Ischemic Heart Disease

Insulin, Carbohydrate, and Lipid Interrelationships

By Menard M. Gertler, M.D., Hillar E. Leetma, M.D., Erich Saluste, Ph.D., James L. Rosenberger, B.A., and Robert G. Guthrie, B.S.

SUMMARY
This study evaluates interrelationships between carbohydrate and lipid metabolism during oral glucose tolerance tests (GTT) in 65 ischemic heart disease (IHD) males and 69 age-matched healthy controls (age range 45 to 69 years). The frequency of abnormal GTT, usually accompanied by type IV hyperlipoproteinemia, was significantly higher in IHD (37%) than in controls (19%). The mean immunoreactive insulin (IRI) response curve of IHD patients with abnormal GTT showed an elevated and delayed peak at 2 hours. The mean free fatty acid response curve of IHD patients had a significantly lower rebound at 3 hours. IHD patients and controls with abnormal GTT showed significantly higher and lagging lactate levels at 2 and 3 hours. Incidence of abnormal GTT was neither related to relative weight nor to elapsed time from onset of IHD to time of examination. Canonical correlations revealed that IRI is the common denominator in both carbohydrate and lipid abnormalities in IHD.

Additional Indexing Words:
Immunoreactive insulin Glucose tolerance test Hyperlipoproteinemia
Free fatty acids Lactate Diabetes mellitus

It is generally accepted that serum lipid abnormalities are closely associated with the development of atherosclerosis and ischemic heart disease (IHD) and that one of the major complications of diabetes mellitus is the acceleration of IHD. Thus, it would be of interest to determine whether a relationship exists between serum lipid abnormalities and impaired carbohydrate metabolism in healthy individuals and in the survivors of acute myocardial infarction.

Extensive reviews concerning the frequency of abnormal glucose tolerance tests in IHD are available. Many factors, e.g. the selection of populations, age and sex distribution, differences in laboratory technics, and classification criteria of impaired carbohydrate tolerance have contributed to the disparities in these reports.

Our previous studies on carbohydrate and lipid interrelationships demonstrated that differences between IHD patients and controls do exist in glucose utilization and immunoreactive insulin (IRI) response. These differences were more striking in patients with ischemic thrombotic cerebrovascular disease.

This paper will evaluate and compare glucose utilization and IRI response of IHD patients with age-matched healthy controls during the oral GTT and establish some
interrelationships between carbohydrate and lipid metabolism in these two populations.

Material and Methods

The study population consists of 75 male ischemic heart disease (IHD) patients and 161 healthy male controls. The IHD group was comprised of patients with myocardial infarction or angina pectoris diagnosed by WHO criteria.11

The healthy controls were comparable to the IHD group in their physical activity and socioeconomic status. All subjects were in good nutritional status, on regular diets, consumed between 150 and 200 g of their daily intake as carbohydrates, and were screened to exclude associated diseases, e.g. overt diabetes mellitus, liver disease, and hypo- or hyperthyroidism. None was receiving steroid or thiazide therapy.

A 3-hour oral glucose tolerance test (GTT) was administered to each participant, and blood glucose, plasma immunoreactive insulin (IRI), free fatty acid (FFA), and lactate levels were determined on fasting and following the ingestion of the equivalent of 75 g of glucose in the form of Glucola*12 at %, 1, 2, and 3 hours. The GTTs were classified according to the cutoff levels of glucose recommended by Fajans and Conn,13 and for comparison by the University Group Diabetes Program14 and the Wilkerson's point system.15 In addition, fasting serum total cholesterol, triglyceride, lipid phosphorus, and uric acid levels were determined. These methods have been described in detail elsewhere.16 Cholesterol values were regularly compared with samples from the National Communicable Disease Center. Lactate was accomplished by the method of Hohorst.17 Lipoprotein electrophoresis was performed according to Lees and Hatch18 and typed according to Fredrickson.19 The sum of glucose, IRI, FFA, and lactate was obtained by adding the respective levels at fasting, and at %, 1, 2, and 3 hours during the oral GTT.

Data analyses were accomplished by stratifying the study groups according to age, relative activity, and time elapsed from onset of disease to examination. Relationships were investigated by use of the Student t-test, chi-square contingency tables, and Pearson's product-moment correlation coefficients.20 Multivariate relationships between sets of variables were assessed by computing the canonical correlations.21

Results

Population Description

The IHD group ranged in age from 36 to 72 years with a mean age of 53 years and the control subjects from 21 to 82 years, with a mean age of 46 years (fig. 1).

In the 75 IHD patients, 42 (56%) had a family history (i.e. mother, father, or siblings) of myocardial infarction compared to 60 (37%) of the 161 controls (P < 0.05). There was no relationship between the frequency of abnormal GTT and the elapsed time between the disease onset and the examination.

Height and weight were significantly and negatively correlated to age (r = -0.238 and r = -0.213, respectively) in IHD and controls, and because of the strong correlation between height and weight (r = 0.552) relative weight was used as a measure of obesity.22 Both the IHD and control groups showed a tendency toward relative overweight with mean percentages of 11.0 and 10.5, respectively. There was no increase in the number of abnormal GTT with increasing relative weight in either group.

Incidence of Normal and Abnormal GTT according to Various Criteria

The percentage of abnormal GTT in IHD is significantly higher (P < 0.01) than in healthy control subjects regardless of the GTT classification (table 1). The classification of Fajans and Conn yielded the highest percentage of abnormal GTT in IHD and control subjects, and thus it was chosen to ensure a better analysis of the data.

Metabolic Differences in Subjects with Angina Pectoris, Myocardial Infarction and those with Both Angina Pectoris and Myocardial Infarction

The 75 IHD patients were subdivided as follows: 21 had angina pectoris (AP), 36 had myocardial infarction (MI), and 18 had both MI and AP. The subgroup with both MI and AP showed significantly higher sum IRI and % and 2-hour IRI levels, with a delayed decay at 2 and 3 hours when compared with the subgroup with AP only. There were no other significant differences between the subgroups.

IHD and Age-Matched Control Subjects between 45 and 64 Years

Since IHD is most prevalent in the age range of 45 to 64 (fig. 1), the 65 IHD and 69 healthy control subjects from this age range were selected. The mean ages were 54 (± 5.6)
and 51 years (±5.9), respectively. In the age-matched groups the ratio of abnormal tests in this age range remained consistent with the total populations, and the frequency of abnormal GTT in IHD remained significantly higher than that of control subjects (P < 0.05).

Table 1
Prevalence of Normal and Abnormal GTT in Male IHD and Control Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fajans and Conn [3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>46 (61%)</td>
<td>29 (39%)</td>
<td>75 (100%)</td>
</tr>
<tr>
<td>Control</td>
<td>135 (84%)</td>
<td>26 (16%)</td>
<td>161 (100%)</td>
</tr>
<tr>
<td>X² = 13.3 P &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University Group Diabetes Program [4]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>62 (83%)</td>
<td>13 (17%)</td>
<td>75 (100%)</td>
</tr>
<tr>
<td>Control</td>
<td>158 (98%)</td>
<td>3 (2%)</td>
<td>161 (100%)</td>
</tr>
<tr>
<td>X² = 17.0 P &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilkerson Point System [5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>65 (87%)</td>
<td>10 (13%)</td>
<td>75 (100%)</td>
</tr>
<tr>
<td>Control</td>
<td>157 (98%)</td>
<td>4 (2%)</td>
<td>161 (100%)</td>
</tr>
<tr>
<td>X² = 8.9 P &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean GTT curves of the healthy agematched controls peaked at ½ hour, and that of IHD was shifted to 1 hour with a slightly higher peak. The 2-hour glucose level in IHD was significantly higher (P < 0.01) than in the control subjects. The mean IRI response curves of both groups peaked at 1 hour but the 2- and 3-hour IRI levels were elevated in IHD, though not to a statistically significant degree.

Figure 1
Age distribution of male IHD and control subjects with normal and abnormal GTT. Age-matched groups from 45 to 64 years are indicated.

Mean GTT and IRI Response Curves by Normal and Abnormal Classification of GTT

The mean GTT and IRI response curves are virtually identical in the subgroups of IHD and age-matched control subjects with normal GTT (fig. 2). In the IHD and control subgroups, with abnormal GTT the peaks of the mean GTT curves are shifted from ½ hour to 1 hour. The 2- and 3-hour glucose levels were 20 mg% higher in IHD than in control subjects, and the difference at 3 hours was statistically significant (P < 0.05) indicating slower glucose utilization in IHD despite...
higher IRI response. In both IHD and control subgroups with abnormal GTT, the IRI response rose sharply and identically to 90 μ units/ml at 1 hour and continued to rise in IHD to a delayed 2-hour peak at 106 μ units/ml. The 3-hour IRI levels were nearly identical at 45 and 41 μ units/ml.

The IRI response curves peaked at 2 hours in 63% of the 24 IHD patients and in 31% of the 13 control subjects with abnormal GTT. In IHD and control subjects with abnormal GTT, IRI response levels of 50–150 μ units/ml were found in 83% and 46%, respectively. Maximum IRI response levels above 150 μ units/ml were found in 13% of IHD and 15% of the control subjects. In IHD with abnormal

Figure 2

Mean GTT and IRI response curves in male IHD and control subjects (age range 45 to 64 years) according to normal and abnormal GTT.
GTT, only one in 24 (4%) had a IRI response level less than 50 μ units/ml versus 5 of 13 (39%) in control subjects.

**Free Fatty Acid (FFA) Response**

All groups had nearly identical slopes between fasting and the 2-hour nadir (fig. 3). However, the IHD subgroup with abnormal GTT had an elevated fasting FFA level when compared with the subgroup with normal GTT. In the control group, the FFA response showed a marked rebound between 2 and 3 hours, regardless of whether the GTTs were normal or abnormal, whereas the rebound in IHD patients was considerably less (P < 0.05) at 3 hours, when the total IHD group was compared with the control group.

**Lactate Levels**

It is evident from figure 4 that in the age-matched control subjects with normal GTT, the lactate level reached a sharp peak at 1 hour, followed by a rapid decay to below fasting level at 3 hours. This type of mean lactate curve is similar to that of the mean GTT curve in this subgroup (fig. 2). The mean lactate curves of the control subjects with abnormal GTT and IHD patients with normal and abnormal GTT exhibit lagging maximum lactate levels at 1 and 2 hours. The IHD patients with abnormal GTT have the highest lactate levels at all time intervals and the fasting, the 3-hour lactate, and the sum lactate levels are significantly higher when compared to the control subjects with abnormal GTT.

**Lipoprotein Electrophoretic Patterns, Lipid, and Uric Acid Levels**

Lipoprotein electrophoresis was accomplished on a subsample of 45 IHD subjects and 91 healthy control subjects as shown in table 2.

Chi-square analysis revealed a significantly (P < 0.001) greater frequency of abnormal lipoprotein patterns in IHD than in control subjects. When type II are excluded from the

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**Figure 3**

Mean FFA response curves in male IHD and control subjects (age range 45 to 64 years) according to normal and abnormal GTT.
chi-square analysis, the same significant association of type IV with IHD is obtained.

In the 77 subjects with normal lipoprotein patterns, 62 had normal and 15 abnormal GTT. In the 59 subjects with lipoprotein abnormalities, 37 had normal and 22 abnormal GTT. The chi-square analysis of the lipoprotein and GTT classifications yielded a significant dependence \((P < 0.05)\), indicating that lipoprotein abnormalities accompany abnormal GTT.

The lipid and uric acid interrelationships in IHD and age-matched control subjects are summarized in Table 3.

**Table 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>GTT</th>
<th>Type II</th>
<th>Type IV</th>
<th>Normal</th>
<th>Total</th>
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<tr>
<td>IHD</td>
<td>Normal</td>
<td>1</td>
<td>14</td>
<td>9</td>
<td>24 (53%)</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>1</td>
<td>15</td>
<td>5</td>
<td>21 (47%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2 (4%)</td>
<td>29 (65%)</td>
<td>14 (31%)</td>
<td>45 (100%)</td>
</tr>
<tr>
<td>Control</td>
<td>Normal</td>
<td>2</td>
<td>20</td>
<td>53</td>
<td>75 (82%)</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>0</td>
<td>6</td>
<td>10</td>
<td>16 (18%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2 (2%)</td>
<td>26 (29%)</td>
<td>63 (69%)</td>
<td>91 (100%)</td>
</tr>
</tbody>
</table>

Figure 4

Mean lactate response curves in male IHD and control subjects (age range 45 to 64 years) according to normal and abnormal GTT.
Glucose and Insulin Interrelationships

The correlation coefficients between glucose and IRI levels during GTT provide further evidence that the IRI response is delayed and elevated in IHD. In IHD the 1-hour glucose level is significantly correlated with the 2- and 3-hour IRI levels, the 2-hour glucose with the 2- and 3-hour IRI levels, and the 3-hour glucose with the 3-hour IRI level in a forward manner (i.e. early glucose to later insulin). In the control group, the 1-hour glucose level is correlated with the 1- and 2-hour IRI levels, and the 2-hour glucose with the 2-hour IRI level in a more immediate manner.

Canonical Correlations

Canonical correlations which maximize the relationship between variables were calculated in pairs between glucose, IRI, FFA, and lactate levels at all time intervals during the oral GTT, in order (1) to determine the independence of these metabolic variables and (2) to assess the interdependence which may exist between any two pairs. The strongest canonical correlation was between the glucose and IRI levels (r = 0.68). The remaining correlations in order of descending strength were: IRI-FFA (0.50), IRI-lactate (0.47), GTT-FFA (0.42), GTT-lactate (0.41), and FFA-lactate (0.34).

Discussion

It is difficult to establish the absolute frequency of the abnormal GTT in IHD and control subjects because of the various interpretations in the literature of normal and abnormal GTT. The glucose load employed in this study was compared with that recommended by the Committee on Statistics of the American Diabetes Association.23 The mean (± sd) of height and weight for our total population is 69 in (± 3) and 170 lb (± 22), respectively. The recommended glucose load for a 69-in. and 170-lb subject is 77 g, calculated from 40 g/m² of body surface. This agrees with the 75 g of glucose equivalent used in this study.

Despite the higher frequency of abnormal GTT in the IHD group, comparison of the mean GTT and IRI curves showed only slight elevation in the IHD group. This is due to the relatively small percentage of abnormal GTTs which account for these differences between the groups.

There is a marked delay in the peak time of the IRI response in the IHD subgroup with abnormal GTT when compared to the age-matched healthy control subjects. The IHD patients with abnormal GTT have a 2-hour IRI response peak, versus a 1-hour peak in the control subjects. Similar observations have been made in mild diabetics24 and in patients with premature coronary heart disease.9

Table 3

<table>
<thead>
<tr>
<th>GTT</th>
<th>Variable</th>
<th>IHD group</th>
<th></th>
<th>Control group</th>
<th></th>
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<tr>
<td></td>
<td></td>
<td>X</td>
<td>sd</td>
<td>X</td>
<td>sd</td>
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<tr>
<td>Normal</td>
<td>Triglycerides</td>
<td>135.0</td>
<td>52.1</td>
<td>120.0</td>
<td>55.6</td>
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<tr>
<td></td>
<td>Lipid phosphorus</td>
<td>10.1*</td>
<td>1.38</td>
<td>9.6</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>248.0</td>
<td>49.5</td>
<td>223.0†</td>
<td>39.8</td>
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<tr>
<td></td>
<td>Uric acid</td>
<td>6.0*</td>
<td>1.24</td>
<td>5.4*†</td>
<td>0.99</td>
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<tr>
<td>Abnormal</td>
<td>Triglycerides</td>
<td>153.0</td>
<td>60.1</td>
<td>157.0</td>
<td>94.2</td>
</tr>
<tr>
<td></td>
<td>Lipid phosphorus</td>
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<td>1.60</td>
<td>10.1</td>
<td>1.11</td>
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<tr>
<td></td>
<td>Cholesterol</td>
<td>270.0</td>
<td>56.0</td>
<td>228.0†</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>Uric acid</td>
<td>6.8*</td>
<td>1.3</td>
<td>6.1*</td>
<td>1.05</td>
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</table>

N = 41 N = 56
N = 24 N = 13

Significant difference between subgroups with normal and abnormal GTT: *P < 0.05.
Significant differences between IHD and control subjects: †P < 0.01; ‡P < 0.05.

Correlations

Canonical

Variable
Interaction

Interactions

Significant

Difference

Glucose

Insulin

Correlation

Interrelationship

Frequency

Abnormal

GTT

IHD

Control

subjects

Comparison

Mean

Lipid

Uric

Acid

Levels

Male

IHD

and

Control

Subjects

Table 3

Mean Lipid and Uric Acid Levels in Male IHD and Control Subjects

<table>
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<th>IHD group</th>
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<th>Control group</th>
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<td>1.05</td>
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In the IHD patients but not in the age-matched control subjects, the serum total cholesterol and lipid phosphorus are significantly and positively correlated with the $\frac{1}{2}$- and 1-hour glucose levels, and cholesterol is further correlated with the 1-hour IRI level. It is reasonable to assume that the elevated $\frac{1}{2}$- and 1-hour glucose levels contribute in some significant, as yet unknown, manner to the elevated cholesterol and lipid phosphorus levels in IHD patients only. These observations are somewhat similar to those reported by Hatch et al.\textsuperscript{25} and by Heinle et al.\textsuperscript{26}

In the control group, the triglycerides are more strongly correlated with the glucose and IRI levels than in the IHD group. This may be related to the delayed and elevated IRI response in IHD.

Levy and Fredrickson et al. state that younger individuals with inborn type II or IV lipoprotein abnormalities are more prone to IHD.\textsuperscript{19} The data presented here show that 65\% of IHD patients have type IV lipoprotein patterns and that 52\% of these also have an abnormal GTT. These results confirm the findings of Salel et al.\textsuperscript{27} The ratios of type IV/abnormal GTT are virtually identical in both studies. This raises the possibility that the abnormal GTT alone may not be as important a risk factor of IHD unless it coexists with lipoprotein abnormalities.

The elevated uric acid levels in subjects with abnormal GTT are significant since it has been postulated by Galzigna et al. that uric acid is a potent inhibitor of monoamine oxidase,\textsuperscript{28} and by Cegrell et al. that the inhibition of monoamine oxidase could affect the biogenic amine levels in the pancreatic beta-cells and thereby effect increased insulin secretion.\textsuperscript{29}

A possible explanation for the accumulation of lactate in IHD patients with abnormal GTT would be the excessive availability of FFA and competition for the availability of coenzyme A for the dehydroxylation of pyruvate (fig. 3), which supports the existence of a glucose-FFA cycle as suggested by Randle, Hales, et al.\textsuperscript{30}

The three strongest canonical correlations, found between IRI and glucose, IRI and FFA, and IRI and lactate levels, imply that insulin is the controlling factor in both carbohydrate and lipid metabolism. It is possible that prolonged and excessive availability of insulin will promote conversion of more glucose to FFA and also the trapping of more FFA in tissues as triglycerides, phospholipids, and cholesterol.

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ISCHEMIC HEART DISEASE

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