Insulin Resistance, Glucose Intolerance, and Hyperinsulinemia
Hypertriglyceridemia Versus Hypercholesterolemia


Plasma glucose and insulin responses to oral glucose and mixed meals and the ability of insulin to stimulate glucose disposal were quantified in normal volunteer subjects and patients with types IIA, IIB, and IV hyperlipoproteinemia (HLP). The results indicated that patients with either type IIB or IV HLP had higher plasma glucose (p<0.05–<0.001) and insulin (p<0.001) responses to both oral glucose and mixed meals compared with the normal subjects and patients with type IIA HLP. Steady-state plasma glucose concentrations (mmol/L) were also higher (p<0.001) in patients with types IIB (13.3±0.6) and IV (12.8±1.2) HLP during a continuous infusion of somatostatin, glucose, and insulin than either the control group (volunteer subjects) (6.2±0.9) or patients with type IIA HLP (5.6±1.0). Because the steady-state plasma insulin concentrations were similar in all four groups, patients with either type IIB or IV HLP were resistant to insulin-mediated glucose uptake. These data indicate that patients with hypertriglyceridemia are insulin resistant, glucose intolerant, and hyperinsulinemic, irrespective of the plasma cholesterol concentration. The results further demonstrate that hypercholesterolemic patients with normal triglyceride concentrations do not have any abnormalities of glucose and insulin metabolism.

(Keywords: insulin resistance • glucose intolerance • hypercholesterolemia • hyperinsulinemia • hypertriglyceridemia)

By definition,1 patients with hypercholesterolemia have type II hyperlipoproteinemia (HLP). Within this category individuals are further subdivided into those without (type IIA) or with (type IIB) concomitant hypertriglyceridemia.1 Patients with pure hypertriglyceridemia are determined to have type IV HLP1 and have been shown to be hyperinsulinemic and resistant to insulin-stimulated glucose uptake.2–4 Whether abnormalities of insulin metabolism also exist in patients with type IIA HLP is not clear, and these studies were initiated to address this issue. To accomplish this task we compared several aspects of glucose and insulin metabolism in four experimental groups: normal volunteer subjects and patients determined to have either types IIA, IIB, or IV HLP.

From the Division of Endocrinology and Metabolism (W.H.-H.S., S.-M.S., M.M.-T.F., D.D.-C.S., C.-Y.J.), Department of Medicine, Clinical Research Center, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC, and the Department of Medicine (G.M.R., Y.-D. Ida C.), Stanford, Calif.

Supported by research grants from the National Science Council (NSC 81-0412-B-016-557), the Institute of Biomedical Science Academia Sinica, Taiwan, and the National Institutes of Health, Bethesda, Md. (NHLBI-08506).

Address for correspondence: Wayne H.-H. Sheu, MD, Division of Endocrinology and Metabolism, Tri-Service General Hospital, Taipei, Taiwan 100.

Received September 9, 1992; revision accepted December 9, 1992.

Methods

The dyslipidemic patients in this study were individuals from either the Endocrinology or Lipid Clinics at the Tri-Service General Hospital who volunteered to participate after we informed them of our interest in the evaluation of glucose and insulin metabolism in individuals with abnormal lipoprotein metabolism. The control (volunteer) subjects were individuals who had come to the hospital for annual health examinations and were also willing to participate in these studies. To qualify for inclusion in these experiments, the participants had to be 30–70 years of age, without fasting hyperglycemia,5 in generally good health, and on no medicine or not following any diet aimed at the improvement of lipid metabolism. Blood was obtained after an overnight fast on two occasions for measurement of fasting plasma cholesterol6 and triglyceride (TG)7 concentrations. High density lipoprotein (HDL) cholesterol concentration was measured after precipitation of apolipoprotein (apo) B-containing lipoproteins by phosphotungstic acid and magnesium chloride reagent.8 The participants were divided into four groups according to the following criteria (in millimoles per liter): control, plasma TG <1.5 and cholesterol <5.0; type IIA, plasma TG <1.5 and cholesterol >6.0; type IIB, plasma TG >1.5 and cholesterol >6.0; and type IV, plasma TG >1.7 and cholesterol <5.0. Efforts were made to recruit participants into these four groups who were similar in age, gender distribution, and degree of obesity (determined by body mass index [BMI]). Our success in this effort is
substantiated by the similarity of these variables among the four study groups (see Table 1). The results shown in Table 1 also indicate that plasma TG concentrations were similar in patients with types IIB and IV HLP and higher than the values in either the control group or patients with type IIA HLP. It is also apparent that plasma cholesterol levels were higher in patients with types IIA and IIB HLP than those with type IV HLP or the control group and were not different from each other.

Plasma glucose and insulin responses in each participant were determined by the measurement of plasma glucose and insulin concentrations before and after a 75-g oral glucose challenge as well as before and after mixed meals. In the former instance, blood was obtained after an overnight fast and at 30, 60, 90, 120, and 180 minutes after the oral administration of 75 g glucose. In the latter case, blood was drawn before breakfast at 8 AM and then at hourly intervals until 4 PM. The mixed meals were isocaloric, with each meal containing the following nutrients as percentages of total calories: 17% protein, 40% fat, and 43% carbohydrates. These meals, which were given at 8 AM, noon, and 6 PM, contained 20%, 40%, and 40%, respectively, of the day’s total caloric intake. The total integrated plasma glucose and insulin responses to the glucose challenge and the meals were calculated; these values were used for comparison among the four groups.

The ability of insulin to promote glucose uptake was estimated by a modification of the insulin suppression test originally described by our laboratory. After an overnight fast intravenous catheters were placed in each arm. Blood was sampled from one arm for measurement of plasma glucose and insulin concentrations, and the other arm was used for administration of test substances. Somatostatin was administered at 250 milliunits/m2 per minute and 240 mg/m2 per minute, respectively. Blood was sampled every half hour until 150 minutes into the study and then every 10 minutes until 180 minutes had elapsed. Insulin concentrations typically plateaued by 60 minutes and glucose at 120 minutes. The four values obtained from 150 to 180 minutes were averaged and considered to represent the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations achieved during the infusion.

**Statistical Analysis**

All data are expressed as mean±SEM. The statistical significance of differences among the four groups in plasma glucose and insulin responses to the 75-g oral glucose challenge and the meals, SSPG, SSPI, and HDL cholesterol concentrations were estimated by one-way analyses of variance.

**Results**

Plasma glucose and insulin concentrations for the four groups before and after the oral glucose challenge are shown in Figure 1. The total integrated plasma glucose responses were significantly higher in those with either type IIB (p<0.002) or IV (p<0.05) HLP compared with the control group or those with type IIA HLP. Likewise, patients with either type IIB (p<0.002) or IV (p<0.005) HLP also had greater insulin responses than the other two groups. It is noteworthy that the magnitude of the difference in the insulin response was greater than that for glucose. Finally, the glucose and insulin responses were not different in the control and type IIA HLP groups.

Plasma glucose and insulin concentrations from 8 AM to 4 PM in response to conventional meals are illustrated in Figure 2. Although the difference in the plasma glucose response among the groups was less dramatic than that of a pure glucose load when they were compared after meals (Figure 1), individuals with type

---

**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>TG (mmol/L)</th>
<th>Cholesterol (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7/13</td>
<td>54±2</td>
<td>23.9±0.5</td>
<td>0.87±0.10</td>
<td>4.73±0.15</td>
</tr>
<tr>
<td>Type IIA</td>
<td>5/10</td>
<td>53±2</td>
<td>24.2±0.4</td>
<td>0.97±0.09</td>
<td>7.32±0.30</td>
</tr>
<tr>
<td>Type IIB</td>
<td>6/9</td>
<td>54±3</td>
<td>24.6±0.3</td>
<td>2.95±0.38</td>
<td>7.18±0.43</td>
</tr>
<tr>
<td>Type IV</td>
<td>6/10</td>
<td>55±3</td>
<td>24.5±0.5</td>
<td>3.14±0.34</td>
<td>4.83±0.20</td>
</tr>
</tbody>
</table>

M/F, male/female; BMI, body mass index; TG, triglycerides.

---

**FIGURE 1. Line graphs of plasma glucose (left panel) and insulin (right panel) responses to a 75-g oral glucose load. Symbols represent control subjects (○), and patients with hyperlipoproteinemia types IIA (○), IIB (●), and IV (■). Glucose response: Type IIA=control; type IIB >control, p<0.02; type IV >control, p<0.05. Insulin response: Type IIA=control; type IIB >control, p<0.005; type IV >control, p<0.005.**
IIB \((p<0.005)\) or IV \((p<0.05)\) HLP still had significantly higher day-long glucose responses than the other two groups. The day-long insulin response to meals was also higher in patients with type IIB or IV HLP \((p<0.002)\) than in the other two groups, and the magnitude of the difference in the insulin responses was similar to that seen when measured after a 75-g oral glucose challenge (Figure 1). Again, the control and type IIA HLP groups had similar glucose and insulin concentrations.

SSPG and SSPI concentrations achieved during the insulin suppression test are shown in Figure 3. SSPI concentrations (left panel) are similar in the four groups, whereas SSPG concentrations (right panel) are more than twice as high \((p<0.001)\) in patients with type IIB or IV HLP than in the other two groups.

Although it is self-evident from the data shown in Figures 1–3, it is noteworthy that both the control subjects and patients with type IIA HLP were similar for all the variables measured, as were those with types IIB and IV HLP.

By selection, plasma TG concentrations in patients with types IIB and IV HLP were similar but higher than the other two groups (see Table 1). In addition, HDL cholesterol concentrations were lower \((p<0.05)\) in patients with types IIB \((0.83±0.06\) mmol/L) and IV \((0.75±0.04\) mmol/L) HLP than those in individuals in the type IIA \((1.09±0.07\) mmol/L) and control \((1.25±0.07\) mmol/L) groups. Furthermore, the ratio of total to HDL cholesterol was lower in the control group \((3.95±0.18)\) than in patients with types IIA \((7.40±0.85)\), IIB \((9.52±1.08)\), and IV \((6.44±0.33)\) HLP \((p<0.01–0.001)\).

**Discussion**

The goal of this study was to explore the association between increases in plasma TG and cholesterol concentrations and differences in the ability of insulin to mediate glucose uptake. To discuss the results in the context of this goal, it seems useful to focus on three comparisons. First, we want to summarize the results of the comparison of patients with either type IIA or IIB HLP, i.e., groups with similar plasma cholesterol but different TG concentrations. Second, it is observed that patients with type IIB HLP were insulin resistant, glucose intolerant, and hyperinsulinemic compared with subjects with type IIA HLP. In this instance the presence of hypertriglyceridemia serves as a marker of differences in glucose and insulin metabolism. Should a comparison of patients with type IV HLP with the control group now be made, it is again seen that hypertriglyceridemic subjects are insulin resistant, glucose intolerant, and hyperinsulinemic, in this case in the absence of hypercholesterolemia. Consequently, there is an association between high plasma TG concentrations and defects in glucose and insulin metabolism, irrespective of whether the groups compared are both hypercholesterolemic (types IIA and IIB HLP groups) or both normcholesterolemic (type IV HLP and control groups). Finally, in a third comparison, when groups were matched for plasma TG concentration, differences in plasma cholesterol concentration did not seem to have a significant effect on insulin action, glucose tolerance, or plasma insulin response, i.e., patients with type IIB compared with type IV HLP or type IIA HLP compared with control subjects.

Although the aforementioned comparisons clearly indicate that increases in plasma TG but not cholesterol concentrations identify individuals who significantly differ in insulin-mediated glucose uptake and plasma glucose and insulin responses to an oral glucose challenge, there are at least two noteworthy issues. An association between hypertriglyceridemia and both glucose intolerance and hyperinsulinemia was shown in 1966, and in 1974 highly significant relations among insulin resistance, hyperinsulinemia, and plasma TG concentrations were defined in nondiabetic individuals over a wide range of plasma TG concentrations. Similar relations have also been described in individuals with
normal plasma TG concentrations. Consequently, there is substantial evidence that these relations exist. Despite this apparent consensus of the experimental data, the interpretation of these observations is not self-evident. For example, we-2,5,6 have suggested that the basic defect in patients with hypertriglyceridemia is resistance to insulin-mediated glucose uptake, leading to compensatory hyperinsulinemia, increased synthesis and secretion of hepatic TG, and hypertriglyceridemia. Conversely, one could hold that primary increases in plasma TG concentration result in insulin resistance and compensatory hyperinsulinemia. It is possible to argue in favor of both of these hypotheses, and we do not believe that available data permit a definitive choice to be made between these alternatives.

Finally, the relation between the results of this study and the role of dyslipidemia in the development of coronary heart disease (CHD) deserves attention. The data presented herein demonstrate that all three phenotypes have significantly higher ratios of total to HDL cholesterol than the control group. When given epidemiological evidence that this ratio is the best predictor of the risk of CHD, all dyslipidemic phenotypes are at an increased risk. However, if this criterion is acceptable it is noteworthy that patients with type IIB HLP would be most at risk of CHD. In addition, there are other risk factors for CHD that also deserve attention in this context, and they also differ as a function of phenotype. Indeed, nomenclature that divides hypercholesterolemic patients into those without (type IIA) and with (type IIB) HLP has tended to emphasize the similarity in the plasma cholesterol concentrations of the two groups rather than the differences in other metabolic variables. Furthermore, designation of individuals as of either type IIA or IIB HLP implies an awareness that hypercholesterolemia at the expense of other risk factors for CHD. Conversely, it is apparent from the results of these studies that patients with types IIA and IIB HLP are anything but similar in their carbohydrate metabolism. Should measures of in vivo insulin action, glucose tolerance, and the insulin response to oral glucose be used as the criteria, patients with type IIA HLP would most resemble the normal population, whereas these same measures document an enormous degree of similarity between patients with types IIB and IV HLP. In this context it is necessary to point out that there is evidence that both glucose intolerance and hyperinsulinemia have been shown to increase the risk of CHD. Furthermore, it is well known that a low HDL cholesterol concentration increases the risk of CHD, and the combination of high TG and low HDL cholesterol concentrations, i.e., changes in lipid metabolism seen in patients with types IIB and IV but not IIA HLP, have been shown to represent a highly atherogenic lipoprotein pattern. When these factors are considered, it seems essential to realize that patients with types IIA and IIB HLP are strikingly different in multiple ways. These considerations are not meant to obviate the importance of hypercholesterolemia as an atherogenic risk but only to point out that when the metabolic differences that define and differentiate between the three phenotypes are considered, it seems obvious that therapeutic interventions should consider the characteristics of each syndrome.

References

20. Pyorala K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. Diabetes Care 1979;2:131-141
Insulin resistance, glucose intolerance, and hyperinsulinemia. Hypertriglyceridemia versus hypercholesterolemia.

W H Sheu, S M Shieh, M M Fuh, D D Shen, C Y Jeng, Y D Chen and G M Reaven

doi: 10.1161/01.ATV.13.3.367

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/13/3/367

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/