Relationships of Abdominal Obesity and Hyperinsulinemia to Angiographically Assessed Coronary Artery Disease in Men With Known Mutations in the LDL Receptor Gene

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Background—Patients with a mutation in the LDL receptor gene (familial hypercholesterolemia, or FH) are characterized by substantial elevations in plasma LDL cholesterol and are at higher risk of developing coronary artery disease (CAD). Correlates of abdominal obesity may also contribute to the risk of ischemic cardiac events. Whether the hyperinsulinemic–insulin-resistant state of abdominal obesity affects coronary atherosclerosis among FH patients has not been determined.

Methods and Results—The relation of abdominal adiposity and hyperinsulinemia to angiographically assessed CAD was evaluated in a sample of 120 French Canadian men aged ≤60 years who were heterozygotes for FH and in a group of 280 men without FH. In the present study, the risk of CAD associated with abdominal obesity, as estimated by the waist circumference, was largely dependent on the concomitant variation in plasma lipoprotein and insulin concentrations. In contrast, the association between fasting insulin and CAD was independent of variations in waist girth, triglyceride, HDL, and apolipoprotein B concentrations (odds ratio, 1.86; \( P = .0005 \)). However, the most substantial increase in the risk of CAD was observed among abdominally obese (waist circumference ≥95 cm) and hyperinsulinemic FH patients (odds ratio, 12.9; \( P = .0009 \)). This increase in risk remained significant even after adjustment for LDL cholesterol or apolipoprotein B concentrations.

Conclusions—Results of the present study provide support for the notion that the hyperinsulinemic–insulin-resistant state of abdominal obesity is a powerful predictor of CAD in men, even in a group of patients with raised LDL cholesterol concentrations due to FH. (Circulation. 1998;97:871-877.)

Key Words: hyperinsulinemia ■ obesity ■ hypercholesterolemia ■ coronary disease

Atherosclerosis is a primary feature of CAD, which remains one of the most important causes of morbidity and mortality in the world.1-3 Numerous risk factors contribute to the development of CAD, and the identification of individuals at risk has important public health implications.4-6 FH, which is a disorder generally associated with the premature development of CAD, is a monogenic dyslipidemia resulting from mutations in the LDL receptor gene.7 Features of heterozygous FH also include raised plasma LDL-C concentration and tendinous xanthomas. It has been generally considered that the greater prevalence and earlier manifestation of CAD among heterozygous FH patients was due to raised plasma LDL-C concentrations. However, these patients are also obviously subjected to genetic and environmental influences that may potentially exacerbate their cardiovascular risk.8-10 Among these additional factors, obesity is a condition that is highly prevalent in developed countries.

As opposed to FH, the contribution of obesity and hyperinsulinemia to the risk of CAD has been more difficult to define. Obesity is an important factor associated with the development of NIDDM11,12 and is also associated with alterations in carbohydrate and lipid metabolism as well as in coagulation factors that contribute to increase the risk of cardiovascular disease.13-15 However, there is now convincing evidence showing that the distribution of body fat, namely, abdominal fat deposition, is a more critical variable to consider than excess fatness in the relation of obesity to NIDDM, dyslipoproteinemia, and cardiovascular disease.15-17 The study of the anthropometric correlates of visceral adipose tissue deposition has revealed that the waist circumference is the best anthropometric correlate of visceral adipose tissue accumulation.17 On the other hand, whether hyperinsulinemia, which often accompanies abdominal obesity, is independently associated with ischemic heart disease remains a matter of debate. Indeed, analyses of the Paris Prospective Study cohort suggested that fasting insulinemia was no longer independently associated with ischemic heart disease after controlling for the abdomen-to-thigh ratio.18 However, data from the Quebec
Selected Abbreviations and Acronyms

apo = apolipoprotein
CAD = coronary artery disease
FH = familial hypercholesterolemia
HDL-C = HDL cholesterol
LDL-C = LDL cholesterol
Lp(a) = lipoprotein(a)
NIDDM = non–insulin-dependent diabetes mellitus
PCR = polymerase chain reaction
SLSJ = Saguenay–La–St–Jean
TG = triglycerides

Prospective Cardiovascular Study cohort suggested that the relation of hyperinsulinemia to ischemic heart disease may be largely independent of alterations in body weight, blood pressure, and plasma lipoprotein concentrations. It has been suggested that visceral obesity may be a common component of the cluster of metabolic abnormalities found in insulin-resistant subjects. This metabolic cluster also includes hypertension, low HDL-C, elevated apo B, elevated TG concentrations, impaired fibrinolysis, and impaired insulin-mediated glucose uptake. In this regard, it is likely that the components of the metabolic syndrome may add to the atherogenic potential of hypercholesterolemia due to raised LDL-C concentrations. However, the contribution of abdominal adiposity and hyperinsulinemia to CAD in patients with substantial increases in plasma LDL–C and apo B concentrations has never been specifically examined. In this regard, the present study focused on the effect of important correlates of the metabolic syndrome (namely, abdominal obesity and hyperinsulinemia) on the expression of CAD among well-characterized patients with raised LDL–C and apo B concentrations due to FH.

Methods

Study Design

The present study is a case-control analysis of the relationships of abdominal adiposity to angiographically assessed CAD among men with or without a mutation in the LDL receptor gene. The study population was derived from all unrelated patients aged <60 years who had been monitored at the Chicoutimi Hospital Lipid Clinic (Chicoutimi, Quebec, Canada) between January 1991 and January 1996 and who underwent coronary angiography for the investigation of ischemic heart disease (typical angina or a positive exercise tolerance test or both) (n=1014). The diagnosis of FH was based on the following: (1) the presence of a mutation in the LDL receptor gene; (2) the presence of a mutation in the LDL receptor gene in a first-degree relative and either typical tendinous xanthomata or plasma LDL-C above the 95th percentile in the absence of a secondary cause of hypercholesterolemia; or (3) LDL-C above the 95th percentile as well as tendinous xanthomata and a family history of raised plasma LDL-C transmitted in an autosomal dominant pattern. Patients with a mutation in the LDL receptor gene (case subjects) were matched on the basis of age and smoking with 2 or 3 patients without FH who underwent coronary angiography over the same period (control subjects). The mean difference for age between matched case and control subjects was 0.7 year. All nonsmokers were matched with nonsmokers. Patients were excluded if they were homozygous for FH (n=1), if they had a known mutation in the LDL gene (n=37), if they had a diagnosis of diabetes mellitus before angiography (n=105), or if they were receiving lipid-lowering or thyroid medication during the month preceding the lipid-lipoprotein measurements (n=188). According to these criteria, 120 patients with raised plasma LDL-C concentrations were included in the FH group whereas 280 patients remained in the non-FH group. To control for spurious associations that may arise from population admixture, all patients selected were born in the SLSJ region located in the eastern part of the province of Quebec, Canada. The prevalence of FH in the SLSJ population is six-fold higher than what has been reported in most other populations (1.2% versus 0.2%).

Regarding the assessment of coronary stenosis, four coronary arteries were considered: left main coronary, left anterior descending, circumflex, and right coronary. Patients with ≥1 lesion leading to a narrowing of at least 50% of the lumen of any of these four coronary arterial segments were considered as having coronary stenosis. Results of coronary angiograms were also analyzed by use of a score based on the number of diseased vessels. This score ranged from 0 (no vessel with at least 50% narrowing) to 4 (all four vessels with at least 50% narrowing). Interpretation of coronary angiograms was performed independently by two cardiologists and one radiologist who were not aware of the patients’ inclusion in the study. This project received the approval of the Chicoutimi Hospital Ethics Committee.

Mutations in the LDL Receptor Gene

All patients from the present study were screened for the presence of mutations in the LDL receptor gene after obtaining their informed written consent. Almost 90% of FH cases in the SLSJ could be attributed to only two mutations: (1) a missense mutation in exon 3 (W66G), leading to an impaired lipoprotein binding (class III mutation), and (2) a deletion of >15 kb in the promoter and exon 1, which is a receptor negative mutation due to the absence of transcriptional signal (class I mutation). However, screening of FH included detection of the six mutations explaining the majority of cases in the province of Quebec, namely, two deletions (5 kb and >15 kb) and four point mutations in exons 3, 4, 10, and 14, respectively. The detection of the two deletions was performed by Southern blotting as described by Ma et al. The presence of point mutations in exons 3, 4, and 14 was detected by dot-blot hybridization of genomic DNA amplified by PCR with allele-specific oligonucleotide probes, according to Leitersdorf et al, or by PCR-based restriction fragment analysis according to Vohl et al. The presence of the nonsense stop 468 mutation in exon 10 was detected by PCR-based restriction fragment analysis according to Vohl et al.

Estimation of Abdominal Fat Deposition and Evaluation of Other Risk Factors

Biological and lifestyle variables as well as medical and nutritional histories were obtained through questionnaires and physical exams performed at the Chicoutimi Hospital Lipid Clinic by trained nurses, dietitians, and physicians. Waist and hip circumferences were measured according to the procedures recommended at the Anife Conference. Body weight and height were recorded, and the body mass index was calculated in kilograms per meter squared. Fasting plasma glucose was enzymatically measured, whereas fasting insulinemia was measured by radioimmunoassay with polyethylene glycol separation. Individuals diagnosed as having NIDDM were excluded when one of the following criteria was met: (1) previously established diagnosis of NIDDM; (2) two fasting glucose values ≥7.8 mmol/L obtained before the coronary angiogram; or (3) at least one value >11.1 mmol/L during a 75-g oral glucose tolerance test. Smoking habits were defined as follows: (1) men who never smoked and (2) men who ever smoked. Men who ever smoked were further classified into three categories (0 to 10 cigarettes/d, 11 to 25 cigarettes/d, and >25 cigarettes/d). A subject was considered hypertensive if diagnosis of essential hypertension had been previously established or when three values of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg were recorded in the patient’s medical chart. Resting blood pressure measurements were performed after the subjects had a 5-minute rest in a sitting position, phases I and V of Korotkoff sounds being used for systolic and diastolic blood pressure, respectively. Alcohol consumption was defined in two categories: (1) regular drinkers (>5 ounces of absolute alcohol/wk) and (2) nonregular drinkers. A family history of premature coronary atherosclerosis was defined as the presence of symptomatic ischemic heart disease or...
coronary death in a first-degree relative aged <55 years (male relative) or <60 years (female relative).

**Plasma Lipid-Lipoprotein Measurements**

Blood samples were obtained the morning after a 12-hour overnight fast from an antecubital vein into evacuated container tubes containing EDTA. Total cholesterol, TG, and HDL-C levels were measured with the use of enzymatic assays. TC was determined in serum and HDL-C was measured in the supernatant after precipitation of the apo B–containing lipoproteins with dextran sulfate and magnesium chloride. LDL-C was calculated by use of the Friedewald formula when TG levels were <5 mmol/L, and subjects with TG >5 mmol/L were excluded from the present study. Plasma apo B levels were measured according to the rocket immunoelectrophoretic method of Laurell. Serum standards for apo B determinations were prepared in our laboratory and calibrated against sera from the Centers for Disease Control (Atlanta, Ga). Standards were lyophilized and stored at −85°C until use. Peak heights between 15 and 35 mm yielded linear and reliable results. Lp(a) levels were measured on an Array 360 system using LPA reagent (P/N 465360) and LPA Cal (P/N 465365) obtained from Beckman Instruments Inc.

**Statistical Analyses**

Differences in continuous variables between groups were compared either by Student’s unpaired two-tailed test or by ANOVA with the use of the Bonferroni procedure for pairwise comparisons. Categorical variables were compared with the χ² test. Associations between potential correlates of abdominal fat deposition were quantified by use of Pearson or Spearman correlation coefficients for parametric and nonparametric variables, respectively. Finally, conditional logistic regression models were constructed to investigate the independent relationship between CAD, considered as the dependent variable, and correlates of abdominal adiposity. The effect of risk factors for CAD as possible confounders was taken into account in the different analyses, and adjustments were used for any significant (P < .1) effect of class of mutation in the LDL receptor gene, hypertension, fasting glucose concentration, alcohol consumption, or use of medication (β-blockers and diuretics). The matching variables did not modify the estimates of the association between other risk factors and CAD. Furthermore, conditional logistic regression analysis, which allows the removal of the confounding factors introduced by the matching, yielded results that were the same as those of the unconditional regression analyses. For these reasons, age and smoking were excluded from the regression models. In all analyses, plasma TG and insulin data were log₁₀-transformed to normalize their distribution. Analyses were performed with the use of the SPSS package (release 6.1, SPSS Inc).

**Results**

Characteristics of men with or without FH who underwent coronary angiography are presented in Table 1. Compared with non-FH men, men with a mutation in the LDL receptor gene tended to be younger at the time of first coronary angiography and more severely affected by CAD as assessed by the proportion of patients having four diseased vessels. Furthermore, FH patients had higher plasma Lp(a), LDL-C, and apo B concentrations. However, plasma HDL-C levels were similar in the two groups, whereas plasma TG concentrations were significantly higher among patients without FH (P=.03). Patients without FH also had higher fasting insulin levels and were more obese as a group than FH patients.

**Correlation coefficients between variables potentially related to abdominal fat deposition revealed that the waist circumference was more closely related to metabolic variables than the waist-to-hip ratio (data not shown). Thus, the waist girth was used in the remainder of the analyses to estimate the contri-

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>FH n=120</th>
<th>Non-FH n=280</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46.7±0.7</td>
<td>46.9±0.4</td>
<td>.58</td>
</tr>
<tr>
<td>Age at first coronary angiography</td>
<td>43.6±0.7</td>
<td>45.6±0.4</td>
<td>.04</td>
</tr>
</tbody>
</table>

**Variables**

- ** BMI, kg/m²:** 26.0±0.3
- **Waist circumference, cm:** 92.3±0.8
- **Waist-to-hip ratio:**
- **Mean blood pressure, mm Hg:** 93.0±13.6
- **TC, mmol/L:** 8.3±1.6
- **LDL-C, mmol/L:** 6.4±0.2
- **HDL-C, mmol/L:** 0.88±0.02
- **TG, mmol/L:** 2.1±0.1
- **Apo B, g/L:** 1.51±0.03
- **Lp(a), mg/dL:** 43.3±3.9
- **Fasting insulin, mU/L:** 16.2±0.8
- **Fasting glucose, mmol/L:** 5.5±1.1

**BMI indicates body mass index; TC, total cholesterol.**

* Geometric mean and approximate SEM. P values after log-transformations.
bution of abdominal obesity. The contribution of an increased waist girth to the variation of common metabolic risk factors is illustrated in Fig 1. In both FH and non-FH patients, a bigger waistline tended to be associated with elevated plasma insulin and TG levels as well as with a reduction in plasma HDL-C concentration. However, for a given waist girth, no difference in plasma insulin, TG, or HDL-C levels was noted between FH and non-FH patients. Nevertheless, plasma apo B concentrations were obviously higher in FH patients, irrespective of the waist circumference. In the present study, 60% of men with FH presented a receptor defective mutation (W66G) in exon 1 and the promoter, and 12.5% presented other mutations in exons 4, 7, 10, and 14, respectively. However, the nature of the mutation in the LDL receptor gene did not alter the expression of coronary atherosclerosis. The nature of the mutation in the LDL receptor gene did not alter the expression of coronary atherosclerosis. The nature of the mutation in the LDL receptor gene did not alter the expression of coronary atherosclerosis. The nature of the mutation in the LDL receptor gene did not alter the expression of coronary atherosclerosis. The nature of the mutation in the LDL receptor gene did not alter the expression of coronary atherosclerosis.

Results of the present study indicate that the combination of hyperinsulinemia and abdominal obesity substantially increased the risk of coronary stenosis among FH patients. However, the risk associated with an increased waist girth in FH was largely explained by the lipid abnormalities that are common among obese, insulin-resistant men, whereas the association of insulin with CAD was at least partly independent of these lipid abnormalities. Overall, men with FH who were characterized by a higher level of coronary stenosis and a lower prevalence of modifiable cardiovascular risk factors than non-FH men, suggesting that mutations in the LDL receptor remain a major cause of CAD among young adults.

FH is a monogenic trait due to mutations in the LDL receptor gene, characterized by raised plasma LDL-C concentrations and tendinous xanthomas. CAD is an early event in heterozygous FH, and 45% to 48% of men and 20% to 21% of women develop coronary atherosclerosis before age 50. It is well known that the nature of the mutation in the LDL receptor gene may affect the expression of coronary athero-
sclerosis. Indeed, recent studies in homozygous as well as heterozygous FH patients have shown that null (class I) mutations are associated with higher plasma cholesterol levels and with earlier manifestations of CAD than missense (class III) mutations. However, the expression of CAD in FH patients not only is determined by the nature of the gene defect but also is influenced by other risk factors, an issue that has been emphasized by many investigators. In the present study, however, the nature of the mutation did not alter the relation of abdominal adiposity to CAD. Furthermore, abdominal obesity, as assessed by waist girth, was associated with numerous metabolic alterations among FH patients: lower plasma HDL-C, higher TG levels, and higher fasting insulin concentrations. The cosegregation of obesity, dyslipidemia, and hyperinsulinemia among families of obese subjects is well documented, and numerous studies have shown that a preferential accumulation of abdominal fat is associated with a metabolic cluster that may contribute to substantially increase the risk of atherosclerotic cardiovascular disease.

In the present study, although average waist circumference and fasting insulin values tended to be significantly lower in FH than in non-FH patients, the contribution of hyperinsulinemia, abdominal obesity, and CAD was evident in FH, and the absolute effect of hyperinsulinemia on CAD among FH patients appeared to be significantly affected by a higher waistline. Small, dense LDL particles, hypertriglyceridemia, and low plasma HDL-C are conditions that are quite prevalent among abdominally obese insulin-resistant patients, and this dyslipidemic profile has been reported to be associated with an increased risk of CAD. In this regard, obese and hyperinsulinemic FH patients are potentially exposed over time to both the quantitative atherogenicity and qualitative alterations of apo B-containing lipoproteins. Indeed, the combination over time of an increased number of LDL particles in circulation, which is a feature of FH, together with the presence of a greater proportion of denser and otherwise modified LDL, which often accompanies the abdominally obese, insulin-resistant state, is likely to increase the risk of CAD in FH.

### TABLE 2. Multivariate Analysis of the Relationships of FH With CAD Before and After Adjustment for Correlates of Abdominal Fat Deposition, Plasma Lipids, Apo B, and Fasting Insulin Levels

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (Baseline Model)</th>
<th>Model 2 (Model 1 and Waist Girth)</th>
<th>Model 3 (Model 2 and TG)</th>
<th>Model 4 (Model 3 and HDL-C)</th>
<th>Model 5 (Model 4 and Insulin)</th>
<th>Model 6 (Model 5 and Apo B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>β</td>
<td>0.72</td>
<td>0.83</td>
<td>0.83</td>
<td>0.78</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>2.07</td>
<td>2.29</td>
<td>2.29</td>
<td>2.19</td>
<td>2.31</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>.002</td>
<td>.0008</td>
<td>.0009</td>
<td>.001</td>
<td>.0008</td>
</tr>
<tr>
<td>Waist girth, cm</td>
<td>β</td>
<td>2.09</td>
<td>1.46</td>
<td>1.41</td>
<td>0.82</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>8.09</td>
<td>4.31</td>
<td>4.10</td>
<td>2.27</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>.04</td>
<td>.10</td>
<td>.20</td>
<td>.47</td>
<td>.60</td>
</tr>
<tr>
<td>TG (log)</td>
<td>β</td>
<td>0.14</td>
<td>0.10</td>
<td>0.07</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>1.15</td>
<td>1.11</td>
<td>1.08</td>
<td>1.11</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>.10</td>
<td>.30</td>
<td>.46</td>
<td>.29</td>
<td>.29</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>β</td>
<td>-0.94</td>
<td>-0.73</td>
<td>-0.73</td>
<td>-0.62</td>
<td>-0.62</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>0.38</td>
<td>0.48</td>
<td>0.54</td>
<td>0.38</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>.05</td>
<td>.15</td>
<td>.19</td>
<td>.05</td>
<td>.19</td>
</tr>
<tr>
<td>Fasting insulin (log)</td>
<td>β</td>
<td>0.62</td>
<td>0.58</td>
<td>0.58</td>
<td>0.62</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>1.86</td>
<td>1.79</td>
<td>1.79</td>
<td>.0005</td>
<td>.0007</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>.0005</td>
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</tr>
<tr>
<td>Apo B, g/L</td>
<td>β</td>
<td>0.78</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Odds ratio</td>
<td>2.10</td>
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<tr>
<td></td>
<td>P</td>
<td>.05</td>
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For variables showing a continuous distribution, odds ratios are expressed as the increase in the risk of CAD associated with a 1-SD increase in the variables studied. β denotes the standardized estimate, which is the parameter estimate of each variable in the multivariate logistic model. All models included the following covariates when probability values were <.1: hypertension, family history of CAD, alcohol consumption (>5 oz/wk), fasting glycemia, and use of medication (β-blockers or diuretics). The study design eliminated the potentially confounding effects of age and smoking on the risk of ischemic heart disease. Only the variables included in each model are shown.
hyperinsulinemia to CAD also could not be explained by the presence of Lp(a) concentration, before (top) and after (bottom) adjustment for plasma LDL-C and apo B concentrations. Odds ratios are from a logistic regression model, controlling for the covariates identified in Table 2. Low indicates waist circumference $<50$th percentile (95 cm); High, waist circumference $>$50th percentile (95 cm).

Indeed, previous studies clearly demonstrated that in addition to elevated LDL-C concentrations, elevated plasma TG levels (type IIB dyslipidemia) contribute to the severity of coronary ischemic disease among FH heterozygotes. Furthermore, the density of LDL has been proposed recently as an independent predictor of CAD risk in the Quebec Cardiovascular Study. However, in the FH patients of the present study, fasting TG concentration was not independently associated with CAD, a finding generally consistent with most of the literature on non-FH patients. The increased CAD risk associated with abdominal obesity and hyperinsulinemia found in FH patients of the present study could not be explained by a concomitant elevation in Lp(a) levels. The contribution of abdominal obesity and hyperinsulinemia to CAD also could not be explained by the presence of known defects in the LPL gene that are quite prevalent among French Canadians, because patients bearing these mutations were excluded from the present study.

In conclusion, results of the present study provide further support to the notion that hyperinsulinemia is a powerful predictor of coronary heart disease in men, even among heterozygous FH patients with well-defined genetic defects and substantial elevations in plasma LDL-C concentrations. Furthermore, abdominal obesity and hyperinsulinemia appear to act synergistically to substantially increase the odds of CAD among men with FH. This finding suggests that the estimation of abdominal adipose tissue deposition, at least by measurement of waist circumference, must be considered important in the evaluation of the cardiovascular risk profile, even among FH patients. Furthermore, it is proposed that results of the present study have important therapeutic implications. Indeed, because abdominal obesity and hyperinsulinemia appear to be important risk factors for CAD even among well-characterized FH patients and even after controlling for LDL-C and apo B concentrations, emphasis should not only be placed on the relevant and justified lowering of LDL concentrations but also on the treatment of abdominal obesity and the related insulin-resistant hyperinsulinemic state for an optimal reduction of CAD risk. Finally, further studies are required to verify whether these conclusions derived from the study of male FH patients are also valid for women with FH.

Acknowledgments

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References


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