Prevalence of Carotid Atherosclerosis and Serum Cholesterol Levels in Eastern Finland

Riitta Salonen, Katariina Seppänen, Rainer Rauramaa, and Jukka T. Salonen

We investigated the prevalence of carotid atherosclerosis and its association with serum lipoprotein cholesterol fractions in 412 Eastern Finnish men ages 42, 48, 54, or 60 years who were examined between February and December 1987 in the Kuopio Ischaemic Heart Disease Risk Factor Study. Carotid atherosclerosis was assessed with high-resolution B-mode ultrasonography. Of the participants, 37% had thickening of the intimal or medial layer of the arterial wall, 10% had plaques, 2% had stenosis in the right or left common carotid artery or in the carotid bifurcation, and only 51% were free of any detectable carotid atherosclerosis. The prevalence of atherosclerosis was 14.1%, 32.0%, 67.7%, and 81.9% in the four age groups, respectively. The mean age-adjusted serum low density lipoprotein (LDL) cholesterol concentration was 3.67 mmol/l (142 mg/dl) in men free of carotid atherosclerosis and 4.02 mmol/l (155 mg/dl) in those with at least intimal thickening ($p=0.003$ for difference). The mean age-adjusted serum cholesterol concentration in the high density lipoprotein (HDL) fraction was 1.34 mmol/l (52 mg/dl) in the atherosclerosis-free and 1.27 mmol/l (49 mg/dl) in the atherosclerotic men ($p=0.029$ for difference). There was a similar difference in both the serum HDL$_2$ and the HDL$_3$ cholesterol levels. Serum LDL and HDL (inverse) cholesterol were significant determinants of severity of carotid atherosclerosis in a multivariate regression model adjusting for age, obesity, plasma fibrinogen, cigarette-years, and duration of hypertension. Our data reveal the high prevalence of atherosclerosis in middle-aged Eastern Finnish men and provide further evidence of the roles of LDL and HDL cholesterol in atherosclerosis. (Arteriosclerosis 8:788-792, November/December 1988)

The prevalence of nonstenotic atherosclerosis has not been studied in representative population samples. Earlier studies assessing atherosclerosis with high-resolution ultrasonography were carried out in patient populations or small groups of selected subjects, or have concerned only obstructive lesions. Autopsy studies in cases of accidental or violent death indicated that the majority of middle-aged Caucasian men have macroscopically observable atherosclerosis in the arteries. The populations of these studies, however, were not geographically defined. No such data are available for Eastern Finnish men, the population with the highest recorded incidence and mortality of ischemic heart disease. The purpose of this study was to estimate the prevalence of carotid atherosclerosis in a geographically defined population of middle-aged men in Eastern Finland and to investigate the relationship of carotid atherosclerosis to serum low density lipoprotein (LDL), high density lipoprotein (HDL), HDL$_2$, and HDL$_3$ cholesterol concentrations.

Methods

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is a population study to investigate previously unestablished risk factors for ischemic heart disease and carotid atherosclerosis. Since February 1987, an ultrasonographic assessment of carotid arteries has been carried out by a physician (RS) as a part of the KIH. Fifty participants were examined each study week on Tuesdays, Wednesdays, and Thursdays. The present study is based on data collected between February and December 1987. During this period, 490 men ages 42, 48, 54, or 60 years (a 33% sample of the population of the city of Kuopio and six neighboring rural communities) were invited to join the study. Of these, 78 men refused or could not be contacted. The participation rate was 94.1%. The number of participants in the four age strata were 92, 122, 93, and 105 men, respectively. All these participants underwent the ultrasonographic assessment of carotid arteries. Data on serum lipoproteins were missing for 22 men.

The ultrasonographic assessment of carotid arteries was performed while the subject was supine with his head turned away from the sonographer at an angle of 45°. The scan head was in a perpendicular position in relation to the arterial walls. A duplex ultrasound system with 10 MHz scanning frequency in B-mode and 5 MHz frequency in pulsed Doppler-mode was used. The Doppler was used to identify the vessels and to evaluate flow disturbances. The Doppler spectral analysis did not prove useful in the evaluation of less severe atherosclerotic lesions.

The B-mode scanning protocol involved the scanning of the right and left common carotid artery and the carotid bifurcation, the site in the carotid vessels which is most often first affected by atherosclerosis. The sites of most
advanced atherosclerotic lesions were located. A high-resolution thermal printer recorded three kinds of images of the most severely affected site in the right and the left common carotid arteries: 1) longitudinal B-mode image, 2) cross-sectional B-mode image, and 3) M-mode image covering several cardiac cycles. The scanning lasted an average of 30 minutes. The whole scanning procedure was recorded on a video cassette recorder. During the scanning, the sonographing physician classified her findings into four categories: 1) no atherosclerotic lesions, 2) intimal-medial thickening, 3) nonstenotic plaque, and 4) any degree of stenosis at the most severely affected site. The same physician checked the original classifications in one session from the hard copies of images of the most affected sites.

"Intimal-medial thickening" of the arterial wall was defined as a distance of more than 1.2 mm between the lumen-intima interface and the media-adventitia interface. The measurement of this distance was carried out by using two cursors during the scanning from a frozen frame of longitudinal B-scan during the diastole of the cardiac cycle. The atherosclerotic lesion was defined as a "plaque" when a distinct area with more than 50% greater intimal plus medial thickness (usually more than 2.0 mm) as compared with neighboring sites could be identified. If the plaque obstructed more than 20% of the lumen diameter, the finding was called a "stenosis."

Fifty randomly selected participants were invited to a repeated carotid ultrasonographic assessment 7 days after the original assessment. One subject refused. The distribution of the severity of carotid atherosclerosis in the reassessment compared to that in the original one is presented in Table 1. There was an agreement of 89.8% between assessments. The Kappa-coefficient for agreement\(^\text{11}\) was 0.82 (91.9% of maximum) with a 95% confidence interval of 0.62 to 1.02.

Blood was drawn on the same day as the ultrasonographic assessment after a fast and abstinence from smoking of 12 hours and an abstinence from alcohol of 3 days. No tourniquet was used. The main serum lipoprotein fractions—very low density lipoprotein (VLDL), LDL, and HDL were separated according to the method of Carlson.\(^\text{12}\) HDL\(_2\) and HDL\(_3\) were determined using the method of Kirstein and Carlson.\(^\text{13}\) The cholesterol content of all lipoprotein fractions was measured enzymatically (CHOD-PAP method, Boehringer-Mannheim, Mannheim, FRG). Plasma fibrinogen concentrations were determined based on clotting of diluted plasma with excess thrombin\(^\text{14}\) with the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, FRG).

The number of cigarettes, cigars, and pipefuls of tobacco currently smoked daily and the duration of regular smoking in years, as well as the presence of hypertension and its duration in years, were recorded using a self-administered questionnaire, which was checked by an interviewer.

The crude and age-adjusted means of serum cholesterol fractions and the statistical significance of their variation over atherosclerosis categories were computed with the SPSS-X software.\(^\text{15}\) The age-adjusted and Quetelet Index (weight in kg/height squared in cm) -adjusted relative probabilities (estimated as antilogarithms of logistic regression coefficients) and prevalence rates of atherosclerosis in the quartiles of the serum cholesterol fractions were estimated and tested for statistical significance with the multivariate logistic analysis of the SAS statistical package.\(^\text{16}\) The joint contribution of serum cholesterol fractions, age, body mass index, plasma fibrinogen, cigarette-years, and duration of hypertension to the variation of carotid atherosclerosis was estimated and tested with the SPSS-X, least-squares, multivariate regression technique.

**Results**

In the whole study population, 48.8% of the men had detectable atherosclerotic lesions. The age-specific prevalence rates for intimal thickening, plaque, and stenosis in the carotid arteries are presented in Table 2.

The crude mean and 95% confidence intervals of serum LDL cholesterol concentration in the four categories of severity of carotid atherosclerosis (normal, intimal-medial thickening, plaque, and stenosis) was 3.68 (±0.12), 3.98 (±0.17), 4.06 (±0.35), and 4.56 (±1.06) mmol/l

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>No atherosclerosis (n)</th>
<th>Intimal-medial thickening (n)</th>
<th>Nonstenotic plaque (n)</th>
<th>Stenosis (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>79 (85.9)</td>
<td>12 (13.0)</td>
<td>1 (1.1)</td>
<td>—</td>
</tr>
<tr>
<td>48</td>
<td>83 (68.0)</td>
<td>34 (27.9)</td>
<td>5 (4.1)</td>
<td>—</td>
</tr>
<tr>
<td>54</td>
<td>30 (32.3)</td>
<td>50 (53.8)</td>
<td>11 (11.8)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>60</td>
<td>19 (18.1)</td>
<td>57 (54.3)</td>
<td>24 (22.9)</td>
<td>5 (4.8)</td>
</tr>
</tbody>
</table>
(142, 154, 157, and 176 mg/dl), respectively ($p=0.0007$ for linear trend in one-way analysis of variance, ANOVA). The respective means and 95% confidence intervals of serum HDL cholesterol were 1.35 ($\pm$0.04), 1.28 ($\pm$0.04), 1.24 ($\pm$0.08), and 1.21 ($\pm$0.15) mmol/l ($p=0.004$ for linear trend).

The mean age-adjusted serum LDL cholesterol concentration was 3.67 mmol/l in men with no atherosclerotic lesions, 3.99 mmol/l in those with intimal-medial thickening, 4.08 mmol/l in the ones with nonstenotic plaque, and 4.58 mmol/l in men with stenosis ($p=0.014$ in two-way analysis of covariance, ANCOVA, Figure 1). The respective age-adjusted means of serum HDL cholesterol were 1.35 mmol/l, 1.28 mmol/l, 1.24 mmol/l, and 1.21 mmol/l (NS in two-way ANCOVA).

In men with atherosclerotic lesions, the age-adjusted mean for serum LDL cholesterol was 4.02 mmol/l ($p=0.003$ for difference with controls); for serum HDL cholesterol, the mean was 1.27 mmol/l ($p=0.029$). In men with and without carotid atherosclerosis, the age-adjusted means of serum HDL$_2$ cholesterol were 0.83 mmol/l and 0.88 mmol/l ($p=0.093$), respectively, and the means for serum HDL$_3$ cholesterol were 0.44 mmol/l and 0.46 mmol/l ($p=0.016$), respectively.

A five-variable logistic model, which included terms for the three highest quartiles of serum LDL cholesterol levels, age, and body-mass index, was computed. The quartiles of serum LDL cholesterol were: less than 2.50, 2.50 to 4.49, 4.50 to 5.99, and 6.00 mmol/l or more. The relative probabilities of carotid atherosclerosis in the three highest quartiles were 2.4 (95% confidence interval (CI)=0.85 to 6.69), 4.0 (95% CI=1.28 to 12.23), and 30.2 (95% CI=2.50 to 364.62) as compared to serum LDL cholesterol, which was less than 2.50 mmol/l (Figure 2). In another five-variable logistic model, the age- and body mass index-adjusted relative probabilities of atherosclerosis in the three lowest serum HDL cholesterol quartiles (1.25 to 1.49, 1.00 to 1.24, and less than 1.00 mmol/l) were 2.0 (95% CI=1.00 to 3.85), 2.4 (95% CI=1.23 to 4.50), and 3.8 (95% CI=1.49 to 9.82) (Figure 2).

A linear regression model including age, body mass index (as covariates), serum LDL, HDL$_2$ and HDL$_3$ cholesterol, plasma fibrinogen, cigarette-years, and years of hypertension, accounted for 35% of the variation in the severity of carotid atherosclerosis as a four-categorical variable (Table 3). Serum LDL cholesterol concentration remained an independent predictor of carotid atherosclerosis even when the above-mentioned covariates were taken into consideration. The severity of carotid atherosclerosis had a significant inverse univariate regression effect on serum HDL$_2$ and HDL$_3$ cholesterol levels, but these associations were weakened substantially by the adjustment for age. Cigarette-years was the strongest single determinant of carotid atherosclerosis in the multivariate model. Plasma fibrinogen had the strongest unadjusted association with carotid atherosclerosis. About 60% of this association was explained by the correlation of plasma fibrinogen with age ($r=0.245$) and almost 20%, by the correlation with cigarette-years ($r=0.187$). Neither the current level of blood pressure (not shown in Table 3) nor the duration of hypertension had any notable association with carotid atherosclerosis.

**Discussion**

The early phases of atherosclerosis can be best assessed noninvasively in selected arterial segments with the B-mode ultrasonography. A linear regression model including age, body mass index (as covariates), serum LDL, HDL$_2$ and HDL$_3$ cholesterol, plasma fibrinogen, cigarette-years, and years of hypertension, accounted for 35% of the variation in the severity of carotid atherosclerosis as a four-categorical variable (Table 3). Serum LDL cholesterol concentration remained an independent predictor of carotid atherosclerosis even when the above-mentioned covariates were taken into consideration. The severity of carotid atherosclerosis had a significant inverse univariate regression effect on serum HDL$_2$ and HDL$_3$ cholesterol levels, but these associations were weakened substantially by the adjustment for age. Cigarette-years was the strongest single determinant of carotid atherosclerosis in the multivariate model. Plasma fibrinogen had the strongest unadjusted association with carotid atherosclerosis. About 60% of this association was explained by the correlation of plasma fibrinogen with age ($r=0.245$) and almost 20%, by the correlation with cigarette-years ($r=0.187$). Neither the current level of blood pressure (not shown in Table 3) nor the duration of hypertension had any notable association with carotid atherosclerosis.

**Discussion**

The early phases of atherosclerosis can be best assessed noninvasively in selected arterial segments with the B-mode ultrasonography. Although fatty streaks on the arterial wall have not yet become detectable with ultrasound, high-resolution B-mode ultrasonography can detect intimal-medial thickening even though there would be neither lumen obstruction nor consequent flow disturbances. An increase in the combined thickness of intimal and medial layers in the carotid artery wall can be seen using the high-resolution B-mode ultrasonography. However, whether these are fatty streaks, diffuse or subendothelial intimal thickening, or medial hypertrophy cannot yet be determined ultrasonographically.

Arteriography cannot be used in studies of random population samples because of ethical considerations and cost. Also, arteriography defines only the lumen and is not sensitive for detecting arterial wall thickening in its early
phase. Early atherosclerosis can lead to compensatory dilation of the arterial diameter, which may make arteriographic assessment irrelevant in the detection of early atherosclerotic lesions. X-ray computed tomography, nuclear magnetic resonance, and positron emission tomography are, at the moment, too expensive for population studies and have not been modulated for detecting early atherosclerosis. Even though Doppler spectral analysis has proved a sensitive method in the assessment of severe, hemodynamically significant carotid stenosis, it is less useful in detecting minimal atherosclerotic lesions, due to its lower axial resolution.

The short-term reproducibility of our ultrasonographic assessment of the severity of carotid atherosclerosis was high, as indicated by the 90% agreement between the original and blindly done re-assessment in a random subsample by the same observer. The long-term tracking of the severity assessment and the between-observer variation is being studied.

In a group of 134 male patients ages 45 to 64 years referred to a neurological clinic in the area of Paris, France by general practitioners for ultrasonic examination of cervical arteries "as part of general check-up or symptoms usually unrelated to cerebrovascular disease," the prevalence of carotid plaques was 32.1%; less than 50% stenosis, 2.2%; and more than 50% stenosis, 1.5%. These rates are comparable to our findings. In 100 male volunteers ages 50 to 69 years from the Maastricht area of the Netherlands, van Merode and co-workers found atherosclerotic lesions in 23% of the men by using the high-resolution pulsed Doppler system. The ratio of HDL to total cholesterol in serum was lower in men with carotid atherosclerotic lesions or with a history of ischemic heart disease or claudication. In a study in 254 asymptomatic patients over the age of 55 years, Jackson and Bendick detected atherosclerotic disease in 80% of carotid vessels with duplex sonography. This study population was screened from a General Surgery service in Indianapolis, Indiana. Several other studies have reported prevalences of atherosclerotic lesions in hospital-based populations.

Table 3. Regression of Severity of Carotid Atherosclerosis on Serum Lipoproteins, Plasma Fibrinogen, Smoking Exposure, and Duration of Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standardized regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Serum LDL cholesterol</td>
<td>0.163†</td>
</tr>
<tr>
<td>Serum HDL₂ cholesterol</td>
<td>-0.107§</td>
</tr>
<tr>
<td>Serum HDL₃ cholesterol</td>
<td>-0.154‡</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>0.205†</td>
</tr>
<tr>
<td>Cigarette-years of smoking</td>
<td>0.141†</td>
</tr>
<tr>
<td>Duration of hypertension (yrs)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

*From a model including age and body mass index in addition to the six variables shown here. The multiple correlation squared was 0.35.

†p<0.001, ‡p<0.01, and §p<0.05 (two-sided).

No inferences can, however, be drawn from these to the prevalence in the general population.

In our study in a randomly selected population sample of middle-aged Eastern Finnish men, the overall prevalence of detectable carotid atherosclerosis was 49% and this proportion rose sharply with increasing age. On the basis of our data, carotid atherosclerosis appears to become measurable by ultrasonography in male populations over age 40. Our study confirms the high prevalence of peripheral atherosclerosis in Eastern Finnish men. The prevalence is somewhat higher than that reported from Northern France and strikingly higher than that reported from the Netherlands, although the comparison is obscured by the differences in methodology and equipment for carotid assessment.

In this cross-sectional population study, we observed a strong and graded relationship between serum LDL cholesterol concentration and the prevalence of carotid atherosclerosis. This finding implies a good predictive validity of both our B-mode measurements and the classification of atherosclerosis severity that we used. The observation also agrees with preventive trials which studied the effect of lowering serum LDL cholesterol on the progression of coronary atherosclerosis and prospective population studies of the association of serum LDL cholesterol with the risk of ischemic cerebrovascular disease. The prevalence of carotid atherosclerosis started to increase at low serum LDL cholesterol levels, 2.5 to 3.5 mmol/l, as compared to levels below 2.5 mmol/l. On the basis of our finding and that by Blankenhorn and co-workers, we suggest that lowering serum LDL cholesterol concentration from a level traditionally considered normal to very low levels (under 2.5 mmol/l) could reverse the progression of atherosclerosis.

The absence of the association between serum LDL and a score for severity of carotid atherosclerosis in a study of 376 patients hospitalized for elective coronary angiography may be due to the smaller variation and range of serum LDL cholesterol than in our study population in which there was a high mean LDL cholesterol level.

We found an equally strong inverse relationship between serum HDL cholesterol concentration and the prevalence of carotid atherosclerosis. Our finding is in agreement with that of Crouse et al. This observation supports the evidence from prospective population studies concerning the role of HDL cholesterol in atherosclerotic vascular diseases. In our data, serum HDL₂ and HDL₃ subfractions were equally strongly related to carotid atherosclerosis. This is consistent with an early study by Goffman and co-workers in which both HDL subfractions were equally predictive of subsequent coronary death.

References

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