Nonobese Patients With Familial Combined Hyperlipidemia Are Insulin Resistant Compared With Their Nonaffected Relatives


Abstract Familial combined hyperlipidemia (FCH) is a heterogeneous lipid disorder caused by overproduction of VLDL and characterized by the occurrence of small, dense LDL particles, all features that are also associated with insulin resistance. Therefore, insulin sensitivity was examined directly by means of the euglycemic hyperinsulinemic clamp technique in male nonobese, normotensive FCH patients and compared with that of their nonaffected relatives, matched for age and body mass index (BMI). In addition, an oral 75-g glucose tolerance test (OGTT) was performed and lipid values, including the LDL subfraction profile, were determined. During the clamp, forearm blood flow (FBF) was measured by venous occlusion plethysmography. All participants had a normal glucose response after the glucose load, whereas FCH patients showed hyperinsulinemia after OGTT and higher fasting C-peptide levels. During the clamp, insulin concentrations increased equally in both groups. Mean whole-body glucose uptake (M) (120 to 180 minutes) was lower in FCH patients than in nonaffected relatives (6.89±0.31 versus 8.94±0.76 mg · kg⁻¹ · min⁻¹; P=.01). In addition, the glucose uptake per unit insulin (I) was lower in FCH patients (insulin sensitivity index [M/I], 7.46±0.50 versus 9.51±0.53; P=.009). M significantly correlated with BMI, plasma cholesterol and triglyceride concentrations, and the individual LDL density. The FBF correlated with insulin sensitivity and increased significantly in nonaffected relatives (1.9±0.12 to 2.5±0.4 mL · min⁻¹ · dl⁻¹; P=.025) but not in patients. Thus, FCH patients characterized by a predominance of small, dense LDL are insulin resistant compared with their nonaffected relatives. This insulin resistance may partly be explained by a decreased insulin-induced vasodilation in skeletal muscle. (Arterioscler Thromb Vasc Biol. 1997;17:1465-1471.)

Key Words • familial combined hyperlipidemia • insulin clamp • small, dense LDL

Familial combined hyperlipidemia is a common heritable and heterogeneous lipid disorder characterized by the presence of a multiple-type hyperlipidemia with elevated plasma cholesterol and/or plasma triglyceride levels and the frequent occurrence of premature cardiovascular disease in first-degree relatives. Originally, FCH was supposed to be caused by the variable expression of a single autosomal dominant gene primarily regulating plasma triglyceride levels and secondarily affecting cholesterol levels. However, several metabolic and biochemical defects that have recently been related to the trait suggest that the genetic basis of FCH is more heterogeneous. As a consequence, the spectrum of FCH also comprises other related phenotypes, such as hyperapobetalipoproteinemia, the LDL subclass pattern B phenotype, familial dyslipidemic hypertension, and some features of the insulin resistance syndrome.

Insulin resistance, defined as a decreased ability of insulin to stimulate glucose uptake, is increasingly recognized as a common factor underlying various conditions, all of which predispose to coronary heart disease. Resistance to normal action of insulin is related to alterations in lipid metabolism such as an excessive postprandial release of NEFAs due to impaired suppression of hormone-sensitive lipase activity. An increased supply of fatty acids to liver cells is associated with VLDL overproduction, whereas an impaired activation of lipoprotein lipase adds to reduced clearance of triglyceride-rich lipoproteins. In addition, insulin resistance may coincide with a predominance of small, dense LDL, as demonstrated in some studies, although this observation has been counteracted by others. Since these features (ie, VLDL overproduction, impaired lipoprotein lipase activity, and a predominance of small, dense LDL) are also characteristics of FCH, the existence of insulin resistance may be an important factor modulating FCH phenotypes. The interpretation of data concerning the association between insulin sensitivity and lipid disturbances is, however, hampered by the fact that several features related to lipid disorders, such as visceral obesity, age, sex, hypertension, and existence of cardiovascular disease, are themselves also associated with insulin resistance. Furthermore, hyperinsulinemia, as a consequence of insulin resistance, has been directly associated with cardiovascular disease.

Recent reports hypothesized that diminished glucose uptake may partly be explained by a decreased insulin-induced vasodilation in skeletal muscle. Furthermore, insulin’s effect on vascular tone has been reported to be nitric oxide dependent. Interestingly, in dyslipidemic patients, endothelium-dependent vasodilation has been shown to be diminished.

Several earlier reports have suggested the presence of insulin resistance in various forms of hyperlipidemia. However, these findings were either based on rather indirect measurements such as determination of plasma
nation of the individual distribution of LDL subfractions in the
more, blood was sampled for determination of baseline values
homozygous for the apoE2 allele.
75th percentile for age and sex. None of the subjects was
plasma cholesterol and triglyceride concentrations below the
demias was based on the presence of constant elevated choles­
or a combined hyperlipidemia. The assessment of hyperlipi­
tives (nine were brothers; two were cousins) had both total
and sex after dietary advice and after withdrawal of lipid-
and triglyceride concentrations above the 90th percentile for age
quality cardiovascular disease before the age of 60 years.
relatives, with at least two first-degree relatives with a different
patients and two relatives were habitual smokers.
measurement criteria: BMI <27 kg/m2; blood pressure <165/90 mm Hg
subjects were apparently healthy and met the following inclu­
unaffected) for age, BMI, and waist-to-hip ratio. In addition, all
scores were determined using a commercially available ACS-
conformed by obesity of the study group,9 or obtained by steady state plasma glucose and insulin concentration
determinations after somatostatin administration.7 Somatostatin in itself may exhibit vascular effects.
Therefore, in this study we have determined the sensitiv­
ty to the metabolic and hemodynamic effects of insulin
directly by means of the euglycemic hyperinsulinemic
combined technique in combination with skeletal blood flow
measurements. The studies were performed in a care­
fully selected sample of well-defined nonobese normo­
tensive male FCH patients, which were compared with
matched unaffected relatives.

Methods

Subjects

For this study, initially 12 unrelated nonobese normotensive
male FCH patients, selected from an available sample of well-
defined Dutch FCH families, were compared with one of their
nonaffected male relatives. To anticipate environmental influ­
ences, we carefully matched related individuals (ie, affected and
unaffected) for age, BMI, and waist-to-hip ratio. In addition, all
subjects were apparently healthy and met the following inclu­
sion criteria: BMI <27 kg/m2; blood pressure <165/90 mm Hg
(measured in the supine position after 5 minutes’ rest); absence
of diabetes mellitus, a medical history of vascular disease, and
use of any medication except lipid-lowering drugs, which were
discontinued at least 1 month before participation. Two FCH
patients and two relatives were habitual smokers.

The FCH diagnosis was based on the following criteria: (1)
the presence of a multiple-type hyperlipidemia in first-degree
relatives, with at least two first-degree relatives with a different
hyperlipidemia (ie, hypertriglyceridermia, hypercholesterolemia,
or a combined hyperlipidemia). The assessment of hyperlipi­
demia was based on the presence of constant elevated choles­
terol and/or triglyceride levels above the 90th percentile, in
spite of dietary advice24; (2) a positive family history of prematu­
re cardiovascular disease before the age of 60 years.

Participating FCH patients had both total plasma cholesterol
type and triglyceride concentrations above the 90th percentile for age
and sex after dietary advice and after withdrawal of lipid-
lowering drugs for at least 4 weeks. In contrast, unaffected rela­
tives (nine were brothers; two were cousins) had both total
plasma cholesterol and triglyceride concentrations below the
75th percentile for age and sex. None of the subjects was
homozygous for the apoE2 allele.

Protocol and Procedures

All participants were asked to visit the department twice after
an overnight fast. During a first visit, a questionnaire was filled
out to collect information on medical status, and supine blood
pressure, BMI, and waist-to-hip ratio were measured. Fur­
thermore, blood was sampled for determination of baseline values
for lipids, lipoproteins, HbA1c, and C-peptide and for determi­
nation of the individual distribution of LDL subfractions in the
LDL subfraction profile. Moreover, a 75-g OGTT was per­
formed to exclude impaired glucose tolerance or overt diabetes
mellitus. In these tests, glucose and insulin concentrations were
determined at baseline and 30, 60, 90, and 120 minutes after the
insulin load. Only when participants showed 2-hour postload
glucose levels ≤7.8 mmol/L was a hyperinsulinemic euglycemic clamp
performed, combined with hemodynamic measurement of
blood pressure, heart rate, and FBF, during a second visit, 1 to 2
weeks later. After OGTT, one FCH patient and his related con­
trol subject were excluded from further analyses due to impaired
glomerular filtration rate of this FCH patient (2-hour glucose level of
0.2 mmol/L). The experimental protocol was approved by the
ethical committee of our hospital, and all participants gave their
written informed consent.

Euglycemic Hyperinsulinemic Clamp

Experiments were performed with the participants in the
supine position in a quiet, temperature-controlled room (24°C to
25°C). Under local anesthesia (0.3 to 0.4 mL lidocaine HCl, 20
mg/mL), a 20-gauge catheter (Angiocath, Deseret Medical Inc,
Becton Dickinson) was inserted into the left brachial artery and
connected with an arterial pressure monitoring line (Viggo
Catalog No. 992399A/14368) to a Hewlett Packard monitor
(type 78335B, Hewlett Packard GmbH). MAP was determined
by an electronically integrated area under the brachial arterial
pulsed-wave form. The arterial line was kept patent with saline
infusion (with 2 U heparin per milliliter added). On the con­
trolateral side, an identical venous catheter was inserted into a
large forearm vein for infusion of insulin and glucose. Insulin
(Actrapid, Novo-Nordisk) was infused in a dose of 60 mU/m2
per minute for 180 minutes. Insulin was diluted in 50 mL 0.9% NaCl
with addition of 2 mL albumin, to a concentration of 1
U/mL. According to the clamp technique,25 plasma glucose
concentration was kept at a euglycemic level by a variable infusion
of glucose 20% solution, adjusted by arterial plasma glucose
levels measured at 5-minute intervals. All subjects were
clamped at fasting glucose levels minus 0.3 mmol/L. The glu­
cose infusion rate was calculated as the given amount of glucose
in milliliters per kilogram body weight per minute, which equals
M. The glucose uptake per plasma unit of insulin (1) insulin
sensitivity index, calculated as M/I was determined as an addi­
tional measure of insulin sensitivity. In addition, the concen­
trations of NEFAs were determined before and at the end.

FBF Measurement

FBF was measured using a mercury-in-silicone elastomer
strain-gauge venous occlusion plethysmography on both arms as
previously described.26 One minute before the start of the mea­
measurements (which were taken every 30 minutes), a wrist cuff
was inflated to 100 mm Hg above the systolic blood pressure, to
be sure that the measurement referred only to the forearm skele­
tal muscle vascular bed.27 The collecting cuff around the upper
arm was inflated to a pressure of 45 mm Hg during 8 to 10 heart
cycles by using a rapid cuff inflator (Hokanson E20) rapid cuff
inflator, Hokanson Inc). The strain gauges were connected to a
plethysmograph (Hokanson EC4 plethysmograph, Hokanson
Inc). Changes in FBF during the clamp procedure were calcu­
lated with the means of the left and right FBF.

Analytical Methods

Glucose concentrations were measured in duplicate by using
the oxidation method (Beckman Glucose Analyzer2, Beck­
man Instruments Inc). Plasma insulin concentrations were deter­
mined using an "in-house" assay (double antibody method) with
an interassay variability of 6%. C-peptide was determined using
a commercial double antibody kit (Diagnostic Products Corp,
catalog No. KPED1 double antibody), with an interassay vari­
ability of 4.3%. HbA1c was determined with a high-perform­
ance liquid chromatography technique (Biorad Laboratories),
with a reference range of 4.8% to 6.2%. The concentrations of
NEFAs were determined using a commercially available ACS-
ACOD method (Waco Chemicals GmbH, catalog No. 994-
75409). Total plasma cholesterol and triglyceride concentrations were determined by commercially available enzymatic reagents (Boehringer-Mannheim, catalog No. 237574 and Sera Pak, catalog No. 6639, respectively). VLDL was isolated from whole plasma by sequential ultracentrifugation at d=1.019 g/mL for 16 hours at 36,000 rpm in a fixed-angle rotor (TFF 45.6 rotor, Kontron) in a Beckman L7-55 ultracentrifuge (Beckman). HDL cholesterol was determined with the polyethylene glycol 6000 method. 26 LDL cholesterol was calculated by subtraction of VLDL and HDL cholesterol from total plasma cholesterol. Total plasma apolipoprotein B was determined by immunonephelometry. 26 To achieve accurate results in relation to the Centers for Disease Control Lipid Standardization Program, the obtained plasma apoB results were recalculated on the basis of exchange of sera with Dr S. Marcovina (Northwest Lipid Research Laboratory, Seattle, Wash). LDL subfractions were detected by single-spin density-gradient ultracentrifugation, according to a method described elsewhere. 30,31 After ultracentrifugation, up to five LDL subfractions, stained with Coomassie brilliant blue R, were visible as distinct bands in the middle of the tube. Accurate documentation of the different LDL subfraction patterns was obtained by scanning slides of the tubes in triplicate on an LKB 2202 ultrascan laser densitometer (Pharmacia LKB). The mean peak heights (h1 to h5) of the LDL subfractions (LDL1 to LDL5) on the three scans were used to calculate a continuous variable K (−1<K<1), as described elsewhere. 32,33 This continuous variable K appeared to reflect appropriately the individual LDL subfraction profiles. 32,33 A negative K value (−1<K<0) reflects an LDL subfraction profile more or less predominated by small, dense subfractions. A profile with a predominance of buoyant LDL subfractions reveals a positive K value (0<K<1).

### Statistical Analysis

Differences in baseline characteristics and baseline values for lipid, lipoproteins, glucose, and HbA1c were tested by the nonparametric two-sample Wilcoxon signed rank test. The results of the glucose tolerance test were tested by comparing areas under the curve of both the glucose excursion curve and the insulin response. To compare M and the insulin sensitivity index of the affected with that of the unaffected subjects, controlling for possible influence of confounding variables, an ANOVA was performed, with age, BMI, and waist-to-hip ratio as covariates. To investigate differences in the time of action of insulin on hemodynamic parameters between the two groups, the time/group interaction was calculated by repeated-measures ANOVA, with insulin as the dependent factor. All statistical analysis were performed using the SPSS/PC+ program (SPSS Inc). Results in tables and figures are presented as mean±SEM unless otherwise indicated. Differences with a test value <.05 were considered to be significant.

### Results

#### Baseline Characteristics

Baseline characteristics of both 11 FCH patients and their 11 nonaffected relatives are presented in Table 1. Age, BMI, waist-to-hip ratio, and blood pressure were not different between the groups. As a consequence of the selection procedure, all lipid and lipoprotein concentrations (except the LDL cholesterol concentration) were less predominated by small, dense subfractions. A profile with a predominance of buoyant LDL subfractions reveals a positive K value (0<K<1).

#### Table 1. Baseline Anthropomorphic Measurements; BP; and Lipid, Lipoprotein, and ApoB Levels in FCH Patients and Their Unaffected Relatives

<table>
<thead>
<tr>
<th></th>
<th>Affected</th>
<th>Unaffected</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41.9±9.0</td>
<td>44.9±11.5</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.9±1.2</td>
<td>24.3±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.99±0.05</td>
<td>1.00±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>122.7±11.7</td>
<td>132.7±16.5</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>79.5±6.9</td>
<td>81.8±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total chol*</td>
<td>7.70±1.01</td>
<td>5.59±0.85</td>
<td>.003</td>
</tr>
<tr>
<td>Total TG*</td>
<td>3.73±2.50</td>
<td>1.24±0.43</td>
<td>.003</td>
</tr>
<tr>
<td>VLDL chol*</td>
<td>1.90±1.40</td>
<td>0.50±0.29</td>
<td>.003</td>
</tr>
<tr>
<td>VLDL TG*</td>
<td>2.80±2.14</td>
<td>0.71±0.41</td>
<td>.003</td>
</tr>
<tr>
<td>LDL chol*</td>
<td>4.90±1.39</td>
<td>4.03±0.88</td>
<td>.006</td>
</tr>
<tr>
<td>HDL chol*</td>
<td>0.89±0.17</td>
<td>1.20±0.15</td>
<td>.006</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>178.9±45.3</td>
<td>122.8±26.8</td>
<td>.003</td>
</tr>
<tr>
<td>K value</td>
<td>−0.92±0.13</td>
<td>−0.06±0.24</td>
<td>.004</td>
</tr>
</tbody>
</table>

*BP* indicates blood pressure; chol, cholesterol; TG, triglyceride; and NS, not significant. All values except n and waist-to-hip ratio are means±SD.

#### Table 2. Baseline Concentrations of Parameters of Glucose Metabolism in 11 FCH Patients and 11 Unaffected Relatives

<table>
<thead>
<tr>
<th></th>
<th>Affected</th>
<th>Unaffected</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L</td>
<td>5.45±0.12</td>
<td>5.22±0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>8.55±0.95</td>
<td>7.00±0.98</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.45±0.10</td>
<td>5.36±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>C peptide, nmol/L</td>
<td>0.65±0.03</td>
<td>0.47±0.04</td>
<td>.02</td>
</tr>
<tr>
<td>insulin-to-glucose ratio</td>
<td>1.57±0.18</td>
<td>1.35±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>NEFA</td>
<td>0.86±0.16</td>
<td>0.75±0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant. All values except those for l-to-glucose ratio are means±SEM.

Fig 1. Results of the 75-g OGTT in 11 FCH patients and 11 unaffected relatives. Upper panel, mean glucose curves of FCH patients (■) and unaffected control subjects (□). Calculated areas under the curve were not significantly different, but mean glucose concentration at 120 minutes was significantly higher in patients than in control subjects. Lower panel, mean insulin response curves of FCH patients (■) and unaffected control subjects (□). Calculated areas under the curve were significantly higher in FCH.
significantly higher in FCH patients than in the unaffected relatives. Total plasma apoB was also higher in FCH patients than in unaffected relatives. The K value, as a description of the LDL subfraction profile, was more negative in FCH patients than in unaffected relatives, corresponding with the predominance of small, dense LDL particles in FCH patients.

Responses to Oral 75-g Glucose Load

Baseline values of fasting glucose, fasting insulin, HbA1C, C-peptide, and the calculated insulin-to-glucose ratio are presented in Table 2. C-peptide concentrations were significantly higher in FCH patients than in their unaffected relatives. Concentrations of glucose, insulin, HbA1C, and insulin-to-glucose ratio all tended to be higher in FCH patients than in the unaffected relatives, but these differences did not reach significant levels. Glucose concentrations after oral glucose load were comparable in both groups (Fig 1), although a significantly higher glucose concentration after 2 hours was observed in FCH patients compared with the control subjects (5.73±0.52 mmol/L versus 4.36±0.29 mmol/L, P=0.019). Plasma insulin responses during the 2 hours after the oral glucose load, also presented in Fig 1, were significantly higher in patients than control subjects. All included participants had a normal glucose tolerance by exhibiting plasma glucose levels <7.8 mmol/L 2 hours after an oral 75-g glucose load.

Metabolic Response to Clamp Procedure

Plasma glucose values during the last 60 minutes of the clamp procedure were stable in patients and unaffected relatives (coefficient of variation, 3.4±0.3% and 4.1±0.3%, respectively). Plasma insulin concentrations increased in all subjects and were similar after 3 hours of insulin infusion in both groups (94.6±4.3 mU/L in FCH patients and 93.8±4.8 mU/L in unaffected relatives). M, calculated from the glucose infusion rate of both groups during the clamp procedure, is presented in Fig 2 and was significantly different over the last 60 minutes between FCH patients and unaffected relatives (6.89±0.31 versus 8.94±0.76 mg · kg⁻¹ · min⁻¹, respectively; P=.01 by ANOVA). The M value of the control

Effects on FBF

At baseline, the mean values of hemodynamic parameters (FBF and MAP) of both groups were similar. Only unaffected relatives exhibited a significant increase of 31.8±14.3% in FBF (FBF from 1.85±0.16 to 2.45±0.35 mL · min⁻¹ · dL⁻¹, ANOVA P=.025), whereas FCH patients showed no significant change in FBF (1.87±0.15 to 2.06±0.24). MAP did not change in either group (FCH patients: 92.7±2.3 to 93.0±3.6 and relatives: 95.3±3.0 to 98.4±2.7 mm Hg). The time course of the changes in FBF showed the major and statistically significant changes during the last hour of the clamp, reflecting a phenomenon with slow onset.

Relationship Between LDL Subfraction Distribution and M

The individual LDL subfraction profile, described as parameter K, correlated significantly with the glucose
uptake during the clamp procedure (Pearson's $r=0.51$, $P=0.008$; Fig 4). When the groups were compared separately, FCH patients were more insulin resistant and exhibited a predominance of small, dense LDL subfractions. The unaffected relatives, with the exception of one individual, were characterized by the presence of more buoyant LDL particles.

**Discussion**

In this study, we demonstrated directly by means of the euglycemic clamp technique a reduced insulin sensitivity in well-defined male FCH patients compared with one of their normolipidemic relatives. Since it has been established that insulin resistance is also associated with obesity, age, and sex alone, it is important to emphasize that these observations were not confounded by differences in sex or age and were registered in the absence of obesity, hypertension, and impaired glucose tolerance in the participants. Furthermore, we selected the affected and unaffected participants in genetically related pairs, presuming that by this study design, differences in environmental or genetic influences were reduced. Apart from the metabolic resistance to insulin (reduced glucose uptake), FCH patients also exhibited resistance to the vasodilator effects of insulin. Finally, diminished $M$ correlated with the presence of small, dense LDL subfractions.

Because of the similarity in presenting lipid disturbances and the association with increased cardiovascular risk, diminished insulin sensitivity may be related to FCH. This observation is further supported by the finding that insulin resistance affects both hepatic VLDL production and lipoprotein lipase action features also met in FCH. Previous studies indicate that insulin resistance is associated with elevated concentrations of VLDL triglyceride. Recent studies, however, showed no improvement in insulin sensitivity after substantial reduction of plasma triglyceride levels with fibrate treatment in both nondiabetic men with type IIb hyperlipidemia and in type II diabetic patients with hypertriglyceridemia. This factor may indicate that in some patients insulin resistance is of an inherited nature, not dependent on plasma triglyceride concentrations but probably preceding VLDL triglyceride overproduction.

A proposed mechanism responsible for VLDL overproduction is the impaired postprandial suppression of NEFA release in adipose tissue due to resistance to the normal suppressive effect of insulin on hormone-sensitive lipase. An elevated concentration of NEFA is associated with increased hepatic VLDL triglyceride secretion, possibly due to reduced intracellular apoB degradation. Furthermore, when normal insulin-mediated activation of lipoprotein lipase in adipose tissue is diminished, an impaired postprandial clearance of triglyceride-rich lipoproteins may occur. Several reports mentioned an impaired lipoprotein lipase activity as one of the factors contributing to FCH.

A postprandial status with prolonged circulating triglyceride-rich lipoproteins is a provoking situation for the formation of small, dense LDL particles. In the Kaiser Permanente Women Twin study and other studies, small, dense LDL was found to be an integral feature of the insulin resistance syndrome. Others, however,
showed a significant correlation between LDL particle size and triglyceride levels but not insulin resistance in mildly hypertriglyceridemic subjects. Here, the authors considered small, dense LDL a feature of the insulin resistance syndrome more as a consequence of abnormalities in VLDL metabolism. Our observed correlation between glucose uptake as a measure of insulin sensitivity and LDL density is in accordance with these reports but cannot discriminate between metabolic influences, such as the correlation with hypertriglyceridemia, causing a dense LDL subfraction profile, or primarily genetic effects related to diminished insulin sensitivity and small, dense LDL in FCH. The recently reported major gene effect on LDL subfraction size in FCH may possibly be found in mutations causing insulin resistance underlying hypertriglyceridemia and the formation of small, dense LDL. On the other hand, reported linkage of small, dense LDL to a locus near the LDL receptor and the insulin receptor gene on chromosome 19p45 may indicate that the allele responsible for expression of small, dense LDL also predisposes to insulin resistance.

Disorders related to insulin resistance seem to exhibit their major defect on the level of glucose uptake in skeletal muscle rather than at the level of the liver or the adipose tissue. Furthermore, several groups, including ourselves, have demonstrated the vasodilator effect of systemic hyperinsulinemia, which was reduced in non–insulin-dependent diabetes mellitus. It is hypothesized that decreased insulin sensitivity in humans may be due not only to lower insulin-mediated glucose extraction in insulin-sensitive tissues but also to a lower blood flow to these tissues, due to a decreased ability of insulin to stimulate skeletal muscle blood flow. In accordance with other studies in which comparable systemic insulin concentrations were reached, we observed a 30% increase in FBF in nonaffected subjects but not FCH patients. Although part of the present reported insulin resistance may be related to this diminished insulin-induced vasodilation, this factor could in fact only account for the last 60 to 80 minutes of the clamp, since differences in FBF between the groups became statistically significant in this period.

The insulin-induced vasodilation seems to be endothelium dependent. Reduced insulin-induced vasodilation may be due to direct endothelium–disturbing action of elevated lipid levels. Therefore, in FCH patients, the elevated lipoprotein concentration may directly influence the endothelium function, resulting in decreased nitric oxide release during hyperinsulinemia. Because insulin resistance itself may underlie VLDL overproduction, the reduced hemodynamic effects of insulin in hyperlipidemia can amplify metabolic disturbances found in FCH patients.

Recently, the Insulin Resistance Atherosclerosis Study demonstrated an inverse association between insulin sensitivity and atherosclerosis, as assessed by B-mode ultrasonography of the carotid artery wall. This association was eliminated, although not completely, by correction for traditional cardiovascular risk factors. Insulin resistance in our FCH patients, who were exposed to elevated lipid levels for a relatively short period of time (mean age <42 years) and without signs of atherosclerosis, represents more likely a metabolic defect rather than the consequence of existing atherosclerosis.

In conclusion, this study suggests that FCH patients exhibit a diminished insulin sensitivity. This insulin resistance may underlie the observed hyperlipidemia, characterized by elevated concentrations of VLDL cholesterol and triglycerides and a predominance of small, dense LDL in the affected subjects, and may be partly explained by a reduced capacity of insulin to induce vasodilation in skeletal muscle of the patients. Therefore, interactions between insulin action and lipid metabolism in FCH warrant further investigation.

Acknowledgments

This work was supported by research grant No. 92.056 of the Netherlands Heart Foundation. We especially thank the patients and healthy volunteers who participated in this study and also thank E. Olderiekerink for support during the tests.

References


