel wall irregularities</td>
<td>3</td>
</tr>
<tr>
<td>Mean plaque size</td>
<td></td>
</tr>
<tr>
<td>Slight indentation (&lt;10% reduction of the vessel diameter)</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate size indentation (10%-25% reduction of the vessel diameter)</td>
<td>2</td>
</tr>
<tr>
<td>Large plaque (&gt;25% reduction of the vessel diameter)</td>
<td>3</td>
</tr>
</tbody>
</table>

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atheromatous lesions in each segment were given one score for extension and another for mean plaque size. Points were assigned as presented in table 1. The scores for extension and plaque size were then multiplied to produce a segmental atheromatosis severity score (0 to 9) summarizing the mean severity of lesions within that segment.

Grading of stenoses. Visual estimations were made of the proportional reduction in luminal diameter of the three most stenotic portions in each segment, and a score modified after Gensini was assigned to all classified lesions as follows: normal lumen appearing perfectly smooth and even or trivial lesions reducing the lumen diameter less than 25%, 0; lumen diameter reduced 25% to 50%, 1; lumen diameter reduced 50% to 75%, 2; lumen diameter reduced 75% to 90%, 4; lumen almost totally obliterated, 90% to 99% diameter reduction, but antegrade contrast passage still present, 8; total occlusion, 16.

If multiple lesions were present in the same coronary segment, the scores were added to a maximum of 16. The summary score in each segment (0 to 16) was designated the segmental stenosis severity score.

Coronary atheromatosis and stenosis scores. Since the number of segments available for semiquantitative evaluation of diffuse atheromatosis and stenoses varied considerably between individual patients, depending on the number and locations of total occlusions, the sum of all segmental atheromatosis and stenosis scores, respectively, in each patient were divided by the number of evaluated coronary segments. The mean segmental atheromatosis and stenosis severity scores thus obtained were used as summary estimates of severity of atheromatosis and stenoses in the entire coronary circulation and were designated the coronary atheromatosis and stenosis scores.

Validation of the coronary scores. In figure 1 the individual coronary atheromatosis score values are plotted against the values obtained by using the generally accepted Jenkins score. In the Jenkins score, both hemodynamically insignificant and significant lesions are evaluated, although no semiquantitative estimation is performed of diffuse coronary atheromatosis in each coronary segment studied, thus giving more emphasis to the number and severity of significant stenoses. Since our coronary atheromatosis score was developed primarily to evaluate diffuse atheromatous lesions (producing less than 25% reduction of the coronary vessel diameter), the agreement between the two scoring systems consequently was not high when applied to the young male postinfarction patients.

As shown in figure 2, the relationship between the coronary stenosis score and the Jenkins score was not very close in the lower ranges of the scores, reflecting the more precise grading of slight stenoses obtained by the coronary stenosis score.

Figure 3 shows the relationship between the coronary atheromatosis and stenosis scores. The weak correlation between the two scores implies that diffuse coronary atheromatosis as estimated by the atheromatosis score is clearly distinguished from the number and severity of hemodynamically significant stenoses measured by the coronary stenosis score. As illustrated in the figure, one or several stenoses or occlusions may be present in the absence of widespread atheromatosis in a number of

**FIGURE 1.** Relationship between the coronary atheromatosis and the Jenkins scores (logarithmic scales).

**FIGURE 2.** Relationship between the coronary stenosis and the Jenkins scores (logarithmic scales).
patients, whereas in other patients severe diffuse atheromatosis can be found unaccompanied by multiple hemodynamically significant stenoses.

These comparisons illustrate that the two scoring systems used in the present study clearly differentiate diffuse coronary atheromatosis from distinct stenoses, a prerequisite for the analysis of differences in etiologic mechanisms. Furthermore, the coronary atheromatosis and stenosis scores provide more information than that obtained by the generally accepted Jenkins score.

The intraobserver variability for the coronary atheromatosis score has been evaluated in 20 patients from the present population (227 segments). The angiograms were reviewed on two occasions with an intervening interval of at least 14 days. A total of 212 (93%) of all 227 segments were accorded identical scores in both estimations. There were 93 segments registered as atheromatous in the first assessment, of which 78 (84%) were given the same points for both lesion extension and plaque size in the second determination. In the remaining 15 segments different points were given for extension in six and plaque size in 11 patients.

Data analysis. Statistical methods were applied as recommended by Snedecor and Cochran.34 Distributions of categorical data were compared with the chi-square test with Yates’ correction. Group differences for continuous variables were evaluated by two-tailed t tests. Stepwise multiple discriminant analyses were performed to determine the sets of independent variables to the two groups of subjects was performed by Fisher’s test.

All statistical analyses were performed at the Stockholm Computer Centre for University Education and Research (QZ) with standard BMDP programs.35

Ethical considerations. Before the study, informed consent was obtained from all subjects. The study protocol was approved by the regional ethical committee.

Results

Basic characteristics of the study group. Clinical characteristics and conventional risk indicators in patients compared with control subjects are given in table 2. Smoking habits among patients and controls were identical at the time of the metabolic evaluation. There was a marked overrepresentation of former smokers in the patient group, the majority of whom had stopped smoking at the time of myocardial infarction. Cumulative lifetime tobacco consumption of present and former smokers was much higher in the patient group. Hyperlipoproteinemias were much more frequent among the patients, with increased prevalences of both type II and IV hyperlipoproteinemias. More patients had manifest diabetes or reduced oral glucose tolerance. In addition, young postinfarction patients had a higher weight/height index than control subjects.

Lipid, lipoprotein, and apolipoprotein discriminators between patients and control subjects. In univariate analysis (table 3), the VLDL and LDL lipid concentrations were higher in patients than in control subjects, whereas total HDL, HDL2, and HDL3 cholesterol concentrations were reduced. Whole serum levels of apolipoproteins A-I and A-II were decreased in the patient group, whereas the whole serum apolipoprotein B level was increased. The electrophoretic late pre-beta (Lpbeta)

FIGURE 3. Relationship between the coronary atheromatosis and stenosis scores (logarithmic scales).
trait was more common in the patient group (25% vs 11%; $\chi^2 = 5.43$, $p < .05$).

By stepwise multiple discriminant analysis (table 4), the concentrations of LDL cholesterol, whole serum triglycerides, and total HDL and VLDL cholesterol were selected as the best set of independent lipoprotein and apolipoprotein discriminators between patients and control subjects. When ratios of lipoproteins and apolipoproteins were included in the initial model, the best discrimination was obtained by the LDL/HDL cholesterol ratio, the serum triglyceride concentration, the apolipoprotein A-I/apolipoprotein A-II ratio, and the VLDL cholesterol concentration.

**Distribution of the angiographic scores.** The distributions of the angiographic scores are given in figures 4 and 5. Both scores had a skewed log normal distribution. On the basis of the respective quartiles of the distribution of the coronary scores, patients were divided into four groups (Q1 to Q4) with regard to severity of atheromatosis and stenoses: group Q1 included those in the bottom fourth of scores, groups Q2 and Q3 those in the two middle fourths of scores, and group Q4 those in the top fourth.

The use of $\beta$-adrenergic blocking agents, which have been shown to affect serum lipoprotein levels, was similar in all angiographic quartiles. Furthermore, the means and standard deviations for lipoprotein lipid and apolipoprotein concentrations were practically identical in patients with and without $\beta$-blocker medication.

**Nonlipid risk factors in patients subdivided by degree of CAD.** Since some of the nonlipid risk factors were categorical variables, the relationships to coronary scores were first studied both in patients subdivided by quartiles of these scores and by simple regression analysis. Systolic and diastolic blood pressures were not analyzed except in the diagnosis of hypertension, since the preinfarction blood pressure levels were not known. Table 5 summarizes the nonlipid risk factors in each angiographic quartile. Analyses of variance indi-
TABLE 3
Concentrations of serum lipids, lipoprotein lipids, and serum apolipoproteins in patients compared with control subjects

<table>
<thead>
<tr>
<th></th>
<th>Univariate comparison of serum concentrations</th>
<th></th>
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<th></th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Patients (n = 105)</td>
<td>Controls (n = 105)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.35 ± 1.43</td>
<td>6.08 ± 1.17</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>1.18 ± 0.99</td>
<td>0.55 ± 0.54</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>4.86 ± 1.24</td>
<td>4.01 ± 0.93</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>1.12 ± 0.25</td>
<td>1.42 ± 0.39</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>HDL₂</td>
<td>0.37 ± 0.19</td>
<td>0.57 ± 0.35</td>
<td></td>
<td>&lt; .001</td>
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<tr>
<td>Triglycerides (mmol/l)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.92 ± 2.36</td>
<td>1.49 ± 1.27</td>
<td></td>
<td>&lt; .001</td>
<td></td>
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<tr>
<td>VLDL</td>
<td>2.10 ± 1.90</td>
<td>0.93 ± 1.03</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>0.49 ± 0.17</td>
<td>0.35 ± 0.12</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>0.16 ± 0.06</td>
<td>0.15 ± 0.04</td>
<td></td>
<td>NS</td>
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</tr>
<tr>
<td>Apolipoproteins (mg/100 ml)</td>
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<td></td>
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</tr>
<tr>
<td>A-I</td>
<td>111.5 ± 19.6</td>
<td>124.4 ± 19.4</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>A-II</td>
<td>37.0 ± 7.4</td>
<td>40.0 ± 7.3</td>
<td></td>
<td>&lt; .01</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>128.5 ± 21.3</td>
<td>106.2 ± 19.9</td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD.

cated differences in age (F = 3.63, p < .05) among patients grouped according to the coronary atheromasis score. Age tended to be lower among patients in the lowest quartile. In univariate regression analysis, age correlated significantly with the coronary atheromatosis score (r = .272, p < .01). For all other studied nonlipid risk indicators, no relationships to severity of coronary atheromatosis were indicated by either statistical method. In patients grouped according to coronary stenosis score, similar means and distributions of continuous and categorical data were obtained for all variables, including age. No significant correlations were found between nonlipid risk factors and the coronary stenosis score in regression analysis. Thus generally recognized nonlipid risk factors for CAD such as tobacco consumption, hypertension, manifest diabetes mellitus, and reduced glucose tolerance did not relate to any of the estimates of severity of CAD.

Correlations between lipoprotein variables and coronary scores. The relationships between coronary scores and lipid variables were studied by multiple stepwise linear regression analysis (tables 6 to 8). Age, cumulative tobacco consumption, and the weight/height index were first entered in the regression model as forced variables. Highly significant partial correlation coefficients were noted between the concentrations of serum cholesterol (r = .372, p < .001), LDL cholesterol (r = .408, p < .001), and serum apolipoprotein B (r = .430, p < .001) and the coronary atheromatosis score. Weaker significant negative and positive correlation coefficients, respectively, were found between the HDL₂ cholesterol (r = -.232, p < .05) and LDL triglyceride (r = .225, p < .05) concentrations, and the coronary atheromatosis score. Among lipid and apolipoprotein ratios, several significant correlations with the atheromatosis score were found. The highest r value was obtained for the LDL/HDL cholesterol ratio (r = .472, p < .001). In comparison with the LDL/HDL cholesterol ratio, weaker correlations were shown for the apolipoprotein B/apolipoprotein A-I ratio (r = .367, p < .01) and the ratio of the sum of

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TABLE 4
Best sets of lipoprotein variables predicting myocardial infarction selected by stepwise multiple discriminant analysis

<table>
<thead>
<tr>
<th>Selected variables</th>
<th>No ratios included*</th>
<th>R ratios includedb</th>
<th>F to remove</th>
<th>F to remove</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Chol</td>
<td>39.68</td>
<td>LDL Chol</td>
<td>61.30</td>
<td></td>
</tr>
<tr>
<td>HDL Chol</td>
<td>21.12</td>
<td>HDL Chol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Tg</td>
<td>16.46</td>
<td>Serum Tg</td>
<td>13.20</td>
<td></td>
</tr>
<tr>
<td>VLDL Chol</td>
<td>7.43</td>
<td>Apo A-I</td>
<td>6.82</td>
<td></td>
</tr>
<tr>
<td>Correct classification (%)</td>
<td>84.4</td>
<td>Apo A-II</td>
<td>4.94</td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td></td>
<td>VLDL Chol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>77.2</td>
<td>Correct classification (%)</td>
<td>81.9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>80.8</td>
<td>Infarct</td>
<td>84.6</td>
<td></td>
</tr>
</tbody>
</table>

Chol = cholesterol; Tg = triglycerides; Apo = apolipoprotein.

*Serum lipids, all lipoprotein lipids except VLDL Tg, and serum apolipoproteins A-I, A-II, and B included in the initial model.

bSerum lipids, serum apolipoproteins A-I, A-II, and B, VLDL Chol, LDL Tg, LDL/HDL Chol, (VLDL + LDL)/HDL Chol, HDL₂/HDL Chol, HDL Chol/apolipoprotein A-I, apolipoprotein A-I/apolipoprotein A-II, and the ratios of Chol to Tg in VLDL, LDL, and HDL included in the initial model.
cholesterol in VLDL and LDL divided by the HDL cholesterol level ($r = .339$, $p < .001$). Significant negative correlations were also demonstrated for the HDL$_2$/HDL$_3$ cholesterol ratio ($r = -.272$, $p < .01$). With the exception of the HDL$_2$ cholesterol concentration and the HDL$_2$/HDL$_3$ cholesterol ratio, no other variable reflecting HDL concentration and composition, such as total HDL cholesterol, apolipoprotein A-I, and the apolipoprotein A-I/A-II and HDL cholesterol/apolipoprotein A-I ratios, showed any correlation with the coronary atheromatosis score.

The highest multiple correlation coefficient with coronary atheromatosis score as dependent variable and age, cumulative tobacco consumption, and weight/height index entered as forced variables was obtained with the LDL/HDL cholesterol level alone (multiple $R^2 = .28$). The increase in multiple $R^2$ obtained by addition of the LDL/HDL cholesterol ratio was .22. Addition of other lipoprotein variables did not significantly increase the value of $R^2$. The $F$ values to enter into the equation were similar for LDL cholesterol ($F = 17.54$), apolipoprotein B ($F = 19.93$), and the LDL/HDL cholesterol ratio ($F = 25.16$), as can be inferred from the partial correlation coefficients given in tables 6 to 8. When only lipoprotein lipids and serum apolipoproteins were entered in the initial model, 18% of the variability in coronary atheromatosis score could be accounted for by changes in apolipoprotein B level. No other lipoprotein variable was found to account independently for any variation in the coronary atheromatosis score. Addition of the categorical nonlipid variables hypertension and glucose tolerance as independent variables did not result in a significant increase in the multiple $R^2$.

None of the serum lipid, lipoprotein lipid, or apolipoprotein variables correlated significantly with the coronary stenosis score.

The possible role of treatment with $\beta$-adrenergic blocking drugs and/or furosemide in over half of the patients in the correlations between lipoproteins and...
TABLE 5
Nonlipid risk factors in patients grouped according to quartiles of the coronary angiographic scores

<table>
<thead>
<tr>
<th></th>
<th>Atheromatosis score</th>
<th>Stenosis score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>37.5</td>
<td>39.9</td>
</tr>
<tr>
<td>SD</td>
<td>5.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present smoker</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Former smoker</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cumulative tobacco consumption (cigarette-years)</td>
<td>397</td>
<td>455</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Oral glucose tolerance (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Borderline I</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Borderline II</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Decreased</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Type II</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Weight/height index (kg/cm)</td>
<td>1.04</td>
<td>1.06</td>
</tr>
</tbody>
</table>
| Q1-Q4 = lower to upper quartiles.

coronary scores in the entire study group was analyzed by separate multiple stepwise regression analyses in patients with and without medication. As can be seen in table 9, closely similar partial correlation coefficients were obtained in the two groups for all pertinent lipoprotein variables. Exclusion of patients with ongoing medication with β-blockers and/or furosemide neither altered or negated any of the significant correlations demonstrated in the entire group, nor did it produce new significant correlations among the remaining untreated patients.

**Discussion**

Coronary angiograms showing evidence of CAD are usually classified according to the number of major vessels with significant disease and the degree and location of stenoses. These factors are obviously of great clinical and prognostic importance. However, in the search for etiologic and pathogenetic mechanisms, we considered it more useful to make a distinction between coronary artery stenosis or occlusion on the one hand, and coronary artery atheromatosis on the other. Two reasons justify this distinction. In the first place, coronary angiography occasionally demonstrates complete occlusion of a major coronary artery without any further sign of atheromatosis. In contrast, widespread coronary artery vessel wall irregularities, presumably reflecting diffuse atheromatosis, are sometimes present but unaccompanied by hemodynamically significant stenoses or occlusions.

Second, serum lipoproteins are primarily involved in the formation of the early atheromatous plaque.

**TABLE 6**
Partial correlation coefficients between coronary scores and concentrations of serum lipids and apolipoproteins

<table>
<thead>
<tr>
<th></th>
<th>Total Chol</th>
<th>Total Tg</th>
<th>Apo A-I</th>
<th>Apo A-II</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary atheromatosis score</td>
<td>0.372b</td>
<td>0.075</td>
<td>-0.078</td>
<td>-0.091</td>
<td>0.430b</td>
</tr>
<tr>
<td>Coronary stenosis score</td>
<td>0.081</td>
<td>-0.024</td>
<td>-0.154</td>
<td>-0.077</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Abbreviations as in table 4.

bAge, weight/height index, and cumulative tobacco consumption had first been entered in the regression model.

b p < .001.
whereas occlusion or severe stenosis of a coronary artery might often be the result of a rapidly developing protrusion caused by rupture or fissuring of atheromatous plaques with subsequent intraintimal thrombosis progressing to the formation of intraluminal thrombus.41-43

Separate scoring systems were accordingly applied in the present study for the semiquantitative assessment of diffuse atheromatosis and distinct stenoses or occlusions. Representative young postinfarction patients, in whom predisposing metabolic risk factors for coronary atherosclerosis should be more apparent than in older patient groups because of fewer confounding factors, were selected as the study group. The two separate angiographic scoring systems and the choice of young patients were intended to allow a differentiation between lipoprotein fractions associated with coronary atheromatosis and stenosis, respectively. Furthermore, lipoprotein fractions showing no correlations with the coronary scores but discriminating between patients and controls and thus probably associated with myocardial infarction by other mechanisms than angiographically demonstrable coronary artery disease could be ascertained.

Elevated VLDL cholesterol, LDL cholesterol, and serum triglyceride concentrations and a low HDL cholesterol level discriminated the young patients from the healthy control subjects in univariate and multivariate analyses. These results extend the findings of a recent study of young postinfarction patients by Fager et al.,44 in which the lipoprotein evaluation was restricted to measurement of serum lipid levels and concentrations of apolipoproteins A-I, A-II, B, and D. The present study, however, clearly indicates that only some of the lipoprotein fractions, which have previously been accorded roles as risk factors for coronary heart disease in epidemiologic surveys, are important with respect to atherogenic action. Levels of total HDL cholesterol, HDL apolipoproteins A-I and A-II, and VLDL cholesterol thus contributed strongly to the discrimination between young subjects with myocardial infarction and those without this disease, whereas only LDL cholesterol, serum apolipoprotein B, and serum cholesterol concentrations, besides being powerful discriminators, were also strongly related to the severity of coronary atheromatosis.

The use of β-adrenergic blockers and/or furosemide did not seem to influence the relationships between lipoproteins and angiographic estimates of coronary atherosclerosis. In this respect, our results in part diverge from the findings of Reardon et al.17 However, several differences exist between the two patient groups studied. Notably, we examined young postinfarction patients, of whom only a minority had had any medication before the infarction. Among drugs with a possible influence on lipoprotein levels, only selective

| TABLE 7 | Partial correlation coefficients* between coronary scores and concentrations of serum lipoprotein lipids |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
|                  | VLDL Chol   | LDL Chol    | HDL Chol    | HDL2 Chol   | VLDL Tg     | LDL Tg      |
| Coronary atheromatosis score | 0.134       | 0.408c      | -0.140      | -0.232b     | 0.079       | 0.225b      |
| Coronary stenosis score     | 0.003       | 0.160       | -0.122      | -0.156      | -0.032      | 0.108       |

Abbreviations as in table 4 and text.

*Age, weight/height index, and cumulative tobacco consumption had first been entered in the regression model.

TABLE 8 | Partial correlation coefficients* between coronary scores and various lipid and apolipoprotein ratios |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLDL Chol</td>
<td>HDL2 Chol</td>
<td>LDL Chol</td>
<td>HDL Chol</td>
<td>VLDL Chol + LDL Chol</td>
<td>HDL Chol Apo A-I</td>
</tr>
<tr>
<td>Coronary atheromatosis score</td>
<td>0.176</td>
<td>-0.272c</td>
<td>0.472d</td>
<td>0.228b</td>
<td>0.339d</td>
<td>-0.105</td>
</tr>
<tr>
<td>Coronary stenosis score</td>
<td>0.106</td>
<td>-0.151</td>
<td>0.193</td>
<td>0.077</td>
<td>0.153</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Abbreviations as in table 4 and text.

*Age, weight/height index, and cumulative tobacco consumption had first been entered in the model.

*p < .05.

*p < .01.

*p < .001.
TABLE 9
Effects of medication on the relationships between various lipoproteins and the coronary atheromatosis and stenosis scores

<table>
<thead>
<tr>
<th></th>
<th>VLDL Chol</th>
<th>LDL Chol</th>
<th>LDL Tg</th>
<th>HDL Chol</th>
<th>HDL2 Chol</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary atheromatosis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On β-blocker and/or furosemide</td>
<td>0.176</td>
<td>0.383</td>
<td>0.194</td>
<td>-0.178</td>
<td>-0.265</td>
<td>0.466</td>
</tr>
<tr>
<td>No medication</td>
<td>0.114</td>
<td>0.421</td>
<td>0.231</td>
<td>-0.130</td>
<td>-0.194</td>
<td>0.370</td>
</tr>
<tr>
<td>Coronary stenosis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On β-blocker and/or furosemide</td>
<td>0.064</td>
<td>0.134</td>
<td>0.076</td>
<td>-0.171</td>
<td>-0.196</td>
<td>0.096</td>
</tr>
<tr>
<td>No medication</td>
<td>-0.062</td>
<td>0.208</td>
<td>0.111</td>
<td>-0.076</td>
<td>-0.118</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Abbreviations as in table 4 and text.
Results are partial correlation coefficients with age, cumulative tobacco consumption, and the weight/height index first entered in the regression model.

β-blockers and/or furosemide were prescribed at the time of the event. Thiazides were not taken by any of our patients. It is thus conceivable that differences in age, duration of medication, and drug prescription explain the apparent discrepancy between the results on drug influence from the two studies.

In most previous studies, independent correlations between LDL cholesterol level and coronary angiographic findings have been demonstrated. However, the present data indicate that LDL cholesterol is primarily implicated in the evolution of diffuse atherosclerotic lesions. The present study gives further emphasis to the observation that a high apolipoprotein B concentration is a marker of the presence of more extensive CAD. Furthermore, apolipoprotein B was slightly superior to LDL cholesterol level with respect to the correlation with the coronary atheromatosis score. Interestingly, however, the discriminatory power of serum cholesterol concentration was only modestly surpassed by LDL cholesterol and serum apolipoprotein B levels.

The results of the relatively few angiographic studies attempting to grade CAD have been inconclusive with respect to the demonstration of correlations between severity of CAD and HDL measurements. In some studies, the HDL cholesterol concentration has correlated with the presence but not the severity of CAD, whereas in others HDL cholesterol and HDL2 cholesterol levels have shown strong inverse associations with coronary scores. Despite the strong consistent epidemiologic evidence that implicates HDL as a risk factor for coronary heart disease the exact role of HDL in the pathogenesis of CAD is not clear. The question persists whether HDL has a genuine protective function with regard to the development of CAD by a reverse transport of cholesterol from peripheral tissues to the liver or merely reflects the efficiency of catabolic processes of triglyceride-rich lipoproteins as suggested by Nikkilä and colleagues.

In our study, neither concentrations of total HDL cholesterol nor HDL apolipoprotein levels correlated with the coronary atheromatosis score. Decreased HDL cholesterol levels were found irrespective of severity of angiographically assessed CAD. HDL2 cholesterol concentration and the HDL2/HDL4 cholesterol ratio indicating HDL composition showed an inverse association with coronary atheromatosis, as indicated by the partial correlation coefficients when no lipoprotein variables had been entered in the stepwise multiple regression analysis. The present data thus suggest that ineffective cholesterol mobilization contributes directly to atherogenesis. This interpretation is also supported by the stronger correlation between the LDL/HDL cholesterol ratio, compared with that of LDL cholesterol alone, and the coronary atheromatosis score. However, as indicated by the multivariate analysis, increased cholesterol influx to the coronary artery wall from LDL seemed more important in these young patients than inefficient cholesterol uptake by HDL.

The relationship between VLDL and CAD has been less well defined. Among the young postinfarction patients, neither the VLDL lipids nor the ratio of cholesterol to triglycerides in VLDL correlated positively with the coronary atheromatosis score in univariate or multivariate analysis. However, the LDL triglyceride concentration, an index of intermediate-density lipoprotein (IDL) accumulation, correlated significantly to the coronary atheromatosis score in univariate analysis. Accordingly, the present data did not give clear confirmation of the findings of Tatami et al., who demonstrated that IDLs and cholesterol-rich VLDL combine to contribute to the development of CAD. They corroborate the results of Jenkins et al.
ing an independent relationship between LDL triglyceride levels, an index of IDL accumulation, and severity of CAD.

With the exception of age, limited information has been available concerning the relationships of nonlipid risk factors such as tobacco consumption, hypertension, and reduced glucose tolerance, to angiographically defined CAD. In this study, age correlated significantly with the coronary atheromatosis score in simple regression analysis, whereas the other nonlipid risk factors were not indicated to be in any way related to severity of CAD.

Previous research on young postinfarction patients has established an unequivocal relationship between smoking history and incidence of myocardial infarction. Smoking has consistently been considered a principal risk factor at a young age. It was therefore interesting to find identical measurements of cumulative tobacco consumption in patients with different severity of CAD. These data disagree with the results from autopsy studies showing an increase in atheromatous lesions with the number of cigarettes smoked per day. In microscopic studies, it has also been demonstrated that the presence and extent of fibrous intimal thickening, atheroma, and calcification are all related to smoking history. In the one major study correlating cumulative cigarette consumption with severity of CAD as assessed by angiography, Ramsdale et al. found highly significant correlations with overall severity of CAD, as well as with the number of coronary arteries with stenoses of 50% or more.

The reason for the discrepant findings with respect to smoking history in the present study is not clear. However, patient populations differ markedly between the studies. Our patients were younger and the indication for coronary angiography was recent myocardial infarction in all cases. It might be that gross atheromatous lesions, predominantly caused by effects of cigarette smoking and visible in coronary angiograms, have not developed before the age of 45. Instead smoking could possibly act as a precipitating factor in the evolution of myocardial infarction at a young age. The mechanisms could then influence hemostatic functions or coronary vascular tone. The fact that hypertension does not seem to correlate with severity of angiographically estimated CAD in this and other studies might be due to the simple recording of presence/absence of a history of hypertension or the influence of myocardial infarction and medication on blood pressure levels. Furthermore, the total number of hypertensive patients was limited in this study, restricting the evaluation of hypertension as a risk factor. It should also be emphasized that the present finding regarding presence/absence of hypertension does not pertain to blood pressure level.

It is generally accepted that manifest diabetes mellitus is associated with an enhanced risk of coronary heart disease, whereas conflicting views persist with respect to milder glucose intolerance as an independent risk factor for coronary disease. No support was obtained for a relationship between varying degrees of reduced oral glucose tolerance and severity of coronary atherosclerosis in this study, despite the fact that decreased oral glucose tolerance was significantly more common in patients compared with control subjects without heart disease. However, it has to be emphasized that insulin response was not studied in relation to the angiographic scores.

The absence in this study of associations between the coronary stenosis score and lipoprotein variables might indicate that lipoprotein levels are not closely associated with the progression of more advanced coronary lesions. Instead, our results indicate that LDL cholesterol and serum apolipoprotein B concentrations, as well as whole serum cholesterol level, might have a considerable significance for the occurrence of diffuse coronary atheromatosis at a young age. Furthermore, HDL seems to exert a weak protective influence with respect to the development of atheromatous coronary lesions. The further progression of distinct coronary artery stenoses, however, appears to be largely determined by other mechanisms. The knowledge of the apparently different relationships between lipoprotein levels and early as compared with advanced coronary lesions could have a bearing on the strategies for future secondary-preventive trials in CAD.

We are grateful to Associate Professor Bengt Johansson for providing facilities for the apolipoprotein A-I and A-II analyses.

References

Erratum

An editorial change in the title of the above article resulted in a change in meaning. The correct title should be “The relationships of alcoholic beverage use and other traits to blood pressure: a new Kaiser Permanente study.”
Relationship of angiographically defined coronary artery disease to serum lipoproteins and apolipoproteins in young survivors of myocardial infarction.
A Hamsten, G Walldius, A Szamosi, G Dahlen and U de Faire

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