Lipid and Carbohydrate Studies in Coronary Artery Disease

By HERMAN L. FALSETTI, M.D., J. DAVID SCHNATZ, M.D., DAVID G. GREENE, M.D., AND IVAN L. BUNNELL, M.D.

SUMMARY

Twenty-seven patients with arteriographically proved coronary artery disease, aged 27 to 59 years, were studied for abnormalities of lipid or carbohydrate metabolism. All patients were referred because of cardiac symptoms and none had any prior history of lipid or carbohydrate abnormality. Twenty-three patients were found to have some abnormality of carbohydrate or lipid metabolism, and four had none. Seventeen patients had an abnormal lipoprotein electrophoretic pattern, 12 had elevated serum cholesterol concentrations, and 15 elevated serum triglyceride values. Eighteen patients had an abnormality of carbohydrate metabolism, 11 as determined on standard glucose tolerance tests and seven on cortisone glucose tolerance tests. These abnormalities of carbohydrate and lipid metabolism were not related to age or ponderal-index ratio. This high incidence of carbohydrate and lipid abnormalities in association with coronary artery disease may be important in the pathogenesis of the vascular disease as well as management of these patients and their progeny.

Additional Indexing Words:
Coronary arteriosclerosis  Coronary arteriography  Lipoprotein electrophoresis
Cholesterol  Triglyceride  Glucose tolerance test
Cortisone glucose tolerance test

THE INCREASED INCIDENCE and accelerated appearance of vascular lesions in patients with established diabetes mellitus, hyperlipidemia, or both, is well known. In contrast, the relationship of vascular disease to occult abnormalities in carbohydrate or lipid metabolism is uncertain. Coronary artery disease is so common in patients in their sixth decade and older that it is difficult to distinguish from the normal aging process. It is unusual, however, to have symptomatic coronary arteriosclerosis in earlier life, and thus when it is found one suspects an underlying explanation such as an error in carbohydrate or lipid metabolism.

Formerly, investigation of this problem has been hampered by two major technical difficulties. First, it was difficult to estimate the extent and involvement of coronary artery disease in a living person. Second, the methods used in the study of lipids were tedious, and no simple classification existed. Recently, however, Sones and Shirey have developed a safe and simple method of coronary arteriography which has made it possible to make high quality pictures demonstrating lesions in the coronary arteries. Concurrently Fredrickson and Lees have presented a system of phenotyping lipid abnormalities by lipoprotein electrophoresis.

Methods

Twenty-seven patients, aged 27 to 59 years, with arteriographically proved coronary artery disease form the basis of this study. All patients...
were referred for diagnostic coronary arteriography. None of these patients was known to have abnormal lipid or carbohydrate metabolism prior to the onset of cardiac symptoms. History, physical examination, and appropriate laboratory tests failed to reveal any evidence of thyroid, renal, hepatic, or other diseases which would predispose the individual to abnormal lipid metabolism. The age, height, weight, duration of symptoms, and electrocardiographic findings obtained at the time of the coronary arteriogram are detailed in table 1. The ponderal index (height in inches divided by the cube root of the weight in pounds) was used to measure the degree of obesity.

All patients took their usual diet prior to blood studies. This was assumed to be isocaloric if weight had been stable over a 4-week period. Dietary history generally showed this to be the usual type of American diet, which provides 40% of the calories from carbohydrate, 40% from fat, and 20% from protein. After an overnight fast, serum and EDTA plasma were obtained, chilled, and centrifuged. The cholesterol determinations were performed the same day by the modified method of Schoenheimer and Sperry, and triglyceride values were determined on frozen serum by the Van Handel and Zilversmit procedure.

In all cases lipoprotein electrophoresis was performed on plasma promptly chilled and kept at 4 C. The patient was then placed on a 300-g carbohydrate diet for 3 days. A glucose tolerance test was then performed, and glucose was measured by an autoanalyzer using the ferricyanide reduction technique. If the results fell within the limits of normal, a cortisone glucose tolerance test was performed according to the method of Fajans and Conn. After these tests, selective coronary

Table 1
Summary of Sex, Age, Duration of Symptoms, Electrocardiographic Findings, and Coronary Artery Lesions

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Duration of symptoms (yr)</th>
<th>ECG</th>
<th>Coronary arteriography*</th>
<th>R</th>
<th>LA</th>
<th>LC</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>27</td>
<td>1</td>
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<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>31</td>
<td>6</td>
<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>31</td>
<td>½</td>
<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>34</td>
<td>1½</td>
<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>35</td>
<td>½</td>
<td>Normal</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>37</td>
<td>2</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>39</td>
<td>5</td>
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<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>42</td>
<td>¾</td>
<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>42</td>
<td>¾</td>
<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>43</td>
<td>1/12</td>
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<td>+</td>
<td>+</td>
<td>0</td>
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<tr>
<td>11</td>
<td>M</td>
<td>44</td>
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<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>46</td>
<td>3</td>
<td>Abnormal</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>13</td>
<td>M</td>
<td>46</td>
<td>3</td>
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<tr>
<td>14</td>
<td>M</td>
<td>48</td>
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<td>Normal</td>
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<td>+</td>
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<td>M</td>
<td>49</td>
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<td>+</td>
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<tr>
<td>16</td>
<td>M</td>
<td>51</td>
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<td>M</td>
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<td>18</td>
<td>M</td>
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<td>+</td>
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<tr>
<td>19</td>
<td>M</td>
<td>52</td>
<td>4</td>
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<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>52</td>
<td>2</td>
<td>Abnormal</td>
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<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>53</td>
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<td>+</td>
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<td></td>
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<tr>
<td>22</td>
<td>M</td>
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<td>+</td>
<td></td>
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<td>23</td>
<td>F</td>
<td>55</td>
<td>1</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>55</td>
<td>5</td>
<td>Abnormal</td>
<td>+</td>
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<td>55</td>
<td>6</td>
<td>Abnormal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>59</td>
<td>4</td>
<td>Normal†</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*+ = lesion present; 0 = normal vessel; RA = right coronary artery; LA = left anterior descending artery; and LC = left circumflex artery.
†Positive Master’s test.
arteriography was performed and disease of the coronary arteries was coded according to the distribution of anatomic involvement. Correlation coefficients were determined by standard statistical methods on a 7044 IBM computer.

Results

Age and Sex
Our group included 24 males and three females ranging in age from 27 to 59 years (table 1). Two of the females were still menstruating (cases 5 and 12), and one female (case 24) was postmenopausal.

Family History
Nine patients had significant family histories. Of these, four had a family history of coronary artery disease occurring before age 65 years, four had a family history of diabetes, and two a family history of hyperlipidemia. Only one patient (case 2) had a family history positive for both heart disease and hyperlipidemia.

Type and Duration of Symptoms
These patients had symptoms for periods of 1 month to 6 years (table 1) and were referred by their physicians for varying degrees and combinations of myocardial ischemia, congestive heart failure, and unexplained chest pain (table 2).

Electrocardiography
The resting electrocardiogram was abnormal in 19 of the 27 patients, four (cases 4, 9, 11, and 22) of whom were taking digitalis (table 1). A pattern diagnostic of myocardial infarction was identified eight times. Isolated ST-T wave changes, diagnosed as indicating subendocardial ischemia, occurred in eight patients. Three patients had patterns of complete bundle-branch block, two left and one right. Of the eight patients with normal resting electrocardiograms, six were given a Master's two-step exercise test. Two patients had a positive test when defined as a 0.5-mm depression of the S-T segment, and two had an equivocal response. Of the two patients with equivocal responses one had cinearteriographic involvement of one vessel, and the other had involvement of two vessels. Of two patients (cases 5 and 23) with negative Master's exercise tests, both had involvement of all three coronary vessels by arteriography.

Two patients (cases 20 and 24) with normal resting electrocardiograms did not have provocative exercise tests because they had classical angina at rest. On arteriography both had involvement of all three coronary vessels.

Cinearteriography
Fourteen of the 27 patients had involvement of all three vessels, 10 of two vessels, and three of a single vessel (table 2). The left anterior descending branch was involved in every patient. The three patients with disease of one coronary vessel had symptoms for 1, 2, and 3 years, respectively.

Glucose Tolerance
Eleven of the 27 patients had abnormal glucose tolerance tests, and seven of the remaining 15 had abnormal cortisone glucose tolerance tests (tables 3 and 4). Of the 18 with abnormal glucose tolerance, 15 had no family history of diabetes mellitus.

Table 2
Classification of Patients According to Presenting Symptom and Number of Abnormal Coronary Arteries

<table>
<thead>
<tr>
<th>Presenting symptom</th>
<th>No. of patients</th>
<th>No. of coronary vessels involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina or previous infarct</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure and angina</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain of unknown etiology</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>3</td>
</tr>
</tbody>
</table>

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In order to evaluate the influence of age and body weight on carbohydrate metabolism, the blood glucose 2 hours after oral ingestion of 100 g of glucose was plotted against age and ponderal index. No significant correlation was noted from the correlation coefficients of -0.26 for age and -0.24 for ponderal-index ratio.

### Cholesterol and Triglyceride

Serum cholesterol values determined while patients were on their usual diet were averaged and presented in table 3. Twelve patients had serum cholesterol values of 300 mg/100 ml or greater, and 15 had serum triglyceride levels greater than 150 mg/100 ml. Neither the level of serum cholesterol nor triglyceride correlated with age or ponderal-index ratio.

### Lipoprotein Electrophoresis

Figure 1 illustrates the typical lipoprotein electrophoretic patterns observed in this study. The terminology of Fredrickson and associates\(^9\) has been used. The results are shown in table 3. Type II is identified by an intense \( \beta \)-lipoprotein band indicative of an elevated serum cholesterol. The type II classification also includes patients with a
modest elevation of pre-β lipoprotein in addition to increased β-lipoprotein. Concomitant with the slight increase in pre-β lipoprotein, one would expect a modest increase in the triglycerides as was frequently the case (table 3). A type IV pattern (fig. 1) consists of a large increase in pre-β lipoprotein which is associated with a sizeable increase in serum triglyceride and varying degrees of cholesterol elevation. The pre-β lipoprotein in these cases floated at a density of 1.006 when centrifuged at 100,000 × g for 16 hours. This feature is characteristic of pre-β lipoprotein as well as the β-lipoprotein which occurs in type III. This is in contrast to the floatation of β-lipoprotein of type II which remains in the infranate under these conditions. Seventeen patients had abnormal lipoprotein electrophoretic patterns (tables 3 and 5), of which 13 were type II and 4 were type IV.

Discussion

An increased incidence of pathologically proved coronary vascular disease has been demonstrated in persons who have had diabetes mellitus,10, 11 or hyperlipidemia.12 Until the advent of coronary arteriography it was difficult to be certain of coronary vascular disease in the living since definite abnormalities can occur without signs or symptoms, and symptoms suggestive of coronary artery disease can occur in the absence of demonstrable anatomic alteration. Recently, a high incidence of decreased glucose tolerance,13, 14 and of increased serum triglyceride15 has been demonstrated separately in studies performed on patients with angiographically proved coronary artery disease. The present study describes cardiac findings as well as glucose tolerance and serum lipid values in a group of patients referred for coronary arteriography as a diagnostic procedure or in preparation for surgical revascularization of the myocardium (table 2).

The patients in this study were a select group and consisted of patients referred for coronary arteriography during the period from September 1966, to January 1967, plus three patients seen earlier before a formal series was started. Eight patients in this study had a normal resting electrocardiogram, a long-recognized phenomenon of coronary vascular disease that has been confirmed recently by coronary angiography.16 Three patients with significant cardiac symptoms had involvement of a single coronary vessel. This is in agreement with data collected by Cohen and associates14 and supports the conclusion that angina pectoris may be present with a single arterial lesion.

The ponderal index, a convenient scale to indicate obesity, did not correlate with age,

Table 4

<table>
<thead>
<tr>
<th>Total no. per group</th>
<th>Decreased glucose tolerance</th>
<th>CGTT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (24)</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Female (3)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Family history of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (4)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Negative (23)</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

*GTT = glucose tolerance test.
†CGTT = cortisone glucose tolerance test.
blood glucose, or serum lipids. In contrast to the expected decrease in glucose tolerance and increase in serum lipids with advancing age, the younger individuals in this study had an equally high degree of abnormal glucose tolerance and serum lipids. These findings are consistent with a select population. They differ from the more usual pattern of glucose intolerance or elevated serum lipids which increase in prevalence with age and may be associated with varying degrees of obesity.

In considering the association of coronary vascular disease and decreased glucose tolerance, several possibilities are apparent: (1) The atherosclerotic process of coronary vascular disease may predispose individuals to a decrease in glucose tolerance by virtue of decreased activity, or by pancreatic vascular disease, which may lead to alterations in endocrine function of the pancreas. (2) Some common factor may lead separately to each. A possible example is synalbumin, which has been shown to be present in diabetes and in coronary artery disease. (3) An occult decrease in glucose tolerance may have predisposed these individuals to coronary artery disease. The last appears to be the most likely possibility by analogy with the increased frequency of coronary artery disease in overt diabetes. The metabolic alterations that occur in blood vessels of diabetic animals add further weight to this last possibility.

Previous studies on serum lipids and coronary vascular disease have shown not only
an association between the two, but also that either cholesterol or triglyceride may be increased.\textsuperscript{24} This was also the case in this group of patients in whom an increased cholesterol, an increased triglyceride, or an increase in both was demonstrated (table 3). The possibility that the vascular disease produced the hyperlipidemia is remote, though clearance of plasma lipids depends on an adequacy of the circulation. As postulated for glucose tolerance, it is also possible that a common factor leads to both the lipid abnormalities and to coronary vascular disease. The weight of evidence, however, favors the theory that the altered lipid metabolism predisposes to coronary vascular disease.\textsuperscript{12} In particular, the phenotype II abnormality, which was most prevalent in these studies, is known to be associated with accelerated atherosclerosis.\textsuperscript{8} Nine of the 13 patients with type II hyperlipoproteinemia had glucose intolerance (table 5), a feature not generally recognized with this phenotype. A number of patients with phenotype II demonstrated pre-\(\beta\) lipoprotein and an associated increase in serum triglyceride (table 3). An increase in plasma pre-\(\beta\) lipoprotein has previously been shown to accompany ischemic heart disease as well as diabetes mellitus.\textsuperscript{25}

In the cases in which carbohydrate and lipid abnormalities coexisted (table 5), it may have been by chance or there may have been a relationship between the two. Certainly a decrease in glucose tolerance has been associated with increase in the concentration of both cholesterol and triglyceride.\textsuperscript{26} The lipid abnormality may be secondary to the decrease in glucose tolerance as mediated by decreased removal or increased synthesis of lipid. On the other hand, the decrease in carbohydrate tolerance could be secondary to insulin resistance\textsuperscript{27} as a response to abnormal serum lipids. Resolution of this problem is urgently needed as it may hold an important key to understanding coronary artery disease.

This study demonstrates that in this small group of patients with coronary disease, there was a high degree of multiple and mixed abnormalities in glucose tolerance, serum cholesterol, and triglyceride which had been unrecognized previously. Recognition is important not only to planning further definition of the metabolic error, but also to management of the patients, siblings, and most importantly any progeny who may be shown to have a similar abnormality.

\textbf{Acknowledgment}

We wish to acknowledge the assistance of Mary M. Clayback, Ann Marie Niemiec, Patricia Zuber, and Elizabeth Lynch, Therapeutic Dietician.

\textbf{References}

9. \textsc{Fredrickson, D. S., Levy, R. I., and Lees, R. S.}: Fat transport in lipoproteins—an inte-


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