Additive Effects of Obesity, Hypertension, and Type 2 Diabetes on Insulin Resistance


Abstract Resistance to insulin-mediated glucose disposal has been previously shown to be increased in association with obesity, high blood pressure, and non-insulin-dependent diabetes mellitus. We initiated the present study to quantify the separate effects of hypertension and non-insulin-dependent diabetes mellitus on insulin resistance in both nonobese and obese subjects. To accomplish this, 88 subjects were divided into the following five experimental groups: normal blood pressure, nonobese (n=17); normal blood pressure, obese (n=18); high blood pressure, nonobese (n=18); high blood pressure, obese (n=19); and high blood pressure, obese, non-insulin-dependent diabetes mellitus (n=16). Plasma glucose and insulin concentrations were measured before and after a 75-g oral glucose load. Resistance to insulin-mediated glucose disposal was estimated by determining the steady-state plasma insulin and glucose concentrations during the last 30 minutes of a continuous infusion of somatostatin (5 μg/min), exogenous insulin (25 mU/m$^2$ per minute), and glucose (240 mg/m$^2$ per minute). Since the steady-state plasma insulin concentrations are similar in all subjects, the higher the steady-state plasma glucose, the more insulin resistant the individual. Nonobese subjects with normal blood pressure had the lowest plasma glucose and insulin responses and steady-state plasma glucose concentrations, and their values were significantly different from the other four groups. Obese or nonobese subjects with high blood pressure had significantly higher plasma glucose responses and steady-state plasma glucose concentrations than did their respective weight-matched control subjects. Finally, plasma glucose responses and steady-state plasma glucose concentrations were significantly higher in obese subjects with both high blood pressure and non-insulin-dependent diabetes mellitus. These results support the view that the effects of obesity, high blood pressure, and non-insulin-dependent diabetes mellitus on resistance to insulin-mediated glucose disposal are additive. (Hypertension. 1994;24:695-698.)

Key Words • blood pressure • insulin • glucose • obesity • insulin resistance • diabetes mellitus, non-insulin-dependent

In the past several years it has become apparent that the ability of insulin to stimulate glucose disposal can vary widely from person to person. In addition, it has also been shown that insulin resistance is a common feature in patients who are obese or have either hypertension or non-insulin-dependent diabetes mellitus (NIDDM). Patients with high blood pressure and/or NIDDM tend to be overweight, and it has been suggested that obesity plays a central role in the development of insulin resistance and its associated abnormalities. Thus, obesity can be viewed as the cause of insulin resistance in patients with high blood pressure and/or NIDDM or simply as a factor that modulates insulin-mediated glucose disposal in any individual, thereby making that individual more likely to develop hypertension or NIDDM. We initiated the present study to address these issues.

Methods

This study was performed in 88 volunteers in good general health with the exception of hypertension with or without the codiagnosis of NIDDM. Subjects were recruited to create the following five experimental groups: (1) normal blood pressure, nonobese (n=17); (2) normal blood pressure, obese (n=18); (3) high blood pressure, nonobese (n=18); (4) high blood pressure, obese (n=19); and (5) high blood pressure, obese, NIDDM (n=16). Obesity was defined as a body mass index greater than 27 kg/m$^2$ and hypertension by diastolic blood pressure greater than 90 mm Hg on at least three consecutive visits after subjects had sat for more than 5 minutes in a quiet environment. All subjects with high blood pressure had been off all antihypertensive medication for at least 4 weeks before the study. The diagnosis of NIDDM was established using National Diabetes Data Group criteria. Sulfonylurea-treated subjects with NIDDM were maintained on their usual program, and untreated diabetic subjects with a fasting plasma glucose concentration greater than 14 mmol/L were excluded. All volunteers had normal routine laboratory values and were not taking any drugs (other than sulfonylurea compounds) known to affect carbohydrate metabolism. Table 1 shows the baseline characteristics of the five study groups; it can be seen that they were relatively similar in terms of age and gender distribution. It is also apparent that there were appropriate differences in body mass index, blood pressure, and fasting plasma glucose concentration among the groups by selection.

After subjects gave informed written consent, they were admitted to the General Clinical Research Center and the following tests performed. All subjects were instructed to consume at least 300 g carbohydrate daily during the 3 days preceding all measurements and were always studied after a 12-hour overnight fast. Plasma glucose and insulin concentrations were measured before and 30, 60, 120, and 180 minutes after a 75-g glucose load. On a second occasion, insulin-mediated glucose disposal was estimated using a modification of the insulin suppression test. As previously described, this study consists of a 180-minute infusion of somatostatin (5 μg/min), insulin (25 mU/m$^2$ per minute), and glucose (240...
mg/m² per minute) into a superficial antecubital vein. Venous blood samples were obtained from the contralateral antecubital vein and kept patent by a slow infusion of 0.9% sodium chloride. Blood was obtained every 10 minutes during the last 30 minutes of the infusion for the measurement of plasma glucose and insulin concentrations, and the mean value of these four measurements was used to calculate the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations. Under these experimental conditions, since the SSPI concentrations are similar in all groups, the SSPG concentrations provide a measure of insulin-mediated glucose uptake; the higher the SSPG, the more insulin resistant the individual.

All results are given as mean±SEM. The integrated area above the baseline value was used as the measure of the plasma glucose and insulin responses to oral glucose and the SSPG value as the estimate of resistance to insulin-mediated glucose disposal. The statistical significance of the differences in the plasma glucose and insulin responses and the SSPG concentrations was evaluated by ANOVA. Comparisons between any two groups were performed with Scheffé’s post hoc multiple comparison test. Differences with a value of $P<.05$ were considered to be statistically significant.

### Results

Figs 1 and 2 show plasma glucose and insulin concentrations after the 75-g oral glucose load. By selection, the subjects with NIDDM had significantly elevated plasma glucose concentrations both before and after the glucose challenge compared with all other groups. Plasma glucose concentrations were relatively similar in the other four experimental groups, but there were some statistically significant differences among them. For example, plasma glucose concentrations were significantly lower in the normal, nonobese group than in the other three nondiabetic groups. Furthermore, nonobese or obese subjects with high blood pressure had significantly higher glucose concentrations than did their respective weight-matched, normotensive control subjects. Table 2 shows the statistical significance of all possible comparisons of the insulin responses of the five groups.

Comparison of plasma insulin concentrations (Fig 2) after the oral glucose load also showed that the response was significantly lower in the normal, nonobese subjects than in any other group. Although plasma insulin responses were significantly higher in the nonobese subjects with high blood pressure than in the nonobese, normotensive subjects, the insulin response of the obese subjects with hypertension was not greater than that of the obese, normotensive subjects. It should also be noted that the plasma insulin response of the subjects with NIDDM was not decreased compared with any other group. Table 3 lists the statistical significance of all possible comparisons of the insulin responses of the five groups.

Figs 3 and 4 illustrate the SSPI and SSPG values during the insulin suppression test. SSPI concentrations were similar in all five groups (Fig 3), as opposed to SSPG concentrations (Fig 4), which were quite different. Specifically, values were significantly higher in the diabetic group than in the other four groups, whereas SSPG concentrations were significantly lower in the normotensive, nonobese group. Furthermore, SSPG concentrations were significantly higher in the hypertensive, nonobese group compared with the normotensive, nonobese group. Similarly, SSPG values were significantly higher in the hypertensive, obese group compared with the

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (M/F)</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>FPG, mmol/L</th>
<th>FPI, pmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, nonobese</td>
<td>11/6</td>
<td>55±2</td>
<td>25.1±0.5</td>
<td>118±4</td>
<td>73±2</td>
<td>4.9±0.1</td>
<td>66±4</td>
</tr>
<tr>
<td>Normal, obese</td>
<td>11/7</td>
<td>56±2</td>
<td>31.0±0.3</td>
<td>126±3</td>
<td>77±2</td>
<td>5.1±0.1</td>
<td>103±14</td>
</tr>
<tr>
<td>Hypertension, nonobese</td>
<td>13/5</td>
<td>55±2</td>
<td>26.0±0.5</td>
<td>147±2</td>
<td>95±1</td>
<td>5.4±0.1</td>
<td>87±11</td>
</tr>
<tr>
<td>Hypertension, obese</td>
<td>12/7</td>
<td>53±2</td>
<td>32.2±0.6</td>
<td>151±3</td>
<td>97±1</td>
<td>5.7±0.1</td>
<td>102±10</td>
</tr>
<tr>
<td>NIDDM, hypertension, obese</td>
<td>11/5</td>
<td>59±2</td>
<td>33.0±0.9</td>
<td>153±2</td>
<td>96±1</td>
<td>8.6±0.6</td>
<td>188±25</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FPI, fasting plasma insulin; and NIDDM, non-insulin-dependent diabetes mellitus. Values are mean±SEM.
TABLE 2. Statistical Significance of the Differences in Glucose Responses of the Five Groups

<table>
<thead>
<tr>
<th></th>
<th>N, NOB</th>
<th>N, OB</th>
<th>↑ BP, NOB</th>
<th>↑ BP, OB</th>
<th>↑ BP, OB, NID</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, NOB</td>
<td></td>
<td></td>
<td>P&lt;.01</td>
<td>P&lt;.001</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>N, OB</td>
<td></td>
<td></td>
<td>NS</td>
<td>P&lt;.001</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>↑ BP, NOB</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>↑ BP, OB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;.001</td>
</tr>
</tbody>
</table>

N indicates normal blood pressure; NOB, nonobese; OB, obese; ↑ BP, hypertension; and NID, non-insulin-dependent diabetes mellitus.

Discussion

In this study we have made multiple metabolic measurements in five different population groups, and it would be excessive to discuss all of the possible differences among the experimental populations. Rather, we will address two major questions and put these conclusions into perspective with other relevant published studies.

The first issue is the role played by obesity in modulating the association between resistance to insulin-mediated glucose disposal and blood pressure. The results of the present study have demonstrated that nonobese subjects with hypertension are relatively insulin resistant compared with nonobese subjects with normal blood pressure. These data are consistent with previously published studies, and there seems to be no disagreement with the conclusion that nonobese individuals with high blood pressure tend to be insulin resistant. In contrast, there does not appear to be agreement concerning the effect of high blood pressure on insulin-mediated glucose disposal in obese individuals. The results presented in the present study support the view that resistance to insulin-mediated glucose disposal is present in subjects with high blood pressure irrespective of the degree of obesity. On the other hand, support for a contrary view can be found in the study of Bonora et al., who concluded that there was no difference in the insulin resistance of obese individuals as a function of blood pressure. Although there are no obvious explanations for the discordant results, there are some differences between our study and that of Bonora et al. For example, we compared insulin resistance in 37 obese subjects, almost twice the number (n=20) studied by Bonora et al. In addition, our obese population was on average older and less obese and contained approximately twice as many males as females in contrast to the opposite ratio in the study by Bonora et al. It is possible that none of the above differences are responsible for the discordant results, which may simply be a function of the fact that not all patients with hypertension are insulin resistant. Given the fact that Bonora et al. studied only 10 obese patients with hypertension, their inability to demonstrate increased insulin resistance in these individuals may only be a reflection of having by chance enrolled a somewhat greater proportion of insulin-sensitive patients in their obese group. Obviously, this question cannot be definitively answered, but the inability of Bonora et al. to document a greater degree of insulin resistance in obese patients with hypertension should not negate the fact that the present results have shown that insulin action is decreased in obese subjects with high blood pressure to a greater degree than it is in obese subjects with normal blood pressure.

Since the additive effect of NIDDM on insulin resistance in patients with hypertension has not been previously assessed, we cannot relate our results to published data. However, it is apparent from the data shown in Fig 4 that obese subjects with both NIDDM and hypertension were by far more insulin resistant than were obese subjects with or without high blood pressure.

In summary, the results of the present study have shown that resistance to insulin-mediated glucose disposal was increased in obese or nonobese subjects with hypertension when they were compared with weight-matched subjects with normal blood pressure.

Table 3 shows all possible comparisons of the significance of the differences in SSPG concentration of the five groups.

TABLE 3. Statistical Significance of the Differences in Insulin Responses of the Five Groups

<table>
<thead>
<tr>
<th></th>
<th>N, NOB</th>
<th>N, OB</th>
<th>↑ BP, NOB</th>
<th>↑ BP, OB</th>
<th>↑ BP, OB, NID</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, NOB</td>
<td></td>
<td></td>
<td>P&lt;.005</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>N, OB</td>
<td></td>
<td></td>
<td>P&lt;.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>↑ BP, NOB</td>
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<td></td>
<td></td>
<td>P&lt;.05</td>
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<td>↑ BP, OB</td>
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<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

Definitions are as in Table 2.
more, the greatest magnitude of insulin resistance was seen in subjects who were obese, hypertensive, and diabetic. These data are consistent with the hypothesis that obesity, high blood pressure, and NIDDM have additive effects on resistance to insulin-mediated glucose disposal. However, this conclusion should not be construed to imply that the mechanism responsible for the insulin resistance is similar in all three situations. Indeed, this is most likely not the case. Thus, in patients with NIDDM, at least some portion of the insulin resistance is secondary to "glucotoxicity," which cannot play a role in the insulin resistance of hypertension or obesity. Plasma free fatty acid concentrations have been shown to be elevated in both obesity and NIDDM. Since increases in free fatty acid concentrations can decrease insulin-mediated glucose disposal, it is possible that this change contributed to the insulin resistance seen in obesity and diabetes. On the other hand, it is also possible that there are primary changes at the molecular level leading to insulin resistance that could be similar or different in the case of obesity, hypertension, and NIDDM. However, the fact that we do not completely understand why insulin resistance occurs in any one of the three situations should not obscure the fact that resistance to insulin-mediated glucose uptake can occur in normal, nonobese individuals and in family members of patients with either hypertension or NIDDM in the absence of the full-blown clinical syndrome. Thus, insulin resistance cannot be viewed as being simply a secondary consequence of obesity, high blood pressure, or NIDDM, and its presence helps explain both the development and clinical course of these three syndromes.

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