References


Improvement of Glucose Tolerance and Lowering of Glycohemoglobin and Serum Lipid Concentrations After Discontinuation of Antihypertensive Drug Therapy

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SUMMARY Diuretic-based antihypertensive drug therapy causes a disturbance in glucose tolerance and in serum lipid and lipoprotein concentrations. To determine the reversibility of the glucose intolerance and to identify mechanisms of the metabolic alterations, we examined a short glucose tolerance test and insulin, glycohemoglobin and lipid concentrations during the supervised withdrawal of long-term drug therapy in 35 patients with primary hypertension. An average of 7 weeks after stopping drugs, glucose tolerance and glycohemoglobin improved, total cholesterol decreased 18 mg/dl, triglyceride decreased 27 mg/dl, and the ratio of total to high-density lipoprotein cholesterol decreased (p<0.01 for all variables vs treatment values). The changes in lipid concentrations from the treated to untreated state correlated with the changes in glycohemoglobin and indexes of glucose metabolism. The findings suggest that insulin resistance develops during drug therapy and disturbs both glucose and lipid metabolism. Attention to these alterations may provide directions for further control of atherosclerotic complications during the treatment of hypertension.

DIURETIC DRUGS cause a modest increase in serum lipid and lipoprotein concentrations. Beta-adrenoceptor blocking agents are reported to increase serum triglyceride and decrease high-density lipoprotein (HDL) cholesterol concentrations. These lipid and lipoprotein alterations increase the risk of myocardial infarction. When used alone or in combination with methyl dopa, diuretic drugs also impair glucose tolerance. It seems possible that the glucose and lipid disturbances are related, because there are several links in their metabolic pathways. Elevated serum glucose concentrations can raise the glycohemoglobin content of erythrocytes. Whether the mild carbohydrate intolerance caused by diuretic drugs is sufficient to affect glycohemoglobin has not been examined. We had an opportunity to investigate these issues during the supervised withdrawal of
therapy before the introduction of new antihypertensive drugs. This report summarizes our findings on these metabolic relationships.

Materials and Methods

Patients

Thirty-five outpatients were receiving conventional antihypertensive drug therapy prescribed in our Hypertension Clinic or by their personal physicians at the time of recruitment into our programs for the evaluation of new drugs. All patients gave signed consent for the withdrawal of drug therapy. Twenty-five of the patients were men and 10 were women. Fifteen were black, one was oriental, and 19 were white. The average age was 53 ± 9 years (± SD). Twelve patients were obese (more than 20% above ideal weight for height). Average weight was 173 ± 6 lbs (± SEM) during treatment and 174 ± 6 lbs after discontinuance of drugs (p > 0.1). Systolic blood pressure was 133 ± 2 mm Hg (± SEM) during treatment and 151 ± 3 mm Hg (p < 0.01) after withdrawal of drugs. Diastolic blood pressure was 85 ± 2 mm Hg during treatment and 96 ± 1 mm Hg (p < 0.01) after cessation of drugs.

There was no evidence of clinically important associated disease or secondary hypertension as determined by medical history, physical examination, urinalysis and standard clinical chemistry tests. Three patients had electrocardiographic evidence of old myocardial infarction, but none had angina pectoris. One patient was taking a constant dose of digoxin throughout the study. Two patients had normal renal arteriograms, ruling out renovascular disease. Four patients had serum creatinine values greater than 1.5 mg/dl (i.e., 1.6-1.8 mg/dl), but none had a BUN greater than 26 mg/dl when free of drugs. Two patients had a fasting serum glucose greater than 120 mg/dl (i.e., 125 and 140 mg/dl) after cessation of drug treatment, but both had lower fasting glucose at other times. Six patients were studied twice, once after the withdrawal of diuretic therapy and once after combination therapy. The two complete sets of measurements in these patients were analyzed separately, making a total of 41 paired studies of 35 patients. Of the six patients studied twice, five were men and three were black.

Design of the Study

After recruitment into the program, patients were asked to report to the clinic in a fasting state while still taking their usual antihypertensive drugs. Blood was obtained for glucose, insulin, total cholesterol, triglyceride, HDL cholesterol, and routine clinical chemistries. The patients then ingested 75 g of glucose. Blood was drawn 1 hour later for measurements of glucose and insulin. In the 25 patients studied most recently, four other tests were also obtained. First, glycohemoglobin was measured in fasting blood. Second, cholesterol was determined in the lipoprotein fractions after ultracentrifugation. Third, glucose and insulin were measured 30 minutes after the oral glucose load. Fourth, lipoprotein lipase was analyzed in blood drawn 10 minutes after rapid i.v. injection of heparin. The heparin (Liquaemin sodium, Organon) was administered in a dose of 60 U/kg body weight immediately after the fasting blood specimens were drawn. The blood for lipase activity was drawn into chilled tubes, centrifuged at 4°C, and quickly frozen to −20°C for later assay. Tapering of nondiuretic antihypertensive drugs, if prescribed, was then begun. One week after cessation of nondiuretic drugs, the diuretic agents were stopped. The drugs prescribed and the duration of treatment at the time of the initial blood sampling are listed in Table 1. After discontinuance of drugs, patients were seen at intervals of 1-4 weeks. When diastolic blood pressure was greater than 90 mm Hg on two consecutive visits, the patients were asked to report fasting at the next visit for repeat blood studies. In eight patients, diastolic pressure had not increased above 90 mm Hg at the time of repeat blood sampling. Three of these eight patients were studied at their next visit 4-6 weeks after cessation of drugs because of an expected rapid return of hypertension, based on previous observed or reported high diastolic pressure. Three others were studied 5-21 weeks after discontinuance of drugs because of high systolic blood pressure. Two were studied 9-16 weeks after stopping drugs when repeated measurements showed no upward trend of blood pressure. This protocol for the repeat measurement was chosen because patients with a rapid recurrence of hypertension would not be at risk for an unduly long time and because a long interval, when safe, would allow fuller recovery of glycohemoglobin. With this protocol no patient developed angina or "overshoot" hypertension. One patient had headaches and a return of blood pressure to pretreatment levels 3 weeks after cessation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Dose* (mg/day)</th>
<th>Duration* (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic monotherapy</td>
<td>23</td>
<td>14 ± 5</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>11</td>
<td>77 ± 26</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>Furosemide</td>
<td>5</td>
<td>112 ± 52</td>
<td>18 ± 9</td>
</tr>
<tr>
<td>Ticrynafen</td>
<td>5</td>
<td>500 ± 0</td>
<td>14 ± 0</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>2</td>
<td>75 ± 35</td>
<td>10 ± 9</td>
</tr>
<tr>
<td>Beta-blocker monotherapy</td>
<td>1</td>
<td>320</td>
<td>43</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>17</td>
<td>28 ± 24</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>9</td>
<td>129 ± 62</td>
<td>30 ± 31</td>
</tr>
<tr>
<td>Furosemide</td>
<td>8</td>
<td>108 ± 63</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Antidiurenergic</td>
<td>18</td>
<td>22 ± 17</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>13</td>
<td>234 ± 83</td>
<td>26 ± 18</td>
</tr>
<tr>
<td>Methylxypol</td>
<td>4</td>
<td>1250 ± 646</td>
<td>15 ± 10</td>
</tr>
<tr>
<td>Reserpine</td>
<td>1</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>1</td>
<td>100</td>
<td>13</td>
</tr>
</tbody>
</table>

*Values are mean ± sd.
of chlorthalidone monotherapy. Testing at this time in this patient represented the shortest elapsed interval to repeat study in this series. The average time from discontinuation of drug therapy until repeat blood sampling for the entire group was 7 ± 5 weeks (± sd). The median interval was 5 weeks.

Our laboratory methods have been described. In the first 16 patients, HDL cholesterol was measured by the Lieberman-Burchard reaction after precipitating serum with heparin and manganese. In the last 25 paired studies, HDL as well as low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol were estimated after ultracentrifugation. Glycohemoglobin (hemoglobin Ala + b + c) was determined by the method of Abraham et al. Post-heparin lipolytic activity was measured by the method of Tietz and Fiereck.

Statistical Analysis

Serum concentrations of lipids, lipoprotein cholesterol, glucose, insulin, glycohemoglobin and lipoprotein lipase measured during therapy and again after stopping therapy were compared by paired t tests. Changes in these variables from the treatment to the posttreatment periods for each patient were calculated. Correlations among these changes were sought by least-squares analysis. Correlations of the absolute serum values of these substances during therapy and again after therapy were then tested to verify and strengthen any associations previously found.

Results

Data from patients withdrawn from diuretic monotherapy and from combination therapy were combined in this report because the directional changes of all measurements of interest were similar for both forms of therapy. In fact, total serum cholesterol decreased significantly after withdrawal of diuretics (238 to 223 mg/dl, p < 0.001) and after withdrawal of combination therapy (231 to 210 mg/dl, p < 0.025). Triglyceride decreased significantly after discontinuation of combination therapy (144 to 101 mg/dl, p < 0.01), but not after discontinuance of diuretic therapy (112 to 98 mg/dl, 0.1 > p > 0.05). The ratio of total cholesterol to HDL cholesterol decreased significantly after discontinuance of diuretic therapy (5.1 to 4.5, p < 0.02), but not after discontinuance of combination therapy (5.1 to 4.6, p > 0.1). Glycohemoglobin was significantly lower after cessation of combination therapy (7.9 to 7.2%, p < 0.02), but not after cessation of diuretic monotherapy (7.9 to 7.1%, 0.1 > p > 0.05). Because of these parallelisms, the two treatment groups were combined (table 2). Total serum cholesterol, triglyceride, and glycohemoglobin decreased significantly after withdrawal of antihypertensive drug therapy. LDL, VLDL and HDL cholesterol as well as lipoprotein lipase did not change significantly. The ratio of total cholesterol to HDL cholesterol declined significantly. Serum glucose concentrations were lower after withdrawal of antihypertensive drugs (fig. 1). Serum insulin also declined, but not significantly, after treatment was stopped.

The correlative data showed a direct linear relationship between changes in fasting glucose and changes in glycohemoglobin after discontinuation of drug treatment (r = 0.49, p < 0.02). The change in the sum of fasting glucose plus 30-minute and 1-hour glucose, here termed total glucose, also correlated with the change in glycohemoglobin (r = 0.41, p < 0.05). The absolute values of glycohemoglobin also correlated with the absolute values of several indexes of glucose metabolism during therapy, including fasting glucose (r = 0.46, p < 0.02), 30-minute glucose (r = 0.55, p < 0.01), 1-hour glucose (r = 0.43, p < 0.05) and total glucose (r = 0.41, p < 0.05).

We found a correlation between changes in glycohemoglobin and changes in triglyceride after discontinuance of drug therapy (table 3, part I, item 6). Following this lead, we found multiple correlations between indexes of glucose metabolism and lipid-lipoprotein metabolism. These correlations involved the changes in the variables from the treatment to posttreatment period (table 3, part I), the absolute values of glucose-insulin and lipid concentrations in serum during therapy (table 3, part II), and absolute

Table 2. Comparison of Glycohemoglobin and Indexes of Lipid Metabolism During and After Antihypertensive Drug Therapy

| Abbreviations: LDL = low-density lipoprotein; VLDL = very low density lipoprotein; HDL = high-density lipoprotein. |
|---|---|---|---|
| Glycohemoglobin (%) | 25 | 7.9 ± 0.2 | 7.2 ± 0.2 | < 0.01 |
| Total cholesterol (mg/dl) | 41 | 235 ± 8 | 217 ± 6 | < 0.01 |
| Triglyceride (mg/dl) | 41 | 127 ± 11 | 100 ± 8 | < 0.01 |
| LDL cholesterol (mg/dl) | 25 | 156 ± 8 | 147 ± 7 | NS |
| VLDL cholesterol (mg/dl) | 25 | 21 ± 6 | 13 ± 2 | 0.1 > p > 0.05 |
| HDL cholesterol (mg/dl) | 41 | 49 ± 2 | 49 ± 2 | NS |
| Ratio of total cholesterol to HDL cholesterol | 41 | 5.1 ± 0.3 | 4.5 ± 0.2 | < 0.01 |
| Lipoprotein lipase (IU/ml) | 25 | 106 ± 18 | 111 ± 13 | NS |

*Values are mean ± SEM.
values after cessation of drug treatment (table 3, part III).

Discussion

This study shows that serum glucose and lipid concentrations and glycohemoglobin decrease significantly upon withdrawal of antihypertensive drug therapy. In contrast to the evidence that insulin deficiency accompanies the glucose intolerance of diuretic therapy, we observed that serum insulin concentrations were unchanged or higher during therapy. This insulin pattern, together with increased glucose concentrations in our patients during antihypertensive therapy, suggest that insulin resistance is a more common cause of the carbohydrate intolerance. Further study is needed to ascertain whether abnormal insulin, altered receptors, postreceptor events, or other factors contribute to the apparent insulin resistance.

The elevations in fasting, 30-minute and 1-hour glucose values during therapy seem minor, representing increases of 9.5%, 13.9% and 14.3%, respectively, above the postdrug values. Nevertheless, this slight abnormality was accompanied by an increase in glycohemoglobin from 7.2% to 7.9% during therapy, an increment proportional to that of glucose. Thus, even mild disturbances of glucose metabolism can increase the glycosylation of hemoglobin. If glycosylation of hemoglobin and other proteins presages diabetic complications, then this metabolic alteration may not be trivial. More information is needed about the prognostic implications of raised glycohemoglobin. In accord with the findings of others and the acknowledged relationship of serum glucose to glycohemoglobin, we noted positive linear correlations between the change in fasting glucose and the change in glycohemoglobin. We also noted positive relationships between the absolute values of glucose and glycohemoglobin during therapy. Glycohemoglobin correlated with fasting glucose about as well as with any other index of carbohydrate metabolism.

In contrast to the correlations during therapy, glucose and glycohemoglobin did not correlate in the posttherapy period. The lack of relationship between glucose and glycohemoglobin in the postdrug period may be because the measurements were made only 7 weeks, on average, after discontinuation of the drugs, an interval perhaps too brief to restore glycohemoglobin to basal values. In fact, 19 studies were conducted only 3–4 weeks after cessation of drug therapy. Glycosylation of hemoglobin is considered to be a relatively slow and irreversible reaction and normal red cells have a life of 4 months; thus, the erythrocytes with excessive glycohemoglobin may not have been completely eliminated in some patients. A discrepancy of lag times for normalization of the defects may have obscured a relationship after termination of drug therapy. Correlations during therapy may have been of a higher order because measurements were obtained after prolonged therapy (table 1), a circumstance favorable to stabilization of glycohemoglobin at steady-state concentrations.

The correlations between glucose and lipid concentrations do not prove a causal relationship, but the correlations seem too numerous to be accounted for by chance alone. Systolic and diastolic blood pressure, serum potassium, uric acid, and chloride are affected by diuretic-based antihypertensive therapy, but these variables did not correlate regularly with serum lipid and lipoprotein concentrations in our study. Other investigators have reported correlations between serum lipid concentrations and glucose or glycohemoglobin. Taken together, the evidence points to a common mechanism of the glucose and lipid alterations during diuretic-based antihypertensive therapy. We offer the following tentative explanation to link the metabolic derangements in glucose and lipid metabolism. Insulin resistance is the critical abnormality, and it has several consequences. First, it impairs utilization of glucose, thereby decreasing the availability of glucose for energy requirements and increasing serum glucose concentrations. Second, the state of resistance weakens the inhibitory effect of insulin on lipolysis. As a result of this and perhaps because of the impaired utilization of glucose, fat stores are mobilized. Fat mobilization accelerates fatty acid transport to the liver. The fatty acids are, in part, esterified to triglycerides and secreted in VLDL. VLDL concentrations increase in blood and by
catabolism secondarily raise LDL levels. In the steady state that ensues, increases in VLDL, LDL, total cholesterol or triglyceride, or in all of them, may occur depending on the rate-limiting steps in their synthesis and catabolism. If this explanation is correct, the key question is: What causes the insulin resistance during antihypertensive therapy?

Whether these changes in glucose, insulin, glycohemoglobin and lipid metabolism during antihypertensive therapy promote atherosclerosis or other adverse pathologic effects is not known. However, based on coronary risk tables developed from the Framingham study, an increase in total cholesterol of 18 mg/dl, the average increase noted in this study, together with the development of glucose intolerance in 55-year-old men, the approximate age of our predominantly male population, would increase the probability of myocardial infarction within 6 years from 7.6% to 10.5% (assuming an untreated systolic blood pressure of 150 mm Hg and an absence of other risk factors). The decrease in systolic pressure of 18 mm Hg effected by drug therapy in this study would lower the probability to 8.8%. Thus, the probability of myocardial infarction would not be reduced by the drug therapy, owing to the metabolic derangements. In 35-year-old men, in whom total cholesterol exerts a stronger impact on the subsequent development of myocardial infarction, equivalent metabolic alterations and changes in blood pressure would raise the probability of myocardial infarction in 6 years from 0.9% to 1.2%, a relative increase of 33%. The imprecision of these risk estimates is attested by the fact that the Hypertension Detection and Follow-up Program (HDFP) demonstrated a decrease in myocardial infarction after prolonged drug treatment of hypertension. Nevertheless, our findings may explain, in part, why persons less than 50 years old in the HDFP experienced no reduction in mortality even though enormous numbers of them (n = 2400) were treated for an extended period (5 years). We do not advocate that drug therapy be withheld, because the complications of hypertension that are largely pressure-dependent, that is, stroke and congestive heart failure, benefit from the lowering of pressure. However, alternative therapies, other than more intensive drug regimens, may be required in hypertension for additional lowering of the incidence of myocardial infarction and other complications of atherosclerosis.
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