Coronary Artery Disease in Heterozygous Familial Hypercholesterolemia Patients With the Same LDL Receptor Gene Mutation

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Abstract

Background Familial hypercholesterolemia (FH), an autosomal codominant disease, is characterized by high levels of LDL cholesterol and a high incidence of coronary artery disease (CAD). To date, genetic heterogeneity has hindered the proper assessment of the relation between risk factors and CAD in FH patients.

Methods and Results We studied the association between CAD and common risk factors in a sample of 263 French Canadian FH patients (147 women, 116 men) carrying the same >10–kb deletion of the LDL receptor gene. Thirty-five women and 54 men had CAD. The mean age of onset of CAD was 45.6±12.7 years in women and 38.8±9.4 years in men. Multiple logistic regression analyses were performed to test the association between CAD and age, tendon xanthomas, cigarette smoking, hypertension, diabetes mellitus, apolipoprotein E polymorphism, total plasma cholesterol, triglycerides, VLDL cholesterol, LDL cholesterol, HDL cholesterol, and lipoprotein(a) [Lp(a)]. In FH women, significant multivariate predictors were age (odds ratio, 1.10 for 1 year; \( P<.0001 \)), VLDL cholesterol (odds ratio, 3.85 for 1 natural log unit; \( P<.002 \)), and LDL cholesterol (odds ratio, 1.42 for 1 mmol/L; \( P<.02 \)). In FH men, age (odds ratio, 1.08 for 1 year; \( P<.0001 \)) and HDL cholesterol (odds ratio, 0.14 for 1 mmol/L; \( P=.05 \)) were significant predictors of disease. Lp(a) was not a significant predictor in univariate or multivariate analyses.

Conclusions This study suggests that increased risk of CAD in FH is not solely due to elevated LDL cholesterol levels and demonstrates a sex–specific lipoprotein influence on CAD in a large sample of FH patients carrying the same LDL receptor gene defect.
Introduction

Coronary artery disease (CAD) is the leading cause of death both in women and men in industrialized countries. The identification of subjects at risk of developing CAD is an important public health issue. Epidemiological and clinical studies have demonstrated that elevated LDL cholesterol levels are associated with an increased risk of CAD, whereas HDL cholesterol levels are inversely related to the risk of CAD. Furthermore, treatments that significantly lower LDL cholesterol (LDL–C), with and without significant increases in HDL cholesterol (HDL–C), have reduced the rate of fatal and nonfatal cardiac events and, in selected patients, have diminished coronary artery narrowing. Whether elevated plasma triglyceride (TG) levels act as an independent risk factor for CAD is controversial, although several studies have suggested that TG levels are an important risk factor for CAD in women. Similarly, the relation between lipoprotein(a) [Lp(a)] and CAD still requires clarification. In cross-sectional studies, elevated LDL–C levels, low HDL–C levels, hypertriglyceridemia, and Lp(a) excess have been associated with premature CAD.

Familial hypercholesterolemia (FH) is characterized by markedly elevated LDL–C levels and premature CAD. It is an autosomal codominant disease defined at the molecular level by one of a number of mutations in the LDL receptor gene. Despite the hereditary nature of the disease, FH shows great variability in phenotypic expression. Such interindividual phenotypic variation in heterozygous FH patients could be explained by the variability of the underlying mutation. Other genetic influences, such as apolipoprotein (apo) E polymorphism, also appear to play an important role. The expression of this disease may be affected by age, sex, other risk factors such as smoking and hypertension, or associated lipid abnormalities such as low HDL–C levels, high TG levels, high Lp(a) levels, or presence of type III dyslipoproteinemia. FH is one of the more common inherited metabolic diseases, with a prevalence of 1 in 500 heterozygotes in most populations. However, in French Canadians, Finns, and Afrikaners in South Africa, frequencies of FH are much higher because of a founder effect. Indeed, one of the founder mutations, a >10-kb deletion of the 5′ end of the LDL receptor gene including the promoter and exon 1, has been observed in 60% of French Canadian FH patients.

In previous studies, genetic heterogeneity has hindered the proper assessment of the relation between risk factors and CAD in FH patients. The present study was undertaken to examine the association between various risk factors and CAD in a sample of FH patients, all carriers of the >10-kb deletion of the LDL receptor gene, and to assess whether factors other than increased LDL–C levels could explain the variability in phenotypic expression in FH. In addition, because we have previously reported...
that even in such a homogeneous group of FH patients, considerable sex differences can be observed in the means, variances, and correlations of lipid levels as well as in the influence of concomitants such as age, height, and weight on lipid variables, we have performed the analyses separately by sex.

Methods

Subjects

FH subjects were selected from 383 untreated patients who had been referred to the Lipid Clinic of the Clinical Research Institute of Montreal and who were heterozygous for the >10–kb deletion of the LDL receptor gene as determined by Southern blot analysis. Two hundred sixty-three FH adult patients (age ≥18 years) from 167 families for whom complete clinical and biological data were available were included in the study. All of these FH (10–kb FH) patients (147 women, 116 men) had elevated LDL-C levels (LDL-C >4.2 mmol/L) and either tendon xanthomas or a history of tendon xanthomas in a first-degree relative.

Determination of CAD

Patients were classified according to the presence (n=89) or absence (n=174) of symptomatic CAD. Medical records were obtained for all CAD cases. CAD was considered to be present if patients had a documented history of myocardial infarction, an abnormal coronary angiogram (stenosis >70% in a major vessel), percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting (n=83) or if patients had a history of angina together with either a positive exercise test or an abnormal stress thallium-201 scan (n=6). None of the patients had suffered a major CAD event within the preceding 6 months. For each patient, the age of onset of CAD was defined as the age of the first CAD symptoms ascertained by a standard questionnaire administered by a physician of our Lipid Clinic.

Clinical Risk Factors

Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Cigarette smoking was assessed by self-report, and subjects were classified as current smokers, former smokers, or never-smokers. Blood pressure was measured on subjects in the supine position after a 5-minute rest. Subjects were classified as hypertensive if they were being treated with drugs for previously diagnosed hypertension, if systolic blood pressure was ≥160 mm Hg, or if diastolic blood pressure was ≥95 mm Hg. A patient was classified as having diabetes if she or he was receiving drug treatment for diabetes or if the fasting plasma glucose concentration was ≥7.8 mmol/L.

Biological Risk Factors and Laboratory Methods

After a 12–hour overnight fast, blood samples were obtained in tubes containing 1.5 mg/mL Na_2 EDTA (lipids, lipoproteins) or no anticoagulant (glucose) and were centrifuged within 2 hours. Plasma lipoproteins were separated under standard conditions by a combination of ultracentrifugation at d=1.006 g/mL to isolate VLDL and heparin–manganese precipitation of apo B–containing lipoproteins in the d=1.006 g/mL infranatant to determine LDL-C and HDL-C concentrations according to the Lipid Research Clinics Protocol. Plasma and lipoprotein cholesterol and TG were measured enzymatically using an automated analyzer (Roche Cobas Mira S; F. Hoffmann–La Roche and Co, Ltd; Diagnostica).
Apo E phenotypes were determined after isoelectric focusing of VLDL apoproteins. Lp(a) was measured in plasma using a commercially available ELISA (Macra, Terumo Medical Corp). Fasting plasma glucose was determined by the glucose oxidase method (Boehringer Mannheim).

**Statistical Analysis**

Epidemiological studies have shown that the frequency distributions of plasma lipids differ according to sex. Specifically, in the 10-kb FH population, striking differences in means, variances, and correlations of clinical and lipid parameters between women and men have been reported. Analyses were therefore performed separately for women and men. Evidence for statistically significant quantitative trait differences between patients with and without CAD was evaluated by use of the Student's *t* test with Satterthwaite's correction to take into account heteroscedasticity of variances whenever necessary. Because the distributions of Lp(a), TG, and VLDL cholesterol (VLDL–C) values were highly skewed, a natural logarithmic transformation was performed. The Pearson's χ² test was used to assess differences in the distributions of categorical traits. All tests were two-sided, and the significance level was set at .05. Because of the multicollinearity among the parameters studied, these univariate analyses must be examined with caution.

The relations between demographic, clinical, and biological parameters and the presence or absence of CAD were examined by multiple logistic regression. Likelihood ratio statistics were used to compare models with different combinations of predictors. Both forward stepwise and backward stepwise trait selection procedures were used to identify a parsimonious set of predictors with an inclusion significance level of .15 and an exclusion significance level of .20. Forward stepwise trait selection was also carried out to identify pairwise interactions. The predictors in the most complete logistic regression model, identified by the stepwise procedure, were then evaluated by the likelihood ratio test statistic with a significance level of .05. Finally, an analysis of model fit was undertaken. First, the goodness of fit of the final models was evaluated with the χ²ᵢₙ statistic of Hosmer and Lemeshow. Second, diagnostic statistics (leverages, studentized deleted residuals, Cook’s distances) were obtained to identify observations that may have unduly influenced model fit. Given the number of CAD events in the sample, our study had a power of 0.80, in each sex, to detect an odds ratio of 1.8 for an FH patient with a risk factor of 1 SD above the mean, when controlling for all other variables using a test with a significance level of .05.

**Results**

**Clinical Data**

Clinical findings are listed in Tables 1 and 2 for 10-kb FH women and men, respectively. At the time of the study, the mean age of patients with CAD [CAD(+)] was significantly higher (*P* < .0001) than the mean age of patients without CAD [CAD(−)] for each sex. The mean age of onset of CAD was 45.6±12.7 years in women and 38.8±9.4 years in men. Symptomatic CAD occurred 7 years later in women than in men (*P* < .01). In each sex, anthropometric data (height, weight, and body mass index) did not differ between CAD(+) and CAD(−) groups. The prevalence of tendon xanthomas was significantly higher in CAD(+) than in CAD(−) for women only. There was no difference in the
frequencies of the common risk factors for the CAD(+) and CAD(−) groups except for a significantly higher frequency of hypertension in women with than in women without CAD.

View this table:

<table>
<thead>
<tr>
<th>Table 1. Clinical and Biological Features of 147 Familial Hypercholesterolemia Women With the LDL Receptor Gene &gt;10-kb Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameters</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Height, m</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Tendon xanthomas, %</td>
</tr>
<tr>
<td>Smoking, %</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Former</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
<tr>
<td>Diabetes, %</td>
</tr>
<tr>
<td>Lipid parameters</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>VLDL-C</td>
</tr>
<tr>
<td>LDL-C</td>
</tr>
<tr>
<td>HDL-C</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
</tr>
</tbody>
</table>

- CAD(−) or CAD(−) indicates patients with or without coronary artery disease; BMI, body mass index; VLDL-C, very low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Lipids are in mmol/L and lipoprotein(a) in mg/dL.

- Mean±SD values compared by t test. Untransformed data are given for VLDL-C, TC, and Lp(a) levels; the significance level (P) was evaluated using log-transformed data. Categorical parameters compared by χ² test.

- 1 Age at the time of the study.
Clinical and Biological Features of 116 Familial Hypercholesterolemia Men With the LDL Receptor Gene >10–kb Deletion

Table 2.
Clinical and Biological Features of 116 Familial Hypercholesterolemia Men With the LDL Receptor Gene >10–kb Deletion

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>CAD(−) n=62</th>
<th>CAD(+) n=54</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>36.3±10.3</td>
<td>45.0±10.9</td>
<td>.0001</td>
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<tr>
<td>Height, m</td>
<td>1.72±0.06</td>
<td>1.71±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.6±12.2</td>
<td>75.7±12.9</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8±3.6</td>
<td>25.9±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Tendon xanthomas, %</td>
<td>74.2</td>
<td>85.2</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Current</td>
<td>32.3</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>30.6</td>
<td>44.4</td>
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</tr>
<tr>
<td>Never</td>
<td>37.1</td>
<td>31.5</td>
<td></td>
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<tr>
<td>Hypertension, %</td>
<td>4.6</td>
<td>13.0</td>
<td>NS</td>
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<tr>
<td>Diabetes, %</td>
<td>0</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>8.98±1.23</td>
<td>9.33±1.66</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>1.00±0.64</td>
<td>1.26±1.22</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>7.11±1.26</td>
<td>7.29±1.28</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.87±0.23</td>
<td>0.79±0.19</td>
<td>.045</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.56±0.89</td>
<td>1.72±0.77</td>
<td>NS</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>23.2±24.5</td>
<td>22.3±22.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

• Legend as in Table 1⇑.

Table 2.
Clinical and Biological Features of 116 Familial Hypercholesterolemia Men With the LDL Receptor Gene >10–kb Deletion

Lipid and Lipoprotein Levels

The mean concentrations of plasma lipids and lipoproteins in the CAD(+) and CAD(−) FH groups are summarized in Tables 1⇑ and 2⇑ for women and men, respectively. In women, CAD(+) patients had significantly higher plasma levels of total cholesterol, VLDL–C and LDL–C, and TG than did CAD(−) patients. In contrast, the only significant difference between CAD(+) and CAD(−) men was the level of HDL–C, which was lower in men with than in men without CAD. There was no difference in Lp(a) levels between CAD(+) and CAD(−) patients of either sex.
Apo E Polymorphism and CAD

The apo E phenotype distribution did not differ between 10–kb FH CAD(+) and CAD(−) groups for either sex. In particular, there was no increased frequency of the E4/3 and E4/4 phenotypes in CAD(+) groups (not shown).

Multivariate Analysis

Sex–specific multiple logistic regression analyses are presented in Table 3. In 10–kb FH women, selection procedures identified age, VLDL–C, and LDL–C as predictors of the probability of having CAD. The odds of having CAD increased with increasing age, VLDL–C, and LDL–C. In 10–kb FH men, multiple logistic regression analysis demonstrated that age and HDL–C were associated with CAD. The odds of having CAD increased with increasing age and with decreasing HDL–C. No pairwise interactions attained the significance level of .05. Nonsignificant values of the χ²HL statistics suggested that the models presented in Table 3 fit the observed outcomes well (χ²HL=5.1, df=8, and χ²HL=14.4, df=8 for women and men, respectively). Diagnostic statistics revealed no outlier or influential observations. Because of the family relationships within the study sample (and therefore a possible statistical dependence) and because of the known effects of β–blocker therapy on lipid levels, we repeated our analysis on the reduced sample of 167 unrelated 10–kb FH probands as well as on the entire sample after excluding patients with β–blocker medication. Similar results were obtained in both analyses (data not shown).
Table 3.
Parameters Associated With Coronary Artery Disease in Familial Hypercholesterolemia Patients With the >10-kb Deletion of the LDL Receptor Gene by Multiple Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β±SE(β)</th>
<th>OR</th>
<th>95% CI (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n=147)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.092±0.021</td>
<td>1.10</td>
<td>1.05-1.14</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>1.348±0.446</td>
<td>3.85</td>
<td>1.61-9.23</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.348±0.154</td>
<td>1.42</td>
<td>1.05-1.92</td>
</tr>
<tr>
<td>Men (n=116)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.078±0.020</td>
<td>1.08</td>
<td>1.04-1.12</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-2.002±1.028</td>
<td>0.14</td>
<td>0.02-1.01</td>
</tr>
</tbody>
</table>

- β is the partial regression coefficient; SE(β), standard error of β.
- 1 Odds ratio, defined as $e^\beta$, corresponds to changes in odds for the following increments in each parameter, assuming that the other parameters remain constant at their mean values: 1 year of age, 1 natural log unit of VLDL cholesterol (2.18 mmol/L as compared with 0.8 mmol/L for example), 1 mmol/L of LDL cholesterol, 1 mmol/L of HDL cholesterol. 95% CI (OR) is the 95% confidence interval for population odds ratio.
- 2 P<.0001.
- 3 P<.002.
- 4 P<.02.
- 5 P=.05.

Discussion

The early development of CAD in FH is largely attributed to elevated LDL-C levels. However, it is likely that other lipid and nonlipid factors also influence CAD risk in these patients. The availability of a large sample of FH individuals with an identical LDL receptor gene deletion of >10 kb has enabled us to study the potential causes of variability in CAD expression in 10-kb FH. In the absence of the etiologic heterogeneity found in other clinically defined FH samples, our data suggest a sex-specific lipoprotein effect on CAD in FH patients, such that different lipoproteins influenced CAD risk differently in each sex.

In the general population, CAD rates are higher in elderly compared with younger individuals. In agreement with previous studies, we found that age is also associated with CAD in 10-kb FH. Mabuchi
et al reported that the onset and progression of CAD in FH, estimated by angiography, were correlated with age. In multiple regression analyses, Wiklund et al and Tatò et al found that age significantly predicted CAD in FH. Our study also revealed that the mean age of onset of coronary symptoms was 45.6 years in women and 38.8 years in men. Thus, CAD apparently occurs earlier in >10-kb FH patients than in other FH groups. The 7-year delay in 10-kb FH women, relative to men, is also lower than the 10-year delay generally found in different FH populations. These observations suggest that the >10-kb deletion of the LDL receptor gene, which results in a null allele, is associated with more precocious and severe forms of CAD in heterozygous FH patients (this study) as well as in homozygous FH patients than in other FH samples.

In 10-kb FH men, both age and HDL-C appeared to be independent predictors for CAD. Many epidemiological studies in high-risk populations have shown that low HDL-C level is a significant risk factor. In the Lipid Research Clinics Follow-up Study, HDL-C levels were strongly inversely associated with mortality from CAD at higher LDL-C levels (LDL-C >160 mg/dL), although not at lower LDL-C levels, in both women and men. Low HDL-C levels in FH subjects have been associated with CAD in several studies. This relation was found in both sexes, only in women, or only in men in univariate analyses. After adjustment for age and sex, HDL-C levels were lower in FH patients with CAD in the study of Mbewu et al. In a recent study in 91 FH patients, age, sex, and HDL-C levels were the only variables reaching statistical significance in multiple logistic regression. These results suggest that, even in the presence of very high LDL-C levels, as seen in FH, reverse cholesterol transport assumes the same importance as in nonselected populations.

In contrast with men, the best predictors of CAD in women in the present study were age, VLDL-C levels, and LDL-C levels. In 30 CAD patients who were matched for age and sex with 30 FH patients who had not developed CAD, LDL-C was found to be higher in those with CAD. The role of LDL-C levels as a risk factor for CAD in FH women was difficult to establish in previous studies because of the heterogeneity of the samples studied. In a clinically defined sample, mutations of the LDL receptor gene underlying FH may be numerous in the absence of a genetic founder effect. In French Canadians, total plasma cholesterol and LDL-C levels were found to be higher in FH homozygotes with the >10-kb deletion than in those with the exon 3 mutation of the LDL receptor gene and to result in earlier manifestations of CAD. Our results show that, among women with the same >10-kb LDL receptor gene deletion, the severity of the LDL-C excess has an impact on CAD risk in heterozygous 10-kb FH. The greater variability in LDL-C levels found in 10-kb FH women than in men may partly explain the sex-specific effect of LDL-C on CAD expression.

A striking finding of our study was the strong association of VLDL-C levels with CAD in 10-kb FH women. When we tested a complete model that included age, LDL-C, and the ratio of VLDL-C to plasma TG, or an estimate of β-VLDL, in the >10-kb FH women, the predictive power of this model for CAD was similar to that of the best model we found for women including age, LDL-C, and VLDL-C (data not shown). The role of TG-rich lipoproteins in the development of CAD in FH has been suggested by previous studies. In the work of Hirobe et al, mean TG levels were significantly higher in patients with CAD than in patients without CAD, but only in women. In a recent study, higher plasma TG concentration was the only significant difference between FH female patients with and without CAD. In Quebec, the prevalence of myocardial infarction was found to be three times greater in type IIb (TG >200 mg/dL) than in type IIa familial hypercholesterolemia patients. In a recent study by Wiklund et
the group of FH patients with CAD had higher levels of TG by univariate analysis, but this difference disappeared in multivariate analysis. In the work of Seed et al., multiple discriminant analysis retained TG levels as an independent risk factor for CAD in FH. Two recent studies have indicated that there is an excess risk of CAD in the presence of TG >2.3 mmol/L when the ratio of LDL–C to HDL–C exceeds 5.1

It is likely that fasting TG as measured in the above studies may inadequately reflect the chronic effects of TG–rich lipoproteins. Postprandial lipoproteins such as chylomicron remnants, intermediate–density lipoprotein, VLDL, or particles of different size and composition may be more closely related to CAD. Catabolism of the TG–rich lipoproteins produces remnant particles that appear to be atherogenic, whereas newly secreted VLDL and chylomicrons that are rich in TG and low in cholesterol esters are less atherogenic. The distribution of apo CIII between VLDL and HDL, a crude index of TG metabolic capacity, emerged as the most powerful predictor of CAD angiographic progression in drug–treated patients. Comparison of FH and non–FH subjects showed a markedly higher ratio of VLDL–C to plasma TG and a fivefold increase in mean estimated β–VLDL among FH subjects. In a kinetic study of different VLDL subfractions in homozygous FH patients, James et al. found fourfold increases in intermediate–density lipoprotein and less marked increases in small VLDL, while concentrations of larger VLDL were unaltered compared with those of control subjects. Furthermore, the smaller VLDL in FH homozygotes were enriched with cholesterol and depleted in TG. These smaller cholesterol ester–enriched VLDL share with LDL the ability to deliver cholesterol to the arterial intima in humans. FH is primarily characterized by overproduction and slow catabolism of LDL. However, impaired catabolism of VLDL and its remnants is also a recognized feature of FH.

Whether Lp(a) is a risk factor for CAD in FH is unclear. Lp(a) was found to be a powerful predictor of CAD in FH in two studies, whereas no such relation was found in three other studies. In the last study conducted in FH patients with a heterogeneous genetic background, plasma Lp(a) levels that were found to be higher than in a control population were not associated with a higher risk for developing CAD. In the present study, we did not find any significant association of Lp(a) with CAD in women or in men. All the patients of our sample share the same mutation of the LDL receptor gene, whereas in previous studies, the diagnosis of FH was established on clinical findings. In a recent study of 91 FH patients who were only partly genetically defined (36 of 91), Lp(a) was not associated with CAD in multiple logistic regression. These results suggest that Lp(a) levels alone are not a strong risk factor for CAD in FH. However, in some groups of young patients or in FH patients with particular apo(a) phenotypes, the risk of CAD may be increased.

In our study, the distribution of apo E phenotypes was similar in patients with and without CAD in both sexes. This result contrasts with reports in the general population showing an increased prevalence of the ε4 allele in patients with symptomatic CAD. Only one previous study has shown an effect of apo E phenotypes on CAD in FH, in which a significantly higher prevalence of CAD was observed among apo E4 carriers. Our work adds to previous negative findings of the influence of apo E polymorphism on CAD in FH and suggests that a major gene effect, the >10–kb deletion of the LDL receptor gene, may mask the discrete impact of apo E on CAD.

The present study contains limitations inherent to the study design. This investigation was cross–sectional and was based on the evaluation of the presence of symptomatic CAD. Coronary
arteriography was not performed routinely on asymptomatic FH patients. Since severe coronary lesions may exist without symptoms, symptomatic CAD is therefore an inaccurate measure for the presence and the extent of CAD and may result in occasional misclassifications. The relations between CAD and the predictors that we found in the 10-kb FH patients should be confirmed by other studies designed specifically to evaluate the incidence of CAD in relation to selected risk factors. Prospective studies are thus required to establish the effects of lipoproteins on CAD risk in FH.

Conclusions

Our study shows a sex-specific lipoprotein influence on CAD in a large sample of FH patients carrying a particular LDL receptor gene deletion. Age is a powerful risk factor for CAD in 10-kb FH in both sexes, in addition to lower HDL–C levels in 10-kb FH men and higher VLDL–C and LDL–C levels in 10-kb FH women. CAD risk in 10-kb FH is therefore not solely attributable to high LDL concentrations. Even in the presence of overt hypercholesterolemia, the pathological expression of 10-kb FH is markedly affected by other lipoproteins in a sex-specific manner, supporting the view that CAD in FH can be influenced both by genetic and environmental factors.

Acknowledgments

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47. [Link]
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