Obesity, Glucose Intolerance, Hyperinsulinemia, and Response to Antihypertensive Drugs

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Responsiveness to antihypertensive medications was investigated cross-sectionally in 559 individuals comprising all treated hypertensive patients identified within a representative sample (n=3,532, aged 40-70 years) of the Jewish population in Israel. A rate of dosage score (a summed ranking of dosages of all drugs taken) of two or more increased significantly with increasing levels of body mass index (BMI) from 37.5% in levels less than 23, 54.9% in levels 23.0-29.9, and 76.4% in levels of 30 or greater (p<0.0001). Multivariate analyses, adjusting for age, gender, arm circumference, and ethnic group, confirmed the independent effect of BMI on dosage score (p<0.001). At each level of dosage score, mean blood pressure levels were equivalent at all levels of BMI after adjusting for potential confounders. This indicates that achieved blood pressure level and not BMI itself was the main determinant of the higher dosing regimens prescribed at higher levels of BMI. In representative subgroups, glucose tolerance (n=372) and hyperinsulinemia (n=190) were determined and were found to be positively associated with a dosage score of two or more (p<0.05) independently of BMI. These effects could not be accounted for by poor compliance or by altered drug absorption or disposition since overnight urinary drug excretion and plasma drug concentrations 2 hours after ingestion, measured in 80 randomly selected patients from the study group, were not different across BMI categories at similar dosages. These findings indicate that obesity, even at mild levels, as well as glucose intolerance and hyperinsulinemia, is associated with decreased responsiveness to antihypertensive medications, perhaps as a manifestation of the insulin resistance that characterizes these conditions. (Hypertension 1991;17:565-573)

Patients with high blood pressure vary in their sensitivity to antihypertensive drugs. Truly resistant, or refractory, hypertension has been reported to range in prevalence from 3% to 13% in different series. Many factors contribute to resistance to antihypertensive medications, but it is only recently that obesity has been included among its possible correlates. However, the association has not been definitely established. Obesity and glucose intolerance are strongly associated with each other, as well as with hypertension. All three conditions are characterized by hyperinsulinemia reflecting insulin resistance, which might play a role in the etiology of essential hypertension. If such a mechanism exists, it could interfere with the hypotensive effect of these medications, which themselves cause glucose intolerance, as well as hyperinsulinemia and its attendant insulin resistance.

We report the results of a cross-sectional analysis of the association between response to antihypertensive medications, obesity, glucose intolerance, and hyperinsulinemia in all the treated hypertensive individuals identified within a representative sample of an adult population.

Methods

Participants and Procedures

The Israel Study of Glucose Intolerance, Obesity, and Hypertension is an ongoing, nationwide longitudinal study of risk factors for atherosclerosis in a systematic sample of the adult Jewish population.
The current report addresses a representative subgroup of participants, aged 40–70 years (total study group n = 3,532), who were interviewed at home between 1977 and 1982 by specially trained nurses. Weight, height, and arm circumference were measured. Regular use of any medications, verified by inspection of drug receptacles, was recorded. Blood pressure was determined with a standard mercury sphygmomanometer in the sitting position. Four measurements were obtained: two before and two after the interview. Subsequently, these individuals were requested to attend regional medical centers where glucose tolerance status was determined in 2,475 individuals (glucose tolerance group) by an oral glucose tolerance test (OGTT) or by a history of treated diabetes mellitus. In the last 1,211 participants who underwent the OGTT (insulin group), plasma insulin levels were determined in the 1- and 2-hour postload samples. The total study group as well as the glucose tolerance and insulin groups have been shown to be representative of the original sample with respect to age, sex, and ethnic distribution, as well as rates of hypertension and obesity.5,11

The number of individuals using antihypertensive medications in these three groups was 559, 372, and 190, respectively. Of the 190 patients in the insulin group reporting use of antihypertensive medications, 80 randomly selected individuals were reinvited for determination of blood levels and urinary excretion of these medications. When attending the clinic, these patients were asked to provide an overnight timed urine collection and to refrain from taking their morning medication dose before arrival. A detailed record of medications taken over the past week and preceding 24 hours was obtained. The regular morning dose of medication as prescribed by their treating physician was ingested, and a blood sample was drawn at 2 hours after ingestion. Duration of collection and total volume of the urine sample were recorded. Serum and urine concentrations of respective drugs were determined. The urine concentrations were a measure of compliance, at least with respect to drugs taken the day before. Serum levels were a measure of drug absorption and disposition.

Informed consent was obtained from all patients, and the study was approved by the hospital ethics committee.

Laboratory Methods

Plasma insulin was measured in duplicate by Phadebas Radioimmunoassay (Pharmacia Inc., Piscataway, N.J.); the within-assay coefficient of variation was 4% and the between-assay coefficient was 8%. Plasma glucose was determined with an automated Technicon Autoanalyzer II (Technicon Instruments Corp., Tarrytown, N.Y.) by potassium ferricyanide reduction. Assay methods for plasma insulin, namely, sum of the 1- and 2-hour postload concentrations as a measure of the area under the insulin response curve.17 The categorical form was defined, as in our previous reports, relative to the distribution of sum insulin in the 282 normotensive individuals with normal glucose tolerance and BMI less than 25 within the insulin group; levels in the 75th percentile or greater of this distribution were termed hyperinsulinemia.5

Arm circumference. The continuous form was measured (in centimeters) at the center of the upper arm. The categorical form grouped arm circumference into two groups: less than 30 and 30 or greater. The latter value was the cutoff point reportedly associated with significant false elevation of blood pressure readings.19

Dosage score. The continuous form was a semi-quantitative score devised to allow comparison of overall dosage across drug categories as follows: for each drug, mean daily doses were graded as low, intermediate, or high by accepted standards and assigned scores of 1 through 3, respectively (Table 1). The dosage score for each individual was the sum of scores for all drugs taken. The categorical form

Data Analysis

The association between antihypertensive medication regimens, degree of control of blood pressure, level of obesity, glucose tolerance category, and insulin response were analyzed by using both continuous and categorical forms of the variables, as follows.

Relative weight. The continuous form was BMI (weight/height2 [kg/m2]). In the categorical form BMI was divided into groups: less than 23, satisfactory weight; 23–26.9, mild obesity; 27.0–29.9, moderate obesity; 30 or greater, severe obesity.

Blood pressure. The continuous form was mean (mm Hg) of the four home measurements. In the categorical form, blood pressure was divided in two groups: 1) hypertension in untreated individuals, which was defined as systolic blood pressure 160 or more or diastolic blood pressure 95 mm Hg or more and 2) uncontrolled hypertension in treated individuals, which was defined as mean of the home measurements being 160 mm Hg or greater (systolic) or 95 mm Hg or greater (diastolic) under current medication.

Glucose tolerance. The continuous form was sum glucose, namely, sum of the 1- and 2-hour postload plasma glucose levels representing the area under the glucose response curve.17 The categorical form was glucose tolerance, which was classified according to the National Diabetes Data Group criteria16 into normal glucose tolerance and glucose intolerance, the latter comprising the nondiagnostic and impaired glucose tolerance categories as well as diabetes (all newly found, type II, non-insulin-dependent).

Insulin response. The continuous form was sum insulin, namely, sum of the 1- and 2-hour postload levels as a measure of the area under the insulin response curve.17 The categorical form was defined, as in our previous reports, relative to the distribution of sum insulin in the 282 normotensive individuals with normal glucose tolerance and BMI less than 25 within the insulin group; levels in the 75th percentile or greater of this distribution were termed hyperinsulinemia.5

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liquid chromatography14,15; and chlorthalidone, gas-
grouped the score into two or three categories with scores of 1 and 2 or more or 1, 2, and 3 or more.

**Statistical Analysis**

**Total study group.** Univariate analyses of the rates of hypertension and of drug treatment among hypertensive individuals by BMI categories were done by $\chi^2$ for linear trends. Further analyses were performed only on individuals receiving antihypertensive medication. Univariate analyses of the increase in the rate of uncontrolled hypertension with increasing BMI were done by $\chi^2$ for linear trends and that of dosage score by one-way analysis of variance and Pearson’s correlation coefficient. Multivariate analysis of the significance of the independent effect of BMI on dosage score, adjusted for age, sex, ethnic origin, and arm circumference, in the treated individuals was examined in two ways by using the variables in their categorical and continuous forms as follows: 1) by logistic regression analysis (Biomedical Computer Programs, University of California, BMDP, program LR) with a rate of dosage score of 2 or more as the dependent variable. The independent variables were BMI categories (30.0 or more and 23.0–29.9 compared with BMI less than 23.0), age (60 years or more compared with less than 60 years), arm circumference (30 cm or more compared with less than 30), gender and ethnic group (Yemenite, Middle Eastern, and North African compared with European). Rate ratios for use of dosage score of 2 or more and their 95% confidence limits were computed from the logistic regression coefficients and their standard errors for each independent variable, which had a significant effect on rate of dosage score of 2 or more, adjusting for all other independent variables; 2) by multiple regression analysis (BMDP program 2R) with dosage score as the continuous dependent variable and BMI, age, and arm circumference as the independent variables. The specific portion contributed by each independent variable to the variance of dosage score was obtained by computing the increments in $R^2$.

The significance of the effect of BMI on systolic and diastolic blood pressure as the dependent variables accounting for dosage score was examined by analysis of covariance (BMDP program 2v) with BMI (three categories as above), dosage score (three categories: 1, 2, and 3 or more) and sex as grouping factors, including all possible interactions, and with age and arm circumference as continuous covariates. Means of systolic and diastolic pressure, by BMI and dosage score, adjusted for the covariates, were obtained from the model.

**Glucose Tolerance and Insulin Groups**

All analyses in these groups were performed only on individuals using antihypertensive medications. Since in the analyses of the total study group the major factor independently affecting dosage score was BMI and the number of cases in some of the subgroups by BMI and glucose intolerance as well as by BMI and hyperinsulinemia was small, only BMI was adjusted for in the analyses of the effects of glucose intolerance and hyperinsulinemia. Their association with a dosage score of 2 or more was first assessed by using the categorical forms of the variables by computing Mantel-Haenszel rate ratios adjusted for BMI, with test-based 95% confidence limits for: 1) glucose intolerance versus normal glucose tolerance (in the glucose tolerance group); 2) hyperinsulinemia versus normoinsulinemia (in the insulin group). The analysis using the continuous form of the variables was performed in the insulin group by multiple regression (BMDP program 2R), with dosage score as the dependent variable and BMI, sum glucose, and log transformed sum insulin as the independent variables.

**Urinary and Plasma Drug Levels**

Univariate comparison of serum concentrations and urinary excretion of specific drugs in individuals with BMI of 27 or greater versus less than 27 was done by $t$ test for independent samples. Overall simultaneous comparison of urinary excretion rates and 2-hour plasma levels of all drugs used was done as follows. For each urinary excretion rate and plasma concentration, the median for all individuals taking a specific drug was obtained. The two BMI categories were then compared by $\chi^2$, testing whether drug concentrations or excretion rates were equally distributed above and below their common median.

Values are reported as mean±SD. Rate ratios are followed by 95% confidence limits in brackets.

**Results**

**General**

As expected, the rate of hypertension among all 3,532 individuals comprising the total study group increased consistently with BMI from 12.5% in those with BMI less than 23.0 to 34.5% in those with BMI 30.0 or more. The rate of antihypertensive treatment among the hypertensive subjects was significantly lower in the lowest BMI category (64%, $p=0.03$) but did not differ significantly among the other three BMI categories (73.7–77.2%). Mean number of years of treatment was 3.4±4.1 and was similar in all BMI categories (Table 2).

**TABLE 1. Ranges of Drug Doses Defined as Low, Intermediate, or High for Dosage Score Calculation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low (mg/day)</th>
<th>Intermediate (mg/day)</th>
<th>High (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>&lt;80</td>
<td>80–160</td>
<td>&gt;160</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>&lt;500</td>
<td>500–750</td>
<td>&gt;750</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>&lt;50</td>
<td>50–75</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>&lt;50</td>
<td>50–100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Furosemide</td>
<td>&lt;40</td>
<td>40–120</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>&lt;500</td>
<td>500–750</td>
<td>&gt;750</td>
</tr>
</tbody>
</table>

*Low, 1; intermediate, 2; high, 3.*
TABLE 2. Rate of Hypertension and of Antihypertensive Drug Treatment and Mean No. of Years of Treatment by Body Mass Index Category in the Total Study Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BMI category</th>
<th>&lt;23.0</th>
<th>23.0–26.9</th>
<th>27.0–29.9</th>
<th>≥30.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td></td>
<td>799</td>
<td>1,442</td>
<td>741</td>
<td>550</td>
</tr>
<tr>
<td>Hypertensive (%)</td>
<td></td>
<td>12.5</td>
<td>18.9</td>
<td>26.0</td>
<td>34.5</td>
</tr>
<tr>
<td>Treated/hypertensive (%)</td>
<td></td>
<td>64.0</td>
<td>75.7</td>
<td>77.2</td>
<td>73.7</td>
</tr>
<tr>
<td>Years on treatment</td>
<td></td>
<td>3.2±4.2</td>
<td>3.5±4.1</td>
<td>3.6±4.0</td>
<td>3.2±4.0</td>
</tr>
</tbody>
</table>

TABLE 4. Distribution of Drugs Used by the Treated Hypertensives in the Total Study, Glucose Tolerance, and Insulin Groups

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Total study group</th>
<th>GT group</th>
<th>Insulin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy total</td>
<td>62.8</td>
<td>60.5</td>
<td>59.9</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>16.6</td>
<td>15.9</td>
<td>15.5</td>
</tr>
<tr>
<td>&amp;-Blockers</td>
<td>21.8</td>
<td>20.7</td>
<td>20.8</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>6.3</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Sympathomlytics</td>
<td>18.1</td>
<td>18.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Combined therapy total</td>
<td>37.2</td>
<td>39.5</td>
<td>40.1</td>
</tr>
<tr>
<td>Thiazide diuretics and &amp;-blockers with or without other drugs</td>
<td>22.8</td>
<td>23.9</td>
<td>25.1</td>
</tr>
<tr>
<td>Other combinations</td>
<td>14.4</td>
<td>15.6</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Values are percent of drugs used. GT, glucose tolerance.

All of the following results pertain only to individuals receiving antihypertensive drugs in the total study group (n=559), the glucose tolerance group (n=372), and the insulin group (n=190). These three groups of treated patients were similar with respect to the distribution of age, sex, BMI, mean systolic and diastolic blood pressures, arm circumference, and dosage score (Table 3).

In the total study group, 62.8% of the 559 treated hypertensive subjects were on monotherapy and 37.2% were on combined therapy. Thiazide diuretics and &-blockers, alone or in combination, accounted for 61.2% of the drug regimens. Drug category distributions in the glucose tolerance and insulin groups were similar (Table 4). Dosage scores ranged from 1 to 8 and were 1 in 41.7% of the subjects (all those with dosage score of 4 or more were on combined therapy by definition).

**Total Study Group**

In the 559 treated hypertensive subjects in this group, the overall rate of uncontrolled hypertension was 51.7%. This rate increased significantly with increasing BMI (p<0.01) from 39.1% in the lowest BMI category, through 50.0% and 51.6% in the two intermediate categories, to 59.3% in the highest BMI category (Figure 1). Mean dosage score increased significantly (p<0.01) with BMI from 1.7±1.1 in the lowest to 2.6±1.4 in the highest BMI categories with similar intermediate values of 2.1±1.3 and 2.0±1.1 in the two intermediate BMI categories (Figure 1). Because of the similarity of the two intermediate BMI categories with respect to dosage score and rate of uncontrolled hypertension, they were pooled in all further analyses.

When the cases were stratified by BMI, dosage score, age, and sex (Table 5), the following trends emerged: 1) dosage score increased with increasing BMI in all sex and age categories, 2) dosage score in women was consistently lower as compared with men in all age and BMI categories, and 3) age had no additional apparent effect on dosage score. For all ages combined, the number with a rate of dosage score of 1 decreased with increasing BMI from 52.8% in the low, through 35.3 in the intermediate, to 10.7% in the high BMI category in men; the respective rates in women were 75.0%, 53.7%, and 26.8%. The number with a rate of dosage score of 3 or more increased with increasing BMI—13.9%, 29.9%, and 50% in men and 7.1%, 20.2%, and 40.2% in women.

These trends were confirmed by logistic regression analysis indicating highly significant independent effects of BMI and sex on a dosage score of 2 or more, and no significant effects of age, arm circumference, or ethnic group. After adjustment for the potential confounding effect of all other independent variables, the ratio of the rates of use of a dosage score of 2 or more, relative to the rate in the BMI category less than 23, were 1.95 (1.22–3.16) for the BMI category of 23.0–29.9 and 6.33 (3.63–11.03) for the BMI category of 30 or more. For men as compared with women, the respective adjusted rate ratio was 2.08 (1.51–2.85).

The rate of combined therapy in dosage scores 2 and 3 was not significantly different among the three BMI categories in both men and women, nor did the two sexes or age groups differ in this respect (data not shown).

Although, as described above, dosage scores increased considerably with increasing BMI, the effect of BMI on mean blood pressure stratified by dosage score and adjusted for age, sex, and arm circumference was inconsistent and not significant (Table 6).
In other words, within each dosage score level, adjusted mean blood pressure did not differ significantly across BMI categories. A dosage score of 1 was characterized by significantly lower adjusted mean blood pressure (p<0.001). Sex of the subject had no significant effect on mean blood pressure in this analysis. These findings indicate that the higher dosing regimens prescribed at higher levels of BMI were mainly determined by the blood pressure levels observed by the physician.

In the multiple regression analysis BMI had an independent, highly significant effect on dosage

![Graph showing rate (%) of uncontrolled hypertension and mean dosage score among 559 individuals treated with antihypertensive drugs in the total study group by body mass index (BMI) category. (No. of cases in each BMI category appears in brackets above the abscissa.)](image)
TABLE 6. Adjusted Mean Blood Pressure by Body Mass Index and Dosage Score in Individuals Treated With Antihypertensive Drugs in the Total Study Group

<table>
<thead>
<tr>
<th>Dosage score</th>
<th>BMI category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;23</td>
</tr>
<tr>
<td>1</td>
<td>146.5/85.4</td>
</tr>
<tr>
<td>2</td>
<td>162.2/96.7</td>
</tr>
<tr>
<td>≥3</td>
<td>160.0/97.5</td>
</tr>
</tbody>
</table>

The means for blood pressure (mm Hg) by dosage score and body mass index (BMI) are adjusted for age, sex, and arm circumference.

The variance (multiple R=0.38), but the independent contribution of sum glucose and sum insulin amounted only to about 1% each.

Glucose Tolerance and Insulin Groups

In the 372 treated patients in the glucose tolerance group, the effect of BMI was evident both in the presence or absence of glucose intolerance. However, a rate of dosage score of 2 or more in individuals with glucose intolerance was increased in all three BMI categories (Figure 2). This independent effect of glucose intolerance was significant; the rate ratio of a dosage score of 2 or more associated with glucose intolerance and adjusted for BMI was 1.78 (1.12-2.82).

In the 190 treated patients in the insulin group, the effect of BMI was also evident both in the presence and absence of hyperinsulinemia. However, hyperinsulinemia was also associated with an increased rate of dosage score of 2.0 or more across all BMI categories (Figure 3). This independent effect of hyperinsulinemia was significant, and the rate ratio adjusted for BMI was 2.05 (1.07-3.91). Multiple regression analysis indicated that BMI, sum glucose, and sum insulin explained 12% of the dosage score variance (multiple R=0.35), but the independent contribution of sum glucose and sum insulin amounted only to about 1% each.

Urinary and Plasma Drug Levels

Among the 80 patients of the insulin group whose drug levels were examined, mean dosage scores were 1.9±1.2 and 2.5±1.3, respectively, for those with a BMI less than 27 and 27 or more (p=0.04). However, mean daily doses of individual drugs were not significantly different in the two BMI categories (Table 7). The mean dose reported to have been taken in the 24 hours preceding the examination was practically identical to the mean daily prescribed dose (data not shown). With regard to overnight urinary excretion and mean 2-hour post ingestion blood levels, there were no consistent differences between the two BMI categories. In all comparisons but one, the differences between the two BMI categories were not significant. Urinary excretion of methyldopa was lower in the higher BMI category and the difference reached significance (p=0.03). However, in the overall comparison of cumulative rate of values above and below the common median for each drug, there was no significant difference between the BMI categories.

Discussion

Demonstration of true drug resistance implies that the resistant group requires higher drug dosages to produce equivalent effects or that equivalent doses achieve lesser effect. Our analysis of 559 individuals comprising all those on antihypertensive medication in a representative population sample suggests that obese hypertensive individuals are less responsive to these medications than nonobese individuals. In the absence of information on untreated blood pressure levels in our cross-sectional data, we based our conclusion on two findings: the independent positive association between BMI and
TABLE 7. Mean Daily Dosage and Mean and Percent Below Median Overnight Urinary Excretion Rate and Plasma Drug Levels 2 Hours After Ingestion by Body Mass Index in 80 Representative Individuals Treated With Antihypertensive Drugs in the Insulin Group

<table>
<thead>
<tr>
<th>Drug</th>
<th>BMI &lt;27 (n=35)</th>
<th>BMI ≥27 (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean daily dose (mg)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>21</td>
<td>70.5±47.1</td>
</tr>
<tr>
<td>% &lt;median</td>
<td></td>
<td>52.4</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>10</td>
<td>550±158</td>
</tr>
<tr>
<td>% &lt;median</td>
<td></td>
<td>30.0</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>10</td>
<td>39.3±15.9</td>
</tr>
<tr>
<td>% &lt;median</td>
<td></td>
<td>50.0</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>4</td>
<td>50±36</td>
</tr>
<tr>
<td>% &lt;median</td>
<td></td>
<td>75.0</td>
</tr>
<tr>
<td>Furosemide</td>
<td>2</td>
<td>40±0.0</td>
</tr>
<tr>
<td>% &lt;median</td>
<td></td>
<td>100.0</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>3</td>
<td>381±201</td>
</tr>
<tr>
<td>% &lt;median</td>
<td></td>
<td>33.3</td>
</tr>
<tr>
<td>Total % &lt;median</td>
<td>50.0</td>
<td>48.0</td>
</tr>
</tbody>
</table>

The similarity of dosages of individual drugs is not in contradiction with the increased dosage score in individuals with increased body mass index (BMI), which reflects the higher rate of combined therapy.

dosage score and the similar adjusted mean blood pressures across all BMI levels within each dosage score. Taken together, these findings indicate that higher doses were needed by subjects in the higher BMI levels to achieve blood pressure levels equivalent to those attained by subjects in the lower BMI levels, even after adjusting for major potential confounders.

Studies in which hypertension resistant to drug therapy has been defined unequivocally, report a prevalence range of 3–13%. In these studies, the definition of resistant hypertension was very strict, and thus, these rates may well have underestimated the true prevalence of resistant hypertension. In our study, the overall rate of patients with uncontrolled hypertension among the treated was about 50%,
which is commonly found in population surveys. Obviously, in a considerable portion of these patients the lack of control is attributable to poor compliance or insufficient dosage or inappropriate choice of drugs. This could be especially true in our cross-sectional study of a population sample in which patients were treated by many physicians in the community with no uniform treatment protocol. However, to account for the association of the apparently reduced responsiveness to antihypertensive medications with increasing BMI, differential physician approach to obese patients or lower compliance among these patients would have to be present. With respect to drug choice, it should be noted that during the period of the study, stepped care, relying primarily on thiazide diuretics and β-blockers, was the recommended approach. Our data show that this approach was used in the majority of patients. Also, the distribution of dosage scores and their association with combined therapy indicate that the physicians usually adhered to the accepted practice of adding another drug rather than using maximal doses of any single drug, irrespective of BMI category. These observations, as well as our findings that at each dosage score, mean blood pressure was not affected by BMI and that higher dosage scores were associated with higher blood pressure levels, seem to indicate that treatment policy reflected blood pressure response to drugs and was not influenced by the patient’s BMI. Lower compliance with clinic visit schedules in obese hypertensive patients has been described, suggesting the possibility of decreased compliance with drug regimens as well. This also apparently did not play a major role in our study since overnight drug urinary excretion at similar doses was not significantly affected by degree of obesity. Similar compliance across BMI levels is also supported by the similar mean blood pressures at each prescribed dosage score.

Because our study was cross-sectional, other possible explanations for the observed associations should be considered. Selective referral for treatment does not seem to account for our findings since rate of treatment among hypertensive individuals in the total study group was similar at all levels of BMI at 23.0 or greater. Errorneously high measured blood pressure due to greater arm circumference in the obese was not a factor in our study since arm circumference had no significant effect on dosage score in our analysis. It is also possible that untreated blood pressure level was higher in the obese. However, distinguishing between higher untreated blood pressure level and reduced responsiveness to blood pressure-lowering medications can only be achieved in a prospective study of untreated hypertensive individuals. Finally, diminished drug absorption or altered disposition in the obese did not seem to account for our findings, as indicated by the similar overnight urinary excretion and postingestion plasma drug concentrations at all levels of obesity.

Little attention has been directed to date to a possible differential response to antihypertensive drugs based on relative weight despite the considerable attention given to obese hypertension as a distinct entity in terms of etiology and epidemiology. Recent reviews and policy statements do mention obesity as being associated with refractory hypertension but only in passing and without documentation. We were able to find only one study directly addressing a series of risk factors for resistant hypertension showing that higher BMI was characteristic of individuals defined as resistant to treatment by strict criteria. In the latter report, potential confounders of this association were not accounted for. In particular, the effect of large arm circumference, which could lead to erroneously high measured blood pressure in the obese appearing as resistance to treatment, was not considered. The findings in two large-scale clinical trials were similar to our own in that a larger proportion of overweight hypertensive individuals did not achieve normal blood pressure on treatment or required combined drug regimens to achieve a target blood pressure level. However, in these two studies, the data were analyzed by overweight as a secondary issue; their bearing on treatment of obese hypertensive individuals was not addressed, and arm circumference was not measured. Nevertheless, they do suggest that our data represent a real effect.

We also found that glucose intolerance and hyperinsulinemia were associated with decreased response to antihypertensive therapy independent of BMI. This suggests a role for insulin sensitivity in determining response to antihypertensive medications since both BMI and glucose intolerance are strongly correlated and are also independently associated with hyperinsulinemia and insulin resistance. Our finding of lower dosage scores achieving equivalent blood pressure levels in women as compared with men in all age and BMI categories supports this contention since women are apparently more insulin sensitive than men. The association of glucose intolerance and hyperinsulinemia with reduced response to antihypertensive treatment in our cross-sectional data may have been an outcome rather than a cause of the higher dosage of antihypertensive medication since most of our patients were on thiazide diuretics or β-blockers. However, such an adverse drug effect apparently made only a minor contribution to this association, as suggested by the multiple regression analysis showing that the independent effects of glucose intolerance and hyperinsulinemia on dosage score were considerably smaller than that of obesity. Thus, if our findings were mainly due to the adverse effects of these drugs, a reverse pattern would have been expected, in that the association of glucose intolerance and hyperinsulinemia with dosage score should have been stronger than that of BMI since the effects of these drugs on
glucose intolerance and hyperinsulinemia are not limited to obese individuals.

In conclusion, the most likely explanation for our findings seems to be that obese, glucose-intolerant, and hyperinsulinemic hypertensive individuals are more resistant to antihypertensive drug treatment. Because obesity, glucose intolerance, and hypertension are characterized by insulin resistance, which, except in non-insulin-dependent diabetes, is accompanied by hyperinsulinemia, our findings suggest that the insulin-resistant state may contribute to this drug resistance. To provide a definitive evaluation of these contentions and to fully assess efficacy, antihypertensive drug trials should be reported stratified by BMI and, if possible, include in the follow-up an oral glucose tolerance/insulin response test.

References

Key Words: obesity • glucose • essential hypertension • antihypertensive agents • hyperinsulinemia • drug-resistant hypertension.
Obesity, glucose intolerance, hyperinsulinemia, and response to antihypertensive drugs.
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