Importance of HDL cholesterol levels and the total/HDL cholesterol ratio as a risk factor for coronary heart disease in molecularly defined heterozygous familial hypercholesterolaemia

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Aims To assess the relationship of the lipid profile to coronary heart disease in a group of heterozygous familial hypercholesterolaemic subjects with similar age, sex, body mass index, prevalence of angiotensin converting enzyme DD genotype and type of low density lipoprotein receptor mutation.

Methods and Results A total of 66 molecularly defined heterozygous familial hypercholesterolaemic subjects, 33 of whom had coronary heart disease, were studied. Clinical features, cardiovascular risk factors and lipid parameters were compared in both groups. Familial hypercholesterolaemic patients with coronary heart disease showed significantly lower values of mean plasma HDL cholesterol and a higher total/HDL cholesterol ratio as compared with familial hypercholesterolaemic subjects free of coronary heart disease. Total and LDL cholesterol concentrations were higher in patients with coronary heart disease, without reaching statistical significance. No differences in plasma lipoprotein(a) levels on absolute and log-transformed values were observed between the two groups. In the whole familial hypercholesterolaemia group, plasma HDL cholesterol levels were related to plasma triglyceride values and to LDL receptor gene ‘null mutations’.

Conclusions In familial hypercholesterolaemic subjects of similar age, gender, body mass index, systolic and diastolic blood pressure, and genetic factors that could influence coronary heart disease risk, plasma HDL cholesterol values and total/HDL cholesterol ratios are two important coronary risk factors. Hence, treatment of familial hypercholesterolaemia should focus not only on lowering total and LDL cholesterol levels, but also on increasing HDL cholesterol values for coronary heart disease prevention. More prospective and intervention trials should be conducted to establish the relationship of HDL cholesterol levels and coronary heart disease in familial hypercholesterolaemia.

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Introduction

Familial hypercholesterolaemia is an autosomal dominant disease defined at the molecular level by one of a number of mutations in the low density lipoprotein (LDL) receptor gene and characterized by markedly elevated LDL cholesterol levels, tendon xanthomata, and increased risk of premature coronary heart disease[1,2]. Despite its hereditary nature, familial hypercholesterolaemia shows great variability in phenotypic expression that is dependent on environmental and genetic factors[3]. Considerable variation in the severity of atherosclerotic complications among families with familial hypercholesterolaemia has long been recognised[4–6]. The expression of coronary heart disease...
among familial hypercholesterolaemic patients may be influenced by other risk factors, such as age, male sex, smoking, visceral obesity, high total cholesterol levels, low HDL cholesterol levels, and high lipoprotein(a) levels[3–4]. In addition, the prevalence of coronary heart disease in familial hypercholesterolaemia has been associated with the type of LDL receptor mutation[5] and the angiotensin converting enzyme (ACE) DD genotype[6].

The ACE DD genotype is associated with an elevated plasma concentration of ACE, which results in an increase of angiotensin II, and an elevated influx of $^{125}$I-labelled LDL into the arterial wall of rabbits[7]. Therefore, the ACE gene polymorphism could be a potential coronary risk factor in primary hyperlipaemias. Recently, O’Malley et al. have demonstrated an association between coronary heart disease and the ACE DD genotype in a familial hypercholesterolaemia population[8].

On the other hand, LDL receptor gene ‘null mutations’ that generate no LDL receptor protein have been associated with higher LDL cholesterol levels, poor response to statin treatment and coronary heart disease in familial hypercholesterolaemic subjects[7,10–13].

The present case/control study was undertaken to assess what component of the lipid profile correlated best with coronary heart disease prevalence in a group of heterozygous familial hypercholesterolaemic subjects with similar age, sex distribution, body mass index, prevalence of ACE DD genotype and LDL receptor class mutations.

Patients and methods

Patients

The case/control study consisted of 66 heterozygous familial hypercholesterolaemic subjects (33 coronary heart disease+ cases and 33 coronary heart disease – controls) selected by matching criteria (age, sex distribution, body mass index, prevalence of ACE DD genotype and LDL receptor class mutations) from a total of 280 heterozygous familial hypercholesterolaemia subjects attending our Lipid Clinic. The 280 heterozygous familial hypercholesterolaemic subjects were diagnosed based on clinical criteria for familial hypercholesterolaemia. In 230, a mutation at the LDL receptor gene could be detected (82%). In 40 molecularly defined familial hypercholesterolaemic patients, coronary heart disease could be confirmed. We randomly selected, among the 240 molecularly defined familial hypercholesterolaemia without coronary heart disease, 33 subjects matched for age, sex, body mass index, DD genotype and LDL receptor gene mutation, with 33 out of the 40 familial hypercholesterolaemic subjects with coronary heart disease.

All subjects were Caucasians and lived in the Autonomous Community of Valencia, Spain. The institutional ethics committee approved the protocol and all subjects gave written informed consent to take part in the study.

Clinical and biochemical criteria for diagnosing familial hypercholesterolaemia included: plasma levels of total and LDL cholesterol higher than the 95th percentile corrected for both age and sex, presence of tendon xanthomas, coronary artery disease in the proband or in a first-degree relative, and bimodal distribution of total cholesterol and LDL cholesterol levels in the family (autosomal dominant pattern of lipid IIa phenotype). Clinical diagnosis of familial hypercholesterolaemia was genetically confirmed in 82% of the familial hypercholesterolaemia subjects by the presence of major rearrangements at the LDL receptor locus detected by Southern blot, or minor LDL receptor mutations detected by polymerase chain reaction single-strand conformation polymorphism analysis. There was considerable molecular heterogeneity in the whole familial hypercholesterolaemia group, i.e. six major rearrangements and 23 minor mutations, 112insA, C95R, and C358Y being the most prevalent.

In all patients, a complete physical examination was performed. Body mass index 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 or non-smokers. Blood pressure was measured with a von Recklinghausen sphygmomanometer in the sitting position and after a 5 min rest. The mean value of three measurements was considered. A patient was classified as having diabetes if he or she fulfilled the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[14].

The criteria for positive coronary heart disease were: (a) documented history of myocardial infarction (presence of typical chest pain and electrocardiographic and creatine phosphokinase-MB monitoring during the acute phase, or deep and wide Q-waves as an electrocardiographic manifestation of an old infarction, n=11) or (b) the presence of angina (history of typical exercise-associated chest pain) and positive coronary angiography (70% stenosis on coronary arteriography).

Laboratory methods

Measurement of lipids and lipoproteins

After a 12–14 h fast, blood samples were collected in tubes containing EDTA and were centrifuged within 4 h. Plasma was stored at 4°C for a maximum of 3 days. DNA extraction was performed by standard procedures. Cholesterol and triglyceride levels were measured by enzymatic techniques[15,16]. HDL cholesterol was measured after precipitation of apoB-containing lipoproteins with polyaniions[17] and VLDL cholesterol after separation of VLDL ($d<1.006$ g · ml$^{-1}$) by ultracentrifugation[18]. The LDL cholesterol was calculated by subtracting VLDL and HDL cholesterol from total cholesterol. Total plasma apoB was measured by immunoturbidimetry[19]. Lipoprotein(a) levels were determined.
by a commercially available ELISA (SDI Strategic Diagnosis, Delaware, U.S.A.).

Genetic methods

The genetic diagnosis of familial hypercholesterolaemia was established by identifying different LDL gene mutations. Major rearrangements were detected by Southern blot analysis of BgII and KpnI plus XbaI digested genomic DNA. Small and minor mutations were detected by polymerase chain reaction-SSCP analysis and semi-automated sequencing. The running conditions for SSCP analysis and the oligonucleotides used were performed according to Lombardi et al.[23] and Leren et al.[24], with minimal modifications.

An LDL receptor gene 'null mutation' was considered in the case of: (a) major rearrangements affecting the promoter region, (b) or small rearrangements that create a stop codon (W-18X) or generate a truncated protein (deletion of ATGA at nucleotide 790 in exon 5). Subjects with null mutations included: 112insA, deletion promoter to exon 1, deletion promoter to exon 2, deletion 790 with null mutations included: 112insA, deletion promoter to exon 1 and deletion of promoter to exon 2), (b) W-18X to A change at nucleotide 11 that creates a stop codon, 112insA — an insertion of A in exon 2 that generates a stop codon, and a small deletion of ATGA at nucleotide 790 in exon 5 that creates a stop codon.

Insertion/deletion polymorphism of the ACE gene was determined by amplification of intron 16 following the method of Redon et al.[23], with primers 5’CTGGA GACCACCTCCATCCCTTCT3’ and 5’GATGTGGCC ATCACATTGCATCGAT3’, 1 µg of target DNA, 1 U of Taq DNA polymerase, and reaction mixture containing 10 mM Tris-HCl (pH 8.4), 3 mM MgCl2, 50 mM KCl, and 0.1 mg . ml⁻¹ gelatin. The fragments obtained were analysed by electrophoresis on agarose gel.

Statistical analysis

Data were analysed with the Statistical Package for the Social Sciences (SPSS)[25] and expressed as mean ± standard deviation (SD). Mean values of quantitative variables were compared with the Student’s t-test for unpaired data except for plasma levels of triglycerides and lipoprotein(a) values, which were analysed with the Mann–Whitney U test. The distribution of both triglyceride and lipoprotein(a) values were highly skewed, and a logarithmic transformation was therefore applied to produce approximately normal distribution. Proportions were compared with contingency tables and the chi-square test or the Fisher’s exact test. Pearson’s statistics were used to assess the relationship between variables. Multiple regression analysis was used to determine the variables that were associated with coronary heart disease and to calculate adjusted odds ratios. Age and body mass index were included in the logistic model as covariates. For each odds ratio we estimated two-tail P-values and 95% confidence intervals.

Results

The clinical characteristics of coronary heart disease+ and coronary heart disease – familial hypercholesterolaemic subjects are shown in Table 1. Coronary heart disease+ patients showed a significantly higher prevalence of xanthomas. Both groups showed similar age, sex distribution, body mass index, systolic and diastolic blood pressure, and prevalence of diabetes mellitus.

Table 1 shows the molecular characteristics of LDL receptor gene mutations included in the study. LDL receptor gene null mutations were: (a) major rearrangements affecting the promoter region (deletion of promoter to exon 1 and deletion of promoter to exon 2), (b) W-18X to A change at nucleotide 11 that creates a stop codon, 112insA — an insertion of A in exon 2 that generates a stop codon, and a small deletion of ATGA at nucleotide 790 in exon 5 that creates a stop codon and a truncated protein. LDL receptor gene defective mutations included mutations of aminoacids at different positions: C358Y (G to A at nucleotide 1146, Cys to Tyr), T413R (C to G at nucleotide 1301, Thr to Arg), R395W (C to T at nucleotide 1246, Arg to Pro), C68W (C to G at nucleotide 267, Cys to Trp), G642E (G to A

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Table 1 Clinical parameters of 66 heterozygous familial hypercholesterolaemia patients with and without coronary heart disease (CHD)

<table>
<thead>
<tr>
<th>Data</th>
<th>CHD+ (n=33)</th>
<th>CHD− (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.5 (9.3)</td>
<td>53.9 (9.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Male patients, n</td>
<td>14</td>
<td>14</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index, kg.m⁻²</td>
<td>26.1 (2.9)</td>
<td>26.3 (3.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134±4 (17.3)</td>
<td>133±5 (20.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76±6 (9.7)</td>
<td>78±1 (9.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>Essential hypertension, n</td>
<td>5 (15)</td>
<td>5 (15)</td>
<td>ns</td>
</tr>
<tr>
<td>Current smokers, n</td>
<td>2 (6)</td>
<td>3 (9)</td>
<td>ns</td>
</tr>
<tr>
<td>ACE DD genotype, n</td>
<td>15 (45)</td>
<td>15 (45)</td>
<td>ns</td>
</tr>
<tr>
<td>LDL null mutations, n</td>
<td>18 (54)</td>
<td>18 (54)</td>
<td>ns</td>
</tr>
<tr>
<td>Xanthomas %</td>
<td>24 (72)</td>
<td>9 (27)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data as mean (SD), n or (percentages).
Table 2  Molecular characteristics of LDL mutations included in the study

<table>
<thead>
<tr>
<th>Mutation</th>
<th>N</th>
<th>Type</th>
<th>Exon (nucleotide)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>112insA</td>
<td>16</td>
<td>Null</td>
<td>2 (11)</td>
<td>Ins A→stop</td>
</tr>
<tr>
<td>Deletion promoter to exon 1</td>
<td>4</td>
<td>Null</td>
<td>Promoter-1</td>
<td>Deletion</td>
</tr>
<tr>
<td>Deletion promoter to exon 2</td>
<td>4</td>
<td>Null</td>
<td>Promoter-2</td>
<td>Deletion</td>
</tr>
<tr>
<td>Deletion 790</td>
<td>2</td>
<td>Null</td>
<td>5 (790)</td>
<td>Del ATGA stop</td>
</tr>
<tr>
<td>W-18X</td>
<td>10</td>
<td>Null</td>
<td>1 (11)</td>
<td>G→A stop</td>
</tr>
<tr>
<td>C358Y</td>
<td>8</td>
<td>Defective</td>
<td>8 (1146)</td>
<td>G→A</td>
</tr>
<tr>
<td>T413R</td>
<td>6</td>
<td>Defective</td>
<td>9 (1301)</td>
<td>C→G</td>
</tr>
<tr>
<td>R305W</td>
<td>2</td>
<td>Defective</td>
<td>9 (1246)</td>
<td>C→T</td>
</tr>
<tr>
<td>C68W</td>
<td>2</td>
<td>Defective</td>
<td>3 (267)</td>
<td>C→G</td>
</tr>
<tr>
<td>G642E</td>
<td>2</td>
<td>Defective</td>
<td>14 (1998)</td>
<td>G→A</td>
</tr>
<tr>
<td>C95R</td>
<td>4</td>
<td>Defective</td>
<td>4 (346)</td>
<td>T→C</td>
</tr>
<tr>
<td>E256K</td>
<td>6</td>
<td>Defective</td>
<td>6 (829)</td>
<td>G→A</td>
</tr>
</tbody>
</table>

Table 3  Lipids and lipoproteins in 66 subjects with heterozygous familial hypercholesterolaemia (33 with CHD)

<table>
<thead>
<tr>
<th>Data</th>
<th>CHD+ (n=33)</th>
<th>CHD− (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol. l−1</td>
<td>9.7 (1.7)</td>
<td>9.1 (2.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides, mmol. l−1</td>
<td>1.96 (2.2)</td>
<td>1.34 (0.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Log10 triglycerides</td>
<td>2.14 (0.28)</td>
<td>2.04 (0.21)</td>
<td>ns</td>
</tr>
<tr>
<td>HDL cholesterol, mmol. l−1</td>
<td>1.15 (0.33)</td>
<td>1.37 (0.39)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol</td>
<td>8.9 (2.7)</td>
<td>7.2 (2.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL cholesterol, mmol. l−1</td>
<td>7.54 (1.68)</td>
<td>7.0 (2.1)</td>
<td>ns</td>
</tr>
<tr>
<td>VLDL, mmol. l−1</td>
<td>0.75 (0.4)</td>
<td>0.62 (0.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Apo B, gl. l−1</td>
<td>1.66 (0.5)</td>
<td>1.69 (0.42)</td>
<td>ns</td>
</tr>
<tr>
<td>Log10 Lp(a)</td>
<td>1.14 (0.45)</td>
<td>1.12 (0.55)</td>
<td>ns</td>
</tr>
<tr>
<td>Lp(a) ≥ 20 mg. dl−1 *%</td>
<td>33</td>
<td>23</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data as mean (SD) or percentages.
*Cutpoint for high cardiovascular risk.

Table 3 shows plasma lipid values in both familial hypercholesterolaemia groups. Plasma HDL cholesterol values were significantly lower and total/HDL cholesterol ratios significantly higher in familial hypercholesterolaemia coronary heart disease+ (1.16 ± 0.34 vs 1.37 ± 0.39 P=0.03; 8.9 ± 2.7 vs 7.2 ± 2.9 P=0.02). The triglyceride/HDL cholesterol ratio for the group with familial hypercholesterolaemia and coronary heart disease was 1.7, compared with 0.98 for the non-coronary heart disease group, P<0.02. The odds ratios for coronary heart disease were 3.92 (CI 95% 1.21–12.64, P=0.018) for HDL cholesterol <1.03 mmol. l−1 and 0.28 (CI 95% 0.1–0.8, P=0.016) for the total cholesterol/HDL cholesterol ratio <6.5. Total and LDL cholesterol concentrations were higher in patients with coronary heart disease, but the differences did not reach statistical significance. There were no differences in lipoprotein(a) levels on absolute and log-transformed values among patients with and without coronary heart disease.

In the whole familial hypercholesterolaemia group using Pearson’s correlation coefficient, plasma HDL cholesterol levels were related to plasma triglyceride values (−0.24 P=0.024) and LDL receptor gene null mutations (0.57 P=0.01).

The multiple regression analysis including as independent variables total cholesterol, log of triglycerides, log of lipoprotein(a), apolipoprotein B and HDL cholesterol values, showed that only HDL cholesterol values were associated with coronary heart disease (beta 2.32 ± 0.9, P=0.015).

Discussion

In heterozygous familial hypercholesterolaemia, coronary heart disease has been associated with age, male sex, smoking habits, visceral obesity, elevated total and LDL cholesterol and low HDL cholesterol plasma levels[4,6]. These data indicate that there may be different interactions between lipid fractions and lipoproteins in relation to cardiovascular risk in familial hypercholesterolaemic subjects. Previous studies[5,23] have shown a lack of association between higher lipoprotein(a) levels and coronary heart disease in a population with >10-kilobase deletion of the LDL receptor gene, although this finding has not been reported in other familial...
hypercholesterolaemia populations\[^{26}\]. The study of Ferrières et al.\[^{19}\] also demonstrated a gender-specific lipoprotein influence on coronary heart disease in a large sample of familial hypercholesterolaemic patients carrying the same LDL receptor gene defect. In our study, carried out in a familial hypercholesterolaemia group of similar age, sex distribution, body mass index, ACE DD genotype distribution, and LDL receptor null mutations distribution, we found that only low HDL cholesterol levels and high total/HDL cholesterol ratios are associated with coronary heart disease.

In addition, Hausmann et al.\[^{17}\] have shown by stepwise multiple regression analysis both in heterozygous familial hypercholesterolaemia and in familial combined hyperlipidaemia, that the strongest predictor of plaque burden in the left anterior descending coronary artery was the level of HDL cholesterol and the total/HDL cholesterol ratio. Sudhir et al.\[^{29}\] have also demonstrated a strong association between plasma HDL cholesterol levels and coronary ectasia in heterozygous familial hypercholesterolaemia.

These findings underline the importance of plasma HDL cholesterol values, and probably reverse cholesterol transport, as coronary risk factors in familial hypercholesterolaemic patients. In the general population, several epidemiological studies have demonstrated the importance of low HDL cholesterol plasma levels as an independent coronary risk factor\[^{29-31}\]. Familial hypercholesterolaemic subjects with alterations in HDL transport will have lower HDL cholesterol levels and more severe cholesterol deposits in atherosclerotic plaques, with a higher risk of myocardial infarction. In our study, familial hypercholesterolaemic subjects with coronary heart disease had lower HDL cholesterol levels and a higher prevalence of xanthomas, indicating higher cholesterol deposits in different tissues.

The observed differences in plasma HDL cholesterol levels among familial hypercholesterolaemia populations\[^{27,28}\] could be explained by interactions of environmental factors (i.e. obesity, diet, exercise) with LDL receptor status, by a direct effect of the type of LDL receptor mutations, or by a gene–gene interaction of LDL receptor mutations and other candidate genes.

Visceral fat accumulation, with low HDL cholesterol and high plasma triglyceride levels, was reported as a coronary risk factor in familial hypercholesterolaemic subjects in Japan\[^{32}\] and in French Canadian familial hypercholesterolaemic patients\[^{36}\]. Unfortunately, in our case/control study, we did not measure waist and hip circumferences. Visceral fat accumulation can be assessed by the waist/hip ratio or by computed tomography. We can speculate that our familial hypercholesterolaemic subjects would behave like French Canadian familial hypercholesterolaemics, whose visceral fat deposits were related to HDL cholesterol and triglyceride plasma values\[^{39}\]. Moreover, as suggested by Gaudet et al., a better assessment of coronary heart disease risk in familial hypercholesterolaemia should include fasting plasma insulin levels in addition to the waist to hip ratio\[^{39}\].

The effect of the LDL receptor on the clearance of chylomicron remnants and VLDL particles could directly influence plasma HDL cholesterol levels in familial hypercholesterolaemic subjects. Bowler et al. have demonstrated a 50% reduction in the clearance of chylomicron remnants in WHHL rabbits\[^{37}\], although Kita et al. showed normal clearance\[^{39}\]. In humans, a previous study from Cape Town\[^{35}\] in five homozygous familial hypercholesterolaemia subjects showed a normal clearance of chylomicron remnants. A more recent study in six Japanese homozygote familial hypercholesterolaemia subjects, a markedly delayed clearance of retinol-labelled triglyceride-rich lipoproteins following an oral fat load was demonstrated. In addition, the binding and clearance of chylomicron remnants by fibroblasts was substantially decreased compared with a control group\[^{36}\]. Also, Castro-Cabezas et al.\[^{37}\] reported, in heterozygous familial hypercholesterolaemia, a two-fold delay in the area under the curve for clearance of remnant particles. These differences in experimental and human studies could be explained by methodological differences, differences in LDL receptor mutations and/or as a result of the effects of genetic variations in other receptors or pathways involved in chylomicron remnant clearance. Thus, it is possible that familial hypercholesterolaemic subjects with null mutations could have a lower clearance of remnant particles (VLDL and LDL) and, as a result, higher levels of plasma triglycerides together with lower HDL cholesterol concentrations. In support of this hypothesis, the subgroup of familial hypercholesterolaemic subjects with null mutations studied by Vohl et al.\[^{37}\] presented the highest coronary heart disease risk. However, the hypothesis that familial hypercholesterolaemic subjects with null mutations have lower clearance rates of chylomicron and VLDL particles has not yet been supported by kinetic data.

Moreover, an interaction between LDL receptor mutations and the recently described proteins, SB-RI and ABC1, responsible for reverse cholesterol transport could, theoretically, explain differences in HDL cholesterol plasma values among familial hypercholesterolaemic subjects\[^{38,39}\]. In some familial hypercholesterolaemic patients, low HDL cholesterol levels can be explained by additional heterozygous inheritance of a mutant lipoprotein lipase gene\[^{40}\].

Our study has shown a relationship between LDL receptor gene null mutations and low HDL cholesterol values, as well as with triglyceride levels. The fact that familial hypercholesterolaemia with coronary heart disease showed significantly lower plasma HDL cholesterol values and a higher total cholesterol to HDL cholesterol ratio may carry therapeutic implications. In a recent secondary prevention trial in a high risk group of men with low plasma HDL cholesterol values, a moderate elevation of 6% in HDL cholesterol together with a 31% reduction in triglyceride plasma values with gemfibrozil was associated with a 22% decreased relative risk for coronary heart disease\[^{42}\].

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In conclusion, in familial hypercholesterolaemic subjects with similar clinical and genetic factors that could influence coronary heart disease risk, plasma HDL cholesterol values and total/HDL cholesterol ratios are two important coronary risk factors. Hence, treatment of familial hypercholesterolaemia should not only focus on lowering total and LDL cholesterol levels, but also on increasing HDL cholesterol for the prevention of coronary heart disease in this high risk group. More prospective and intervention trials should be conducted to establish the relationship between HDL cholesterol levels and coronary heart disease in familial hypercholesterolaemia.

References

[33] Bowler A, Redgrave TG, Mano JCL. Chylomicron remnants clearance in homozgyote and heterozygote Watanabe heredi-


