Insulin Resistance Versus Insulin Secretion in the Hypertension of Obesity

Nawfal W. Istfan, Claudia S. Plaisted, Bruce R. Bistrian, and George L. Blackburn

We measured the degree of association between obesity, blood pressure, insulin resistance, and insulin secretion in 72 male and female obese hypertensive, obese nonhypertensive, and normal weight control subjects. Baseline weight, body mass index, percent body fat, waist/hip ratio, and systolic and diastolic blood pressures were obtained. Insulin sensitivity was assessed according to Bergman’s minimal model. Twelve-hour urinary c-peptide was measured after a standard liquid meal. Insulin action was inversely associated with blood pressure status, obesity status, and age. Meal-stimulated c-peptide excretion significantly correlated with systolic blood pressure and percent fat but not with body mass index or age. Multivariate regression analysis indicated that, of the measures of body composition, percent fat and waist/hip ratio had the strongest correlation with insulin action either alone or in combination with c-peptide excretion. Obese hypertensive patients had an index of insulin action (10⁻⁴ min⁻¹/[microunits/ml]) of 1.34±0.19, which was significantly (p<0.003) lower than in the obese nonhypertensive patients (index, 2.26±0.10) or the nonobese subjects (index, 5.41±0.26, p<0.001). Meal-stimulated c-peptide excretion (nmol/kg lean body mass) was increased only in the obese hypertensive group (0.32±0.01) and was significantly higher (p<0.001) than in the obese nonhypertensive (0.16±0.01) or the nonobese subjects (0.14±0.01). These results support the hypothesis that abnormalities in blood pressure regulation, insulin-stimulated glucose uptake, and insulin secretion coexist.

KEY WORDS • essential hypertension • insulin • hyperinsulinemia • obesity

A cardiovascular risk factor, hypertension represents a major medical concern in the obese patient. The increased incidence of hypertension in obesity, as well as the antipressor effect of weight loss, have led to a general acceptance of weight-related hypertension as a pathophysiological entity. Furthermore, the recent findings by several investigators of associations between diminished insulin action and increased circulating insulin on one hand and blood pressure elevation on the other have led to the opinion that hypertension represents an insulin-resistant state. However, because of the coexistence of hyperinsulinemia and reduced insulin action on glucose uptake in the same individuals, it remains unclear whether blood pressure elevation is caused by excess insulin itself or whether it is a manifestation of the complex metabolic state responsible for insulin resistance. Furthermore, the close association of both hyperinsulinemia and insulin resistance with obesity has additionally complicated the relation of insulin action to blood pressure regulation in the obese population.

Despite hypotheses describing the actions of insulin on sodium absorption and the sympathetic nervous system, the direct effect of insulin on blood pressure remains undocumented. However, it should be noted that, although insulin has a wide spectrum of physiological actions, the term insulin resistance has predominantly been used to refer to a decrease in insulin-stimulated glucose uptake. Current understanding of the hormone’s subcellular mechanism of action does not permit distinction between different resistance states applicable to separate insulin actions. Thus, controversy exists whether putative clinical outcomes of insulin resistance are related to excess insulin itself or whether they coexist with the cellular metabolic abnormality responsible for diminished glucose uptake.

The present study tests the hypothesis that insulin secretion independently affects blood pressure in the insulin-resistant obese individual before weight loss. Bergman’s minimal model was used to derive a sensitivity index for insulin action based on a tolbutamide-stimulated intravenous glucose tolerance test. Twelve-hour urinary excretion of c-peptide was used to assess meal-stimulated insulin secretion. These data were analyzed in terms of the relations between insulin sensitivity, insulin secretion, degree of obesity, percent body fat, fat distribution, lean body mass, and blood pressure.

Methods

Obese hypertensive and normotensive subjects were enrolled through an outpatient clinic (Center for the Study of Nutritional Medicine, New England Deaconess Hospital, Boston, Mass.) for medical management of weight-related problems. Male and female subjects, aged 23–62 years, were included in the study after they...
were screened through medical history, physical examination, and baseline blood chemistries. Eligibility was established after exclusion of cardiovascular, kidney, and liver disease, as well as insulin-dependent diabetes mellitus, pregnancy and lactation, psychiatric disorders, and intake of certain medications (birth control pills, steroids, antiinflammatory drugs). The total number of subjects entered into the current data base was 72. Fifty-two individuals were accrued from the obese patient population seeking weight loss treatment. Of these, 10 subjects were previous clinic patients who had relapsed to a significant extent, justifying further weight loss. Additionally, 20 subjects volunteered for the study with no intention of weight loss. Of these, 10 had previous history of obesity but were successful in maintaining their weight (within 130% of ideal body weight [IBW]), and 10 were healthy and had no prior history of weight-related medical problems.

Baseline blood pressure was determined based on a minimum of four readings taken by the same individual on at least two separate occasions. Right arm blood pressures were taken with a standard mercury sphygmomanometer after the subjects had rested in a sitting position for 15–20 minutes. Repeat measurements were then taken after a 3–5–minute rest. All antihypertensive medications were tapered off after consent was obtained from the subject and his or her primary physician. In most instances, subjects were free of antihypertensive medications for 10–20 days before the intravenous glucose tolerance test. Only in three patients was this period shorter than 1 week (minimum 5 days).

Experimental Protocol

The experimental protocol was approved by the Institutional Review Board on Human Studies of the New England Deaconess Hospital, Boston, Mass. After giving written informed consent to the study protocol and meeting eligibility criteria, all subjects were interviewed by the dietitian and given a diet calculated to maintain body weight and to provide a minimum of 200 g carbohydrate/day. The dietitian explained the food exchange and provided each subject a written 3-day diet plan. At 7 PM on the third day of the high-carbohydrate diet, all subjects consumed a liquid meal (Carnation Instant Breakfast, Carnation Co., Los Angeles, Calif.) containing 31.25 g carbohydrate/m² body surface area (BSA). Over the next 12 hours after this meal, subjects were allowed only water. Subjects collected a 12-hour urine sample for measurement of meal-stimulated c-peptide (MSCP) excretion and reported to the outpatient clinic for the intravenous glucose tolerance test and measurement of insulin action, as described below.

At 8 AM the next day, baseline measures were taken at the outpatient clinic. Weight was measured by a digital scale to 0.1 lb (Detecto model 8850, Detecto Scale Co., Webb City, Mo.), and height was measured without shoes by a wall-mount measuring board (Perspective Enterprise, Inc., Kalamazoo, Mich.). Data were used to calculate body mass index (BMI) (kg/m²). Percent of IBW was based on the 1959 Metropolitan Life Insurance Tables. Blood pressure measurements were made between 8 and 8:30 AM by the research dietitian after subjects had rested for approximately 15 minutes. Two measurements were made at 3-minute intervals, and the mean value of the two measurements recorded. Waist/hip ratio was recorded as narrowest waist measurement relative to the widest hip circumference. Percent body fat composition was measured by bioelectrical impedance analysis (BIA) (Bioelectrical Impedance 101, RJL Systems, Detroit, Mich.). Based on tetrapolar bioelectrical impedance plethysmography, BIA measures the conduction of an applied current through the conductive tissues of the body. It uses a painless, radiofrequency signal sent through surface electrodes into the deep tissues. Adjacent surface electrodes measure the voltage drop across the body. Phase-sensitive electronics quantitate the impedance to the flow of current into the geometric components of resistance and reactance. For statistical analysis, lean body mass was calculated as the difference between total body weight and body fat weight. BIA was chosen due to its published accuracy ($r^2 = 0.96$, correlation with densitometric measurements), ease of use, acceptability to patients, and cost-effectiveness.

Stimulated Intravenous Glucose Tolerance Test

A catheter was placed in an antecubital vein for administration of glucose and for removal of blood samples. Baseline blood samples for determination of basic chemistry profiles, liver enzymes, and complete blood count with differential were taken with the fasting glucose and insulin sample. The glucose infusion was then begun.

A dose of 19 g/m² of BSA, given as a 25% solution in normal saline, was administered over approximately 3 minutes. Blood was then withdrawn at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes for measurement of glucose (Beckman Glucose Analyzer II, glucose oxidase method, Diagnostic Systems Group, Brea, Calif.) and insulin (radioimmunoassay double antibody separation, guinea pig serum, in-house method, Joslin Diabetes Clinic, Boston, Mass.) concentration. At 20 minutes, 500 mg tolbutamide (diagnostic Orinase, Upjohn Co., Welle- sley, Mass.) was administered as an intravenous bolus over 45 seconds. Serum analysis was done at the Joslin Diabetes Center, Boston, Mass., and c-peptide was analyzed using a standard c-peptide analysis kit (Novo Biolabs, Copenhagen, Denmark).

Insulin Sensitivity Index: Bergman’s Minimal Model

Insulin sensitivity (Si) index was calculated as described by Bergman et al. and others. Briefly, the minimal model of glucose metabolism assumes that circulating insulin acts through an intracellular signal (remote compartment) enhancing glucose disappearance from the blood. The Si index represents the increase in glucose disappearance from blood due to insulin action. This index was derived from simultaneous glucose and insulin data by use of software provided by Dr. Bergman (USC, Los Angeles, Calif.).

Statistical Analysis

To compare insulin resistance, hyperinsulinemia, and insulin secretion (MSCP excretion) in equally obese hypertensive and nonhypertensive patients, we used cluster analysis to define three separate groups (based on BMI and systolic and diastolic blood pressures).
according to the algorithm of Hartigan and Wong.\textsuperscript{25} Essentially, this method searches for the best group separation by selecting seed cases farthest from the centroid of all data points, using the Euclidean distance. The algorithm assigns the remaining cases to the nearest seed and then tries to reassign each data point to a different cluster to minimize the within-group variance. Thus, the algorithm serves to resolve ambiguous cases that cannot be classified by rigid systems. After defining the three clusters, means of selected variables were calculated. Tukey's honestly significant difference test was used to compare differences between the three clusters for these means as well as for the means of insulin and glucose levels at each time point of the intravenous glucose tolerance test.

The strategy for statistical analysis was to determine whether insulin resistance and insulin secretion are related to systolic and diastolic blood pressure independent of obesity and to determine quantitative associations in the interrelation between insulin resistance, insulin secretion, and indexes of obesity and lean body mass in reference to blood pressure. The first approach compared the means of Si and c-peptide excretion in BMI-matched subjects classified according to blood pressure. The second approach determined significant correlations between insulin resistance and insulin secretion on one hand, and systolic and diastolic blood pressures and measures of body composition on the other. Simple Pearson's correlation coefficients between each of Si and MSCP excretion with selected variables were determined by standard techniques. Based on the significance of these correlations, we then used the general linear model to determine the statistical significance of the differences in Si between the three clusters; covariates included in this analysis were BMI, age, and sex. To determine the strength of the relation between insulin resistance and various measures of obesity and body composition, we used multiple linear regression analysis between each of Si and MSCP excretion (dependent variables) and BMI, percent body fat, and waist/hip ratio and lean body mass (independent variables). Data were pooled for sex whenever this variable was found to be insignificant. Finally, we used multivariate analysis (Wilks statistic) to determine the significance of indexes of obesity (independent variables: BMI, percent body fat, waist/hip ratio, and lean body mass) as determinants of the combination of Si and MSCP excretion (dependent variables).

All statistical analyses were performed by use of a commercial statistical package (Systat Inc, Evanston, Ill.) run on an Macintosh II computer (Apple Computer Inc, Cupertino, Calif.). Except if indicated otherwise, all data are reported as mean±SEM. Results were considered to be statistically significant at values of \(p<0.05\).

**Results**

*Baseline Data for the Three Clusters*

Cluster analysis was used to separate the 72 subjects of this study according to the combination of BMI and systolic and diastolic blood pressures into three groups. Baseline characteristics of subjects in these clusters are summarized in Table 1. One cluster comprises all the nonobese nonhypertensive subjects \((n=20)\). Of the 20 individuals in this group, four were between 120% and 130% of IBW, although none had a systolic blood pressure above 135 mm Hg or a diastolic blood pressure above 85 mm Hg. All subjects in the other two groups were above 130% of IBW.

Two groups comprise the "obese" population of the study \((n=52)\). As shown in Table 1, the two obese groups are similar in weight and age, but significantly differ in blood pressure; however, the use of both systolic and diastolic blood pressures in the cluster analysis produced a slight overlap between the groups. The highest systolic blood pressure in the obese nonhypertensive group was 140 mm Hg; the lowest systolic blood pressure in the obese hypertensive group was 134 mm Hg. Similarly, four patients overlapped in the diastolic blood pressure range of 86–90 mm Hg from the obese nonhypertensive group and three from the obese hypertensive. However, these overlapping patients had different systolic blood pressures consistent with their

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**Table 1. Summary of Patient Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonobese nonhypertensive</th>
<th>Obese nonhypertensive</th>
<th>Obese hypertensive</th>
<th>Differences between means for (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n) (M)</td>
<td>12</td>
<td>9</td>
<td>11</td>
<td>...</td>
</tr>
<tr>
<td>(n) (F)</td>
<td>8</td>
<td>21</td>
<td>11</td>
<td>...</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39.5±3.0</td>
<td>45.1±1.3</td>
<td>47.3±2.1</td>
<td>6.9</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>25.6±0.9</td>
<td>36.3±0.7</td>
<td>38.6±1.3</td>
<td>3.05</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>115.4±3.7</td>
<td>120.9±2.3</td>
<td>157.3±3.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>71.8±2.3</td>
<td>77.6±1.9</td>
<td>97.1±2.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>81.4±3.3</td>
<td>89.0±2.4</td>
<td>95.7±2.6</td>
<td>9.7</td>
</tr>
<tr>
<td>Insulin (microunits/ml)</td>
<td>10.1±0.9</td>
<td>22.0±2.8</td>
<td>21.3±2.0</td>
<td>7.5</td>
</tr>
<tr>
<td>WHR (M)</td>
<td>0.90±0.02</td>
<td>0.96±0.01</td>
<td>0.94±0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>WHR (F)</td>
<td>0.78±0.02</td>
<td>0.82±0.01</td>
<td>0.85±0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>% Fat (M)</td>
<td>21.2±1.8</td>
<td>32.3±0.8</td>
<td>31.4±2.1</td>
<td>6.2</td>
</tr>
<tr>
<td>% Fat (F)</td>
<td>26.7±4.5</td>
<td>44.3±0.9</td>
<td>42.9±1.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Significant difference was determined with Tukey's honestly significant difference test. Values given for glucose and insulin are serum fasting levels. M, male; F, female; BMI, body mass index; BP, blood pressure; WHR, waist/hip ratio; \% fat, percent total body fat.
Blood samples were drawn as explained in text. A dose of 500 mg tolbutamide was administered intravenously at 20 minutes after glucose administration. Data are mean values; SEM deleted for clarity. OH, obese hypertensive patients; ON, obese nonhypertensive patients; NN, normal weight nonhypertensive subjects.

cluster grouping. Thus, average mean blood pressures (diastolic×2/3+systolic×1/3) in the overlapping patients were 125 (SEM 1.7) and 112 (SEM 2.8) mm Hg for the subjects classified as hypertensive and nonhypertensive, respectively. As shown in Table 1, no statistically significant differences existed in either systolic or diastolic blood pressures between the nonobese and obese nonhypertensive groups.

Figures 1 and 2 summarize the results of blood glucose and insulin concentrations during the intravenous glucose tolerance test. Within 10 minutes of administration of the intravenous load, blood glucose levels were similar among the three groups, suggesting equivalency of the administered glucose load when normalized for BSA. The increase in insulin between time 0 and 20 minutes is glucose-stimulated, whereas the peak at 30 minutes is induced by intravenous tolbutamide. Both obese groups had significantly higher insulin levels than the nonobese subjects between 23 and 120 minutes of the test. Glucose and insulin levels were higher in obese hypertensive compared with obese nonhypertensive patients, but the differences did not achieve statistical significance at any time point (Tukey's honestly significant difference test).

**Insulin Sensitivity Index and Meal-Stimulated Insulin Secretion**

Values for Si index (Si in min⁻¹/[microunits/ml]) ranged from 0.014×10⁻⁴ to 9.13×10⁻⁴. Negative estimates were noted in three subjects, two of whom had elevated fasting glucose levels; these three values were excluded from subsequent analyses of the data. Gender differences in Si were not statistically significant in any of the three clusters of subjects, thus allowing pooling of these data for both sexes in subsequent analysis. Mean Si in normal control subjects (no history of obesity, n=10) was 6.68×10⁻⁴ (SD 1.73×10⁻⁴). Subjects with prior history of obesity but who were within 130% IBW at the time of the study had an average Si of 4.83×10⁻⁴ (n=10, SD=1.61×10⁻⁴, p<0.005 versus subjects with no history of obesity). In comparison, the mean Si value for all 52 obese subjects (above 130% of IBW) was 1.99×10⁻⁴ (SD 1.93×10⁻⁴). Both nonobese and previously obese subjects were significantly more sensitive to insulin action than were obese subjects (p<0.001).

Twelve-hour urinary c-peptide excretion after a chemically defined meal adjusted for BSA ranged between 2.35 and 44.1 nmol in the normal-weight subjects and from 2.69 to 96.25 nmol in obese patients. Within each cluster, total c-peptide excretion was significantly larger in male subjects. However, these differences were completely accounted for by gender differences in lean body mass (by analysis of covariance). Therefore, in subsequent analyses, MSCP excretion data were normalized per kilogram lean body mass and pooled for men and women.

Adjusted for sex, age, and BMI, differences in Si and MSCP excretion due to cluster were significant (p=0.004 and 0.024, respectively) by analysis of covariance. The mean values of the adjusted Si and MSCP excretion data are summarized in Figure 3 for the three clusters. Thus, obese hypertensive patients (n=22, Si=1.34±0.19×10⁻⁴) had significantly (p=0.003) lower Si than equally obese nonhypertensive subjects (n=30, Si=2.26±0.10×10⁻⁴). Both of these obese clusters were significantly (p<0.001) more insulin resistant than the nonobese subjects (n=20, Si=5.41±0.26×10⁻⁴). Similarly, obese hypertensive patients excreted more c-peptide in response to a standard meal than nonhypertensive subjects of similar degree of obesity (0.32±0.01 nmol/12 hr versus 0.16±0.01 nmol/12 hr, p<0.001). However, MSCP excretion was similar in the two nonhypertensive clusters regardless of the degree of obesity. Therefore, only the presence of hypertension was associated with increased meal-stimulated c-peptide excretion.
patients had significantly lower Si and significantly higher c-peptide excretion among the normotensive obese and nonobese hypertensive subjects. Both the total population (obese hypertensive patients) and combined for men and women. Obese hypertensive patients had significantly lower Si and significantly higher c-peptide excretion than obese nonhypertensive individuals. The latter subjects were distinguished from nonobese controls only by significantly lower Si. Meal-stimulated c-peptide excretion was similar among the normotensive obese and nonobese subjects.

Table 2 presents the results of simple Pearson's correlation coefficients between Si and MSCP excretion with several selected variables for all the subjects, and separately for the obese (hypertensive and nonhypertensive) and the normotensive (obese and nonobese) subjects. This separation of groups was made because of the imbalance of blood pressure characteristics in the study population, which did not include obese hypertensive patients. Therefore, correlation coefficients between Si and MSCP excretion were not statistically significant (r=0.23, n=55, p>0.1), suggesting that the associations between these two measures of insulin action and insulin secretion with blood pressure were independent. Similarly, the correlation between MSCP excretion and fasting insulin levels (data not shown) was not statistically significant.

Figure 4 depicts the relations between Si and BMI in the nonhypertensive (obese and nonobese) and hypertensive (obese) subjects separately. In the subjects (pooled men and women) with elevated blood pressure, the slope of the regression line of Si relative to BMI was $-0.11$ (SEM 0.040, r=0.51, n=24, p=0.01), whereas in the nonhypertensive subjects, this slope was $-0.24$ (SEM 0.047, n=45, r=0.62, p<0.001). Projection of these regression lines, which have significantly different slopes, to normal BMI range shows significantly different y-intercepts. These data thus suggest that nonobese hypertensive patients, who were not represented in the current study, would have lower Si values than would normotensive individuals. Furthermore, the Si index bears a strong inverse relation with all the measures of obesity. The Si index was also inversely related to age as well as to systolic and diastolic blood pressure. As noted in Table 2, the inverse correlations between Si and BMI and measures of obesity (body fat in men and waist/hip ratio in women) continued to be significant in the obese subjects at BMI larger than 30. On the other hand, measures of lean body mass derived from the difference between total body fat and fat weights were not significantly correlated with Si in the group of obese subjects of the current study. Table 2 also shows that MSCP excretion was only weakly associated with obesity (body fat in the group comprising normotensive men) and blood pressure. Finally, the correlation between Si and MSCP excretion was not statistically significant (r=0.23, n=55, p>0.1), suggesting that the associations between these two measures of insulin action and insulin secretion with blood pressure are independent.

**TABLE 2. Summary of Pearson Correlation Coefficients of Insulin Sensitivity Index and C-Peptide Excretion With Selected Variables**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All subjects</th>
<th>Normotensive</th>
<th>Obese subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Si</td>
<td>C-peptide</td>
<td>Si</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>$-0.634^*$</td>
<td>0.149</td>
<td>$-0.630^*$</td>
</tr>
<tr>
<td>% Fat (F)</td>
<td>$-0.576^*$</td>
<td>$-0.113$</td>
<td>$-0.587^*$</td>
</tr>
<tr>
<td>% Fat (M)</td>
<td>$-0.808^*$</td>
<td>0.430$^+$</td>
<td>$-0.808^*$</td>
</tr>
<tr>
<td>Fat (F)</td>
<td>$-0.575^*$</td>
<td>$-0.121$</td>
<td>$-0.613^*$</td>
</tr>
<tr>
<td>Fat (M)</td>
<td>$-0.767^*$</td>
<td>0.383</td>
<td>$-0.759^*$</td>
</tr>
<tr>
<td>LBM (F)</td>
<td>$-0.388^+$</td>
<td>$-0.078$</td>
<td>$-0.458^+$</td>
</tr>
<tr>
<td>LBM (M)</td>
<td>$-0.428^+$</td>
<td>0.509</td>
<td>$-0.160$</td>
</tr>
<tr>
<td>WHR (F)</td>
<td>$-0.365^+$</td>
<td>0.501</td>
<td>$-0.374^+$</td>
</tr>
<tr>
<td>WHR (M)</td>
<td>$-0.537^+$</td>
<td>0.305</td>
<td>$-0.722^+$</td>
</tr>
</tbody>
</table>

Blood pressure

<table>
<thead>
<tr>
<th>Systolic</th>
<th>$-0.486^*$</th>
<th>0.311$^+$</th>
<th>$-0.318^+$</th>
<th>$-0.165$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic</td>
<td>$-0.535^*$</td>
<td>0.267$^+$</td>
<td>$-0.384^+$</td>
<td>$-0.171$</td>
</tr>
<tr>
<td>Mean</td>
<td>$-0.532^*$</td>
<td>0.262$^+$</td>
<td>$-0.383^+$</td>
<td>$-0.046$</td>
</tr>
<tr>
<td>Age</td>
<td>$-0.434^*$</td>
<td>0.185</td>
<td>$-0.463^*$</td>
<td>$-0.065$</td>
</tr>
</tbody>
</table>

$^*$p<0.05, $^+$p<0.01, $^*$p<0.005.
TABLE 3. Body Composition Parameters as Determinants of Insulin Sensitivity Index and Meal-Stimulated C-Peptide Excretion

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.655</td>
<td>0.902</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>0.011</td>
<td>0.009</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.009</td>
<td>0.020</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>0.225</td>
<td>0.477</td>
</tr>
</tbody>
</table>

Data are probability values. Univariate, univariate F test based on multiple linear regression analysis; multivariate, based on Wilk's lambda multivariate test statistic; BMI, body mass index; Si, insulin sensitivity index; C-peptide, 12-hour meal-stimulated C-peptide excretion normalized per kilogram lean body mass.

Differences in insulin action between hypertensive and nonhypertensive individuals tend to diminish as BMI increases. At a BMI level of approximately 47, the two regression lines meet, which corresponds to an estimated Si index of 0.14 x 10^-4. Beyond this level of obesity, the Si index approaches very low values and may not adequately differentiate between hypertensive and normotensive individuals.

To determine which of the body composition parameters were significant determinants of insulin action (Si) and secretion (MSCP excretion), multiple linear regression analysis was performed; the results of this analysis are summarized in Table 3. In the univariate model (Si the only dependent variable, body composition parameters as independent variables), only percent body fat and waist/hip ratio were significant determinants of Si, whereas BMI and lean body mass were not. On the other hand, none of the body composition parameters appeared to be significant determinants of MSCP excretion in this multiple linear regression model. As Table 3 indicates, only percent body fat and waist/hip ratio were significant determinants of the combined parameters of insulin action and insulin secretion. Therefore, the results of the current study are consistent with the notion that upper body adiposity, rather than BMI itself, is a predictor of metabolic characteristics associated with hypertension in obese individuals.

Discussion

The association of elevated blood pressure with diminished insulin-stimulated glucose uptake and increased glucose-stimulated hyperinsulinemia has led to a general acceptance of hypertension as an insulin-resistant state. In support of this premise, it was proposed that increases in the prevalence of hypertension in obesity and diabetes represents a manifestation of the state of insulin resistance, which is very common in these disorders. It has also been suggested that the hyperinsulinemia of insulin resistance causes blood pressure elevation by stimulating sodium reabsorption and activation of the sympathetic nervous system. A large epidemiological study has documented an association of insulin levels with blood pressure measurements. However, no direct evidence for a pressor effect of insulin exists and resistance to insulin action has been construed as evidence against a direct pressor effect for insulin. Resnick et al have instead suggested that an abnormal state of intracellular magnesium metabolism, rather than hyperinsulinemia, explains the association of hypertension with insulin resistance. Because of the strong covariance of the triad of hyperinsulinemia, insulin resistance, and hypertension with indexes of obesity, and the strong association of insulin resistance and hyperinsulinemia with each other, it has been difficult to determine the association of insulin itself with weight-related blood pressure independent of obesity.

This study, the largest to date to assess the glucoregulatory action of insulin in obese subjects by use of Bergman's minimal model, documents the high incidence of insulin resistance in hypertensive and normotensive obese subjects. The results have also demonstrated that for the same degree of obesity, measured by BMI, hypertensive patients are more insulin resistant than are normotensive individuals. Based on analysis of insulin action measured by the euglycemic clamp technique, Pollare et al have recently concluded that the association between hypertension and hyperinsulinemia is independent of obesity and glucose tolerance. Their study, however, did not include obese individuals among the normotensive group. The current study extends the findings of Pollare et al by demonstrating separate relations between insulin action and BMI among hypertensive and nonhypertensive obese individuals and lends further support to the role of insulin by documenting increased MSCP excretion in obese hypertensive, but not obese normotensive, subjects. Our findings also indicate that differences in Si between hypertensive and nonhypertensive subjects tend to diminish with increasing BMI, thus making detection of hypertension-related insulin resistance difficult in extremely obese subjects. Indeed, baseline fasting insulin levels are not significantly different between the obese hypertensive and normotensive subjects (Table 1).

In general, estimates of insulin action derived from the euglycemic clamp technique and Bergman's minimal model seem to be equivalent. However, although circulating insulin is maintained constant at a predetermined concentration during the clamp procedure, the...
state of hyperinsulinemia achieved during the minimal model is a function of the metabolic response of the subject tested. Thus, for the same level of insulin-mediated glucose disposal, Si could assume lower values if the insulin response is more exaggerated. This is particularly likely if glucose disposal rate is reduced to a minimal value, as in extremely obese individuals. For example, Bogardus et al.36 have shown a linear decrease in clamp-derived glucose disposal rates up to a level of obesity that corresponds to 30% excess body fat (BMI approximately 30) in male subjects. At higher levels of adiposity, glucose disposal measured by the clamp technique ceased to decrease. In contrast, the decrease in Si in obese individuals in the current study persisted beyond a BMI of 30, as depicted in Figure 4 and Table 2, possibly a consequence of increasing stimulated insulin levels during the intravenous glucose tolerance test. By the same token, further reduction of Si in obese hypertensive individuals in comparison with obese nonhypertensive subjects could be a manifestation of more exaggerated hyperinsulinemia in the former group. Further testing of insulin action, simultaneously by the clamp and minimal model procedures, is required to validate this possibility.

Evidence suggests that the hyperinsulinemia of obesity is manifest predominantly by diminished insulin clearance,30 which is supported in the current study by the lack of significant correlation of MSCP excretion with circulating insulin levels. The fact that MSCP excretion correlates with hypertension independent of Si supports a direct role for insulin secretion in blood pressure regulation. Thus, this study supports the possibility of an exaggerated physiological response (hypertension) mediated by increased insulin secretion despite the existence of insulin resistance in obese individuals. For this hypothesis to be consistent, we must postulate that the cellular abnormality in insulin-stimulated glucose metabolism in obese hypertensive patients is distal to the immediate post-receptor events likely to be shared by other insulin actions, including the effects on sodium reabsorption and the sympathetic nervous system.14,15 This explanation is consistent with a derangement specific to the glucose transporter system, as recently suggested.16-18

Classification of obese subjects, as defined by BMI, into hypertensive or nonhypertensive demonstrates similar percent body fat and waist/hip ratios in those clusters (Table 1) despite the significant relation of these parameters to Si (Table 3). This apparent lack of dependence of blood pressure on body fat distribution in the current study's obese population strengthens the direct relation between insulin resistance and hypertension. Thus, Si serves as a sensitive marker for the abnormality in glucose and insulin metabolism that characterizes obesity and that appears to be more exaggerated with hypertension. In populations with a wider distribution of body fat, differences in insulin resistance between hypertensive and nonhypertensive patients may be greater.37-39 In fact, based on the multivariate relation between the combination of Si and MSCP excretion and the measured indexes of obesity (Table 3), we may deduce that excess upper body fat rather than obesity itself constitutes the risk of simultaneously developing lower Si and increased MSCP excretion. Although a previous study has demonstrated a direct relation between lean body mass and blood pressure,40 the results of the current study imply that this association is independent of insulin resistance. Other factors relating lean body mass and blood pressure need to be further investigated. The differences in the Si index of insulin action between the subjects with no history of obesity and the previously obese in the present study suggest that the metabolic effects of obesity may be operative despite weight loss. In addition to percent body fat and fat distribution (waist/hip ratio), factors contributing to the variance in this measure include age and blood pressure. Despite the difference in body fat among men and women, sex does not appear to be a significant determinant of insulin action as measured by Si. Future pursuance of these findings with weight loss and regain and of the effects of exercise will be important for further elucidation of the long-term impact of obesity. Other factors, such as ethnic and genetic background, are probably significant determinants of Si but have not been examined in the current study.

Measurements of 12-hour urinary catecholamine excretion in a subset of our subjects (to be reported separately) did not reveal any consistent relation among epinephrine, norepinephrine, and dopamine with either systolic or diastolic blood pressure.41 However, a significant correlation between Si and dopamine excretion was demonstrated, further suggesting the association of insulin resistance with altered sodium metabolism in obese hypertensive patients.31 The contribution of this mechanism and that of abnormalities in divalent cation metabolism42 to hypertension needs further evaluation. It should also be pointed out that lack of association of urinary excretion of either epinephrine or norepinephrine with blood pressure does not rule out a role for the adrenergic system in view of large variations associated with these measurements.

Muscle-specific insulin resistance may contribute to excess body fat accumulation and obesity by diverting ingested calories toward adipose tissue, as recently suggested.42 However, to date the notion that obesity has a causal effect on insulin resistance is favored. The strongest evidence in support of this causality derives from the reversal this abnormality with weight loss.43 Whether existence of essential hypertension also contributes to insulin resistance remains unknown. Our data showing exaggerated insulin resistance in hypertensive obese individuals are consistent with this possibility. However, evidence that treatment of hypertension could improve insulin resistance is lacking. In fact, despite significant lowering of blood pressure, several antihypertensive medications are known to worsen insulin resistance,44 an effect that may persist even after discontinuation of these treatments. This has led to the speculation that the lack of documented reduction in cardiovascular risk among treated hypertensive subjects could be attributed to the common use of pharmacological agents, such as thiazide diuretics, and subsequent worsening of insulin resistance.44,45

We conclude that although the association of insulin resistance and hypertension remains remote from being causally defined, findings in this study demonstrate that the presence of elevated blood pressure in obese subjects also points to exaggerated insulin resistance. We reiterate the need for caution when evaluating and
prescribing treatment of hypertension, especially in the obese population, with regard to the concomitant effect on insulin resistance.

**References**


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