Insulin Resistance in Familial and Nonfamilial Hypercholesterolemia

Pauli Karhapää, Erkki Voutilainen, Petri T. Kovanen, and Markku Laakso

High levels of very low density lipoprotein triglycerides and low levels of high density lipoprotein cholesterol have been associated with insulin resistance measured by the euglycemic clamp technique. In contrast, the association of isolated hypercholesterolemia with insulin resistance has not been systematically studied. Therefore, we performed two separate studies designed to investigate the degree of insulin resistance in familial hypercholesterolemia (FH) (study 1) and nonfamilial hypercholesterolemia (non-FH) (study 2). Study 1 included eight young adults with FH and 13 corresponding control subjects. Fasting blood glucose, insulin, and C-peptide levels were similar in FH patients and control subjects during an oral glucose tolerance test. During the euglycemic hyperinsulinemic (1,200-1,300 pmol/l) clamp studies, FH patients and control subjects had similar rates of whole-body glucose uptake (73±6 versus 70±3 μmol/kg per minute, respectively; p=NS). Glucose oxidation, glucose nonoxidation, lipid oxidation, suppression of free fatty acid levels, and potassium disposal were similar in both groups. Study 2 included 25 middle-aged non-FH patients and 18 corresponding control subjects. Glucose, insulin, and C-peptide responses in an oral glucose tolerance test were similar in both groups. During the euglycemic hyperglycemic clamp studies, non-FH patients and control subjects had similar rates of whole-body glucose uptake (61±3 versus 58±3 μmol/kg per minute, p=NS). In addition, glucose oxidation, glucose nonoxidation, lipid oxidation, and suppression of free fatty acid levels as well as potassium disposal were similar in non-FH patients and control subjects. We conclude that FH and non-FH are not insulin-resistant states. (Arteriosclerosis and Thrombosis 1993;13:41-47)

Key Words • hypercholesterolemia • insulin • insulin resistance

High levels of very low density lipoprotein (VLDL) triglycerides and low levels of high density lipoprotein (HDL) cholesterol have been associated with insulin resistance measured by the euglycemic clamp technique. In contrast, the association of hypercholesterolemia with insulin resistance has not been systematically studied. In population-based as well as clinical studies, the correlation of fasting insulin, a marker of insulin resistance, with total cholesterol levels has in most cases been weak but in some studies statistically significant. Direct evidence that pure, isolated hypercholesterolemia, which results from a primary increase in low density lipoprotein (LDL) cholesterol level, is associated with insulin resistance is still lacking.

Several lines of evidence from epidemiology, genetics, and laboratory animal and tissue culture studies and clinical trials support the concept that high levels of LDL cholesterol accelerate coronary atherosclerosis. It has been proposed that insulin resistance, through its several effects on lipoprotein metabolism, could also increase the risk of atherosclerosis. Although much is known about the mechanisms of how LDL cholesterol accelerates atherosclerosis, the association of LDL cholesterol metabolism with insulin resistance is poorly known. If it exists, this link could be potentially important. Studies of patients with severe or moderate forms of LDL cholesterol metabolism disorders would probably improve our understanding of the relation between hypercholesterolemia and possible changes in insulin-mediated glucose uptake. Familial (FH) and nonfamilial (non-FH) hypercholesterolemias offer excellent disease models in this respect. FH is an autosomal codominant disorder caused by one or several mutations that interfere with the function of the LDL receptor, which leads to diminished removal of cholesterol from the circulation and consequently to grossly elevated LDL levels. Non-FH is a disease with multiple genetic defects. Cholesterol levels in this disease are usually only moderately elevated; conversely, they do not usually return to normal with diet therapy alone.

The aim of this study was to investigate whether subjects with isolated hypercholesterolemia (FH or non-FH) are more insulin resistant than corresponding control subjects without these forms of hypercholesterolemia.

Methods

Subjects

The male patients with FH and non-FH were selected from the Lipid Clinic of the Kuopio University Hospital. The diagnosis of FH was based on the following laboratory and clinical findings: serum cholesterol ≥7.5 mmol/l in the patient and at least one of his first-degree
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124±1
75±5
83±2
83±5
0.61±0.11
0.74±0.13
0.50±0.06
0.78±0.07†

FH, familial hypercholesterolemia; non-FH, nonfamilial hypercholesterolemia; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein.

*p<0.05, †p<0.01, ‡p<0.001.

TABLE 1. Characteristics of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>FH patients</td>
<td>Controls</td>
<td>Non-FH patients</td>
</tr>
<tr>
<td>No. of men</td>
<td>13</td>
<td>8</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27±2</td>
<td>31±1</td>
<td>56±1</td>
<td>52±1</td>
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<tr>
<td>Weight (kg)</td>
<td>71±2</td>
<td>75±3</td>
<td>81±2</td>
<td>78±2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23±1</td>
<td>23±1</td>
<td>27±1</td>
<td>26±1</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128±4</td>
<td>124±6</td>
<td>136±3</td>
<td>130±3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77±2</td>
<td>75±5</td>
<td>83±2</td>
<td>83±5</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.50±0.21</td>
<td>9.40±0.39‡</td>
<td>4.50±0.14</td>
<td>7.37±0.15‡</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.85±0.19</td>
<td>7.56±0.38‡</td>
<td>2.82±0.14</td>
<td>5.27±0.14‡</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.22±0.05</td>
<td>1.03±0.08*</td>
<td>1.27±0.08</td>
<td>1.38±0.08</td>
</tr>
<tr>
<td>VLDL triglycerides (mmol/l)</td>
<td>2.82±0.14</td>
<td>7.56±0.38‡</td>
<td>2.82±0.14</td>
<td>5.27±0.14‡</td>
</tr>
</tbody>
</table>

FH, familial hypercholesterolemia; non-FH, nonfamilial hypercholesterolemia; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein.

*p<0.05, †p<0.01, ‡p<0.001.

Table 1 shows the characteristics of eight FH and 25 non-FH patients and their corresponding control subjects (13 and 18 control subjects, respectively). In both studies the patients and control subjects were comparable with respect to age, weight, body mass index, and blood pressure readings. Total and LDL cholesterol levels were significantly higher in patients with FH (study 1) or those with non-FH (study 2) than corresponding control subjects. HDL cholesterol was significantly lower in FH patients than corresponding control subjects (study 1). Although in the normal range, VLDL triglyceride values were higher in non-FH patients than corresponding control subjects.

Study Protocol

Study protocols were identical in studies 1 and 2. The subjects were admitted to the metabolic ward for 2 days.

On day 1 an oral glucose tolerance test (75 g glucose in 10% solution) was performed, and samples for blood glucose, plasma insulin, and plasma C-peptide were drawn at 0, 1, and 2 hours to exclude those with impaired glucose tolerance or diabetes. On day 2 the euglycemic glucose clamp study was performed.

Informed consent was obtained from all subjects after the purpose and potential risks of the study were explained to them. The protocol was approved by the Ethics Committee of the University of Kuopio.

Euglycemic Clamp

The degree of insulin resistance was evaluated by the euglycemic clamp technique.

At 8 AM, after a 12-hour overnight fast, an intravenous catheter was placed in an antecubital vein for the infusion of insulin and 20% glucose. Another cannula for blood sampling was inserted into a wrist vein surrounded by a heated box (70°C). After baseline blood withdrawal and measurement of gas exchange (see "Indirect Calorimetry"), a priming dose of insulin (Velosulin Human, Nordisk Insulin, Gentofte, Denmark) was administered during the initial 10 minutes in a logarithmically decreasing manner to acutely raise serum insulin to the desired level, where it was maintained by a continuous insulin infusion of 574 pmol/m² per minute (80 milliunits/m² per minute). Blood glucose was clamped at 5.0 mmol/l for the next 180 minutes by the infusion of 20% glucose at varying rates according to blood glucose measurements performed at 5-minute intervals. The data were calculated for each 20-minute interval.

Indirect Calorimetry

Indirect calorimetry was performed with a computerized flow-through-canopy gas analyzer system (DELTA-TRAC, TM Datex, Helsinki) as previously described. This device has a precision of 2.5% for oxygen consumption and 1.0% for carbon dioxide production. On the day of the experiment, gas exchange (oxygen consumption and carbon dioxide production) was measured for 30 minutes after a 12-hour fast before the clamp and during the last 30 minutes of the euglycemic clamp. The first 10 minutes for each set of data was discarded, and the mean value of the remaining 20 minutes was used in calculations. Protein, glucose, and lipid oxidation rates
were calculated according to the method of Ferran-
nini.\textsuperscript{17} Protein oxidation rate was calculated on the basis
of the urinary nonprotein nitrogen excretion rate by
multiplying this value by 6.25. The rate of carbohydrate
nonoxidation during the euglycemic clamp was esti-
mated by subtracting the carbohydrate oxidation rate
(determined by indirect calorimetry) from the glucose
infusion rate (determined by the euglycemic clamp).

\textbf{Analytical Methods}

Blood glucose in the fasting state and during glucose
clamp studies was measured by the glucose oxidase
method (Glucose Auto & Stat HGA-1120 analyzer,
Daichi Co., Kyoto, Japan). For the determination of
plasma insulin and plasma C-peptide, blood was col-
lected in EDTA-containing tubes. After centrifugation
the plasma was stored at \(-20^\circ\text{C}\) until the analysis.
Plasma insulin and C-peptide concentrations were
determined by radioimmunoassay (Phadeseph Insulin
RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden,
and C-peptide of insulin 125J RIA kit, Incstar Co.,
Stillwater, Minn., respectively). Serum lipids and lipo-
proteins were determined from fresh serum samples
drawn after a 12-hour overnight fast. Lipoprotein frac-
tionation was performed by the use of ultracentrifuga-
tion and selective precipitation\textsuperscript{18} as previously de-
scribed.\textsuperscript{3} Cholesterol and triglyceride levels from the
whole serum and from lipoprotein fractions and plasma
lactate were assayed by automated enzymatic methods
(Boehringer-Mannheim, Mannheim, FRG). Serum free
fatty acids were determined by an enzymatic method of
Wako Chemicals GmbH (Neuss, FRG). Serum potas-
sium was measured by flame photometry. Nonprotein
urinary nitrogen was measured by an automated
Kjeldahl method.\textsuperscript{19}

\textbf{Data Analysis}

All calculations were performed by the use of the
\textsc{spss}/\textsc{pc+} programs (\textsc{spss} Inc., Chicago). Data are
presented as mean±SEM. The two-tailed Student's \textit{t}

test for unpaired samples was used to compare the two
groups.

\textbf{Results}

\textit{Study 1}

Figure 1 depicts glucose and insulin responses to an
oral glucose load. Fasting glucose (5.3±0.1 versus
5.2±0.1 mmol/l, \(p=\text{NS}\)), insulin (48±5 versus 70±8
pmol/l, \(p=\text{NS}\)), and C-peptide levels (0.3±0.04 versus
0.46±0.04 pmol/l, \(p=\text{NS}\); not shown) did not signifi-
cantly differ between FH patients and control subjects.
In addition, at 1 and 2 hours, insulin and C-peptide
responses to the glucose load did not significantly differ
between the patients and control subjects (1 hour:
insulin, 374±56 versus 300±48 pmol/l; C-peptide,
1.65±0.13 versus 1.56±0.15 nmol/l; not shown) (2
hours: insulin, 157±31 versus 217±32 pmol/l; C-pep-
tide, 1.09±0.13 versus 1.36±0.15 nmol/l; not shown).
During the euglycemic clamp studies the blood glu-
cose level was 5.1±0.1 mmol/l in FH patients and
5.1±0.1 mmol/l in control subjects, with a coefficient of
variation <4% during the last 2 hours of clamping. The
steady-state insulin levels during clamping were

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Line plots showing plasma glucose (upper panel)
and plasma insulin (lower panel) responses for the oral
glucose test in patients with familial hypercholesterolemia (●)
and controls (○).}
\end{figure}

1,301±59 pmol/l in control subjects and 1,203±61
pmol/l in FH patients \((p=\text{NS})\).

The rates of whole-body glucose uptake were similar
in FH patients and control subjects during the last hour
of clamping (73.1±5.9 versus 69.5±3.1 \(\mu\)mol/kg per
minute, \(p=\text{NS}\)). Glucose oxidation in the fasting state
was similar in FH patients and control subjects (6.4±1.6
and 8.0±0.7 \(\mu\)mol/kg per minute, respectively). Like-
wise, fasting lipid oxidation did not significantly differ
between FH patients and control subjects (4.6±0.9 and
4.4±0.5 \(\mu\)mol/kg per minute, respectively). As shown in
Figure 2, glucose oxidation during the last 30 minutes of
the euglycemic clamp was similar in FH patients and
control subjects (20.1±1.8 versus 19.4±0.9 \(\mu\)mol/kg per
minute, respectively) as well as glucose nonoxidation
(51.4±5.3 versus 50.0±3.1 \(\mu\)mol/kg per minute, respec-
tively). Lipid oxidation during clamping was almost
completely suppressed and did not significantly differ
between FH patients and control subjects (0.9±0.5
versus 1.4±0.4 \(\mu\)mol/kg per minute).

Plasma lactate concentrations did not significantly differ
between FH patients and control subjects in the
fasting state (0.79±0.08 and 1.06±0.09 mmol/l, respec-
tively) and increased significantly \((p<0.001)\) during the
euglycemic clamp. Lactate levels were similar during
hour 3 of clamping in both FH patients and control
subjects (1.21±0.07 versus 1.24±0.05 mmol/l).
Serum free fatty acid levels did not significantly differ between FH patients and control subjects in the fasting state (0.44±0.05 versus 0.40±0.06 mmol/l) and were suppressed in a similar manner during the euglycemic clamp (0.07±0.01 versus 0.06±0.01 mmol/l, hour 3 of clamping). Serum potassium levels were the same in FH patients and control subjects in the fasting state (4.0±0.1 mmol/l in both groups) and fell by similar amounts, so that at the end of clamping potassium levels were 3.6±0.1 mmol/l in FH patients and control subjects.

Study 2

Figure 3 depicts glucose and insulin responses to an oral glucose load. Insulin (68±6 versus 64±10 pmol/l) and C-peptide levels (0.6±0.6 versus 0.54±0.05 nmol/l) did not significantly differ between non-FH patients and controls, and fasting glucose levels (5.5±1.0 mmol/l) were the same in both groups. In addition, at 1 and 2 hours, insulin and C-peptide responses to the glucose load did not significantly differ between the patients and control subjects (1 hour: insulin, 469±64 versus 459±68 pmol/l; C-peptide, 2.56±0.22 versus 2.38±0.20 nmol/l; not shown) (2 hours: insulin, 216±37 versus 195±36 pmol/l; C-peptide, 1.79±0.21 versus 1.56±0.16 nmol/l; not shown).

During the euglycemic clamp studies the blood glucose level was 5.0±0.03 mmol/l in non-FH patients and 5.0±0.04 mmol/l in control subjects, with a coefficient of variation <4% during the last 2 hours of the clamp. The steady-state insulin levels during the clamp were 1,313±52 pmol/l in non-FH patients and 1,229±62 pmol/l in control subjects (p=NS between the two groups).

The rates of whole-body glucose uptake were similar in non-FH patients and control subjects during the last hour of the clamp (60.7±3.3 versus 57.9±2.9 µmol/kg per minute, p=NS). Glucose oxidation in the fasting state was similar in non-FH patients and control subjects (8.5±0.6 and 8.8±1.5 µmol/kg per minute, respectively). Likewise, fasting lipid oxidation did not significantly differ between non-FH patients and control subjects (3.1±0.3 and 3.1±0.8 µmol/kg per minute, respectively). As shown in Figure 4, glucose oxidation during the last 30 minutes of the euglycemic clamp was similar in non-FH patients and control subjects (20.0±0.6 versus 20.3±0.7 µmol/kg per minute, respectively). Likewise, glucose nonoxidation did not significantly differ between non-FH patients and control subjects (40.5±2.8 versus 37.7±2.7 µmol/kg per minute, respectively). Lipid oxidation during the clamp was almost completely suppressed and did not significantly differ between non-FH patients and control subjects (0.03±0.2 versus 0.07±0.3 µmol/kg per minute).

Figure 2. Bar graph showing glucose oxidation and nonoxidation rates during the euglycemic clamp study in patients with familial hypercholesterolemia (FH) and controls.

Figure 3. Line plots showing plasma glucose (upper panel) and plasma insulin (lower panel) responses for the oral glucose test in patients with nonfamilial hypercholesterolemia (■) and controls (○).
Plasma lactate concentrations were higher in non-FH patients than control subjects in the fasting state (0.82±0.06 versus 0.63±0.04 mmol/l, respectively; *p*=0.002) and increased significantly (*p*<0.001) during euglycemic clamp studies in both groups. Lactate levels were similar during hour 3 of clamping in non-FH patients and control subjects (1.16±0.08 versus 1.14±0.07 mmol/l). Serum free fatty acid levels did not significantly differ between non-FH patients and control subjects in the fasting state (0.47±0.04 versus 0.57±0.07 mmol/l) and were suppressed in a similar manner during the euglycemic clamp (0.05±0.01 versus 0.04±0.01 mmol/l, hour 3 of clamping). Serum potassium levels were similar in non-FH patients and control subjects (1.16±0.08 versus 1.14±0.07 mmol/l). Serum free fatty acid levels did not significantly differ between non-FH patients and control subjects in the fasting state (0.47±0.04 versus 0.57±0.07 mmol/l) and were suppressed in a similar manner during the euglycemic clamp (0.05±0.01 versus 0.04±0.01 mmol/l, hour 3 of clamping). Serum potassium levels were similar in non-FH patients and control subjects in the fasting state (4.2±0.04 versus 4.0±0.04 mmol/l) and likewise fell, so that at the end of clamping potassium levels were 3.5±0.1 mmol/l in non-FH patients and control subjects.

**Discussion**

The aim of our study was to investigate the association of insulin resistance and high cholesterol level by the examination of subjects with FH and non-FH and corresponding control subjects carefully matched for age, sex, and degree of obesity. Our results showed that FH and non-FH are associated neither with insulin resistance, as measured by the euglycemic clamp technique, nor with intracellular defects of glucose metabolism. Furthermore, lipid oxidation, anaerobic glycolysis, and potassium disposal were normal in hypercholesterolemic patients.

Previous population-based studies have shown a weak association between total cholesterol and insulin levels. Therefore, hypercholesteremia has been included as an integral part of the insulin resistance syndrome, but whether this correlation results from the LDL cholesterol fraction is not been studied. In fact, it is possible that the correlation between total cholesterol and insulin results from VLDL cholesterol because this lipoprotein fraction is associated with insulin resistance in euglycemic clamp studies. Furthermore, the correlation analyses have not excluded subjects who had both elevated cholesterol and triglyceride levels; therefore, this association could result from a high triglyceride concentration among these subjects. Studies in which insulin resistance had been directly measured in patients with primary hypercholesterolemia (i.e., due to an increase in LDL level) have not been previously published.

Several mechanisms are involved in the regulation of serum LDL cholesterol level. LDL particles derive from the catabolism of triglyceride-rich VLDL particles, which are secreted by the liver. Lipoprotein lipase, the key enzyme responsible for the hydrolysis of VLDLs, converts them into small VLDL “remnants.” Although the mechanisms by which triglycerides of VLDL remnants are hydrolyzed to yield LDL are not yet completely understood, lipoprotein lipase as well as hepatic lipase probably plays a crucial role in this process. In addition to conversion into LDL particles, VLDL remnants can be directly removed by the liver by way of LDL receptors. Therefore, LDL concentrations depend on the hepatic secretion of VLDL particles, the direct hepatic removal of VLDL remnants, the conversion of VLDL remnants into LDL particles, and the activity of hepatic LDL receptors, which remove LDL particles from the circulation.

In normal humans insulin resistance has several effects that could potentially affect LDL cholesterol level. Hyperinsulinemia has been shown to associate with a high VLDL level, which potentially leads to elevated LDL formation. However, in different insulin-resistant states, for example, in non-insulin-dependent diabetes mellitus, the direct removal of VLDL remnants is increased, which leads to relatively lower production rates of LDL. Chait et al have shown that insulin increases LDL receptor activity in cultured human skin fibroblasts, independent of glucose concentration. In their study binding, uptake, and degradation of LDL were concurrently stimulated and to a similar extent. Therefore, insulin appears to enhance LDL degradation by stimulation of the receptor-dependent catabolism of LDL. Furthermore, these authors have demonstrated a significant increase in the fractional catabolic rate of LDL after parenteral nutrition, which caused a rise in plasma insulin levels approximately 10- to 15-fold. These observations have also been confirmed in vivo by applying the euglycemic clamp technique. Mazzone et al demonstrated that insulin in vivo stimulated LDL catabolism because it caused the accelerated disappearance of 125I-labeled LDL from plasma in subjects previously injected with autologous 125I-LDL. All the aforementioned in vitro and in vivo observations accord
with the notion that insulin could lead to delivery of more serum cholesterol to cells; therefore, it would have the potential to lower circulating LDL concentration. By analogy, cellular resistance to insulin could blunt the stimulating effect of insulin on LDL receptor expression and elevate plasma LDL cholesterol concentration. However, the latter conclusion is based on the assumption that cellular resistance to insulin is not confined to cellular glucose metabolism but affects cellular LDL receptor metabolism as well. Although direct demonstration of the effect of insulin resistance on cellular LDL expression is still lacking, some epidemiological studies have indirectly supported this contention by showing an association between LDL cholesterol concentrations and obesity, the most common cause of insulin resistance.

Although insulin has the potential capacity to modify LDL cholesterol level, this does not necessarily imply that patients with high cholesterol levels, which result from genetic, environmental, or both causes, would have an altered insulin sensitivity. Patients with FH have an inherited defect in the gene that encodes for LDL receptors, and those who have heterozygous FH show half the normal number of LDL receptors. In non-FH the genetic defects have not been defined at the molecular level. These patients probably show several genetic defects that result in a moderate elevation of LDL cholesterol level. The manifestations of these defects include low clearance rates for LDL, increased input of LDL, and enrichment of LDL with cholesteryl esters. Therefore, it is likely that our non-FH patients also showed a variety of different genetic defects in LDL metabolism. However, independent of the causes of hypercholesterolemia, patients with a high cholesterol level showed no greater degree of insulin resistance than our control subjects. This indicates that cholesterol metabolism in hypercholesterolemic states is primarily regulated independent of mechanisms that are related to insulin resistance.

Measurements based on indirect calorimetry to assess the intracellular metabolism of glucose showed that glucose and lipid oxidation and glucose nonoxidation did not differ between the patients and control subjects in the fasting state or during the euglycemic clamp. These results are not surprising because the rates of whole-body glucose uptake did not differ between the groups, and free fatty acid concentration, which is one of the most important determinants of glucose oxidation rate, was similar in both groups in the fasting state and during the clamp studies. No systematic difference in lactate levels between hypercholesterolemic patients and control subjects was observed, which suggests that anaerobic glycolysis was also similar in patients and control subjects.

We studied our subjects with an insulin concentration of 1,200–1,300 pmol/l, which is a high physiological insulin concentration and one that stimulates glucose uptake in insulin-sensitive tissues to >80% of the maximum response. The insulin concentration obtained in our study completely suppresses the liver glucose production in normoglycemic individuals, therefore, the rates of whole-body glucose uptake reflect insulin sensitivity in tissues capable of using glucose, primarily skeletal muscle. Because we did not perform a dose–response study on our patients, the possibility cannot be excluded that patients with hypercholesterolemia would show insulin resistance at lower levels of hyperinsulinemia. However, this is unlikely because during physiological hyperinsulinemia induced by the 40 milliunits/m^{2} per minute insulin infusion (insulin level, 700 pmol/l) in our previous study, which included both a completely separate sample of subjects with normal glucose tolerance and the measurement of hepatic glucose output by intraduodenal glucose during the clamp studies, the correlation coefficients between total and LDL cholesterol levels and insulin sensitivity were only –0.02 and –0.03, respectively. Further support to our finding that primary hypercholesterolemia is probably not associated with insulin resistance in peripheral tissues is revealed in the previous studies that indicate that the liver, not skeletal muscle, is the key organ that regulates the catabolism and level of LDL cholesterol.

Previous studies have shown that insulin resistance is associated with high blood pressure levels, low HDL cholesterol, and high VLDL triglyceride concentrations, a cluster of risk factors known to promote atherosclerosis. Our result that hypercholesterolemia is not an insulin-resistant state has significant practical implications. This observation implies that in the prevention of cardiovascular disease, a high LDL cholesterol level should be treated, independent of other metabolic disorders related to insulin resistance.

References


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