Clustering of Cardiovascular Risk Factors in Confirmed Prehypertensive Individuals

Steven M. Haffner, Eleuterio Ferrannini, Helen P. Hazuda, and Michael P. Stern

Numerous studies have indicated that hypertensive subjects have an atherogenic lipoprotein pattern, hyperinsulinemia, and impaired glucose tolerance relative to normotensive individuals. These abnormalities could be due to adverse effects of certain antihypertensive agents, to pathophysiological concomitants of the hypertensive state itself, or to both. In this report, we describe the cardiovascular risk factor profile of 1,440 subjects who were normotensive and were not taking any antihypertensive medications when first examined and who subsequently participated in the 8-year follow-up of the San Antonio Heart Study. Hypertension developed in 130 subjects during the follow-up period. At baseline these prehypertensive individuals had significantly higher levels of blood pressure, fasting total and low density lipoprotein cholesterol, triglyceride, glucose, and insulin, and 2-hour glucose than those who remained free of hypertension. In addition, they had higher body mass indexes, a less favorable body fat distribution, and lower levels of high density lipoprotein cholesterol. In multiple linear regression analyses, baseline levels of triglyceride and blood pressure remained significantly higher and high density lipoprotein cholesterol remained significantly lower in the subjects who later converted to hypertension than in those who remained normotensive. Although baseline insulin levels were also higher in the prehypertensive subjects, this difference was not statistically significant. In nonobese subjects, however, those with high baseline insulin concentrations had an increased incidence of hypertension compared with those with low insulin concentrations. The present results suggest that the cluster of atherogenic changes associated with hypertension actually precede the development of the hypertensive state. (Hypertension 1992;20:38–45)

KEY WORDS • essential hypertension • lipids • lipoproteins • insulin • glucose • obesity • cardiovascular risk factors

Prospective studies have shown that age, overall adiposity, alcohol consumption, and glucose intolerance are all related to the incidence of hypertension.1-7 Dietary minerals such as increased sodium and decreased potassium intake have also been implicated in the etiology of hypertension.8-11 Little is known, however, about possible metabolic precursors of hypertension, especially dyslipidemia and hyperinsulinemia. Previous epidemiological studies that report clustering of cardiovascular risk factors in patients with hypertension are limited because, in general, they have been cross-sectional.12-16 It is possible, therefore, that this clustering of risk factors could result from compensatory mechanisms that induce secondary metabolic changes (e.g., increased catecholamine concentrations secondary to the hypertensive state). Alternatively, certain antihypertensive agents have been reported to induce dyslipidemia and to increase insulin resistance.17 In metabolic ward studies, insulin resistance as measured by the euglycemic clamp technique has been associated with both hypertension18,19 and lipid disorders.20,21 Several reviews and editorials have called attention to the possible role of insulin resistance in contributing to the cluster of lipid disorders, hypertension, and glucose intolerance,22-25 although other reports have disputed this concept.26-29 Donahue et al30 in a recent review of hyperinsulinemia and hypertension have noted the lack of prospective data in this area. The significance of the clustering of cardiovascular risk factors in hypertensive patients can be clarified to a considerable degree by examining these associations prospectively. Prospective studies of non-insulin-dependent diabetes mellitus (NIDDM) have indicated that an atherogenic pattern of lipids and lipoproteins and elevated levels of blood pressure and insulin precede the onset of clinical diabetes.31-34 In view of the cross-sectional relation between insulin and blood pressure, we postulated that similar atherogenic changes might precede the onset of clinical hypertension. Thus, we examined metabolic and anthropometric precursors of hypertension in the 8-year follow-up of the San Antonio Heart Study cohort.

Methods

The San Antonio Heart Study is a population-based study of diabetes and cardiovascular disease in Mexican Americans and non-Hispanic whites. Between 1979 and 1982, a total of 1,288 Mexican American and 929 non-Hispanic white men and women, aged 25–64 years...
when first examined, were randomly selected from three neighborhoods in San Antonio, Tex. The overall response rate was 63.9%. A detailed description of this survey has been published previously. Mexican Americans were defined as persons whose ancestry and cultural traditions derived from a Mexican national origin. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and all subjects gave informed consent.

At the baseline examination blood specimens were obtained after a 12-14-hour fast for serum lipid, lipoprotein, and insulin and plasma glucose determinations. A 75-g glucose-equivalent load (Glucola, Ames Laboratories, Elkhart, Ind.) was then administered, and blood specimens were obtained 1 and 2 hours later for plasma glucose concentrations. Glucose, insulin, and lipid and lipoprotein methods have been published previously. Diabetes mellitus was diagnosed according to the criteria of the World Health Organization (fasting plasma glucose level 7.8 mmol/l or greater and/or 2-hour glucose level 11.1 mmol/l or greater). Subjects who did not meet the World Health Organization's plasma glucose criteria, but who were under treatment with oral antidiabetic agents or insulin, were also considered to have diabetes. Impaired glucose tolerance was also diagnosed according to the criteria of the World Health Organization (fasting plasma glucose level less than 7.8 mmol/l and 2-hour plasma glucose between 7.8 and 11.1 mmol/l).

Systolic (first phase) and diastolic (fifth phase) blood pressures were measured to the nearest even digit using a random-zero sphygmomanometer (Hawksley-Gelman, London, England). Three readings were recorded for each individual, and the average of the second and third reading was defined as the subject's blood pressure. Hypertension was defined as a diastolic blood pressure of 95 mm Hg or greater. Individuals with blood pressure levels below this cutoff point were also considered to have hypertension if they met both of the following criteria: having a history of having been diagnosed as hypertensive, and they were currently receiving antihypertensive medications. Subjects were asked to bring their medications to the clinic, and these medications were checked to see if they were recognized antihypertensive agents. Ninety percent of subjects characterized as hypertensive in this report had been previously diagnosed by a physician and were taking antihypertensive medications. Thus, only 10% were characterized as being hypertensive solely on the basis of an elevated blood pressure (95 mm Hg or greater diastolic blood pressure) at their clinic examination.

Anthropometric measurements (height, weight, and subscapular and triceps skinfold measurements) were made after participants had removed their shoes and upper garments and donned an examining gown. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. The ratio of subscapular-to-triceps skinfold (centrality index) was used as a measure of central adiposity.

In October 1987, an 8-year follow-up study was begun to ascertain the incidence of type II diabetes, hypertension, and coronary heart disease. Vital status was ascertained on 97.8% of the 2,217 subjects enrolled in the original 1979-1982 survey. The follow-up examination consisted of an initial home or telephone interview (completed by 96.9% of surviving subjects) and a medical examination (which was attended by 82.9% of subjects who completed the telephone interview). The overall response rate was thus 80.3% (969×0.829). The medical examination was performed in a mobile clinic located in the participants' neighborhoods. Blood pressure was determined in a manner identical to that used at the baseline examination. A total of 969 Mexican Americans and 704 non-Hispanic whites attended the follow-up examination; of these, 871 Mexican Americans and 598 non-Hispanic whites were normotensive and not taking antihypertensive medications at baseline. Twenty-nine subjects did not have information available on blood pressure or medication at follow-up, leaving 1,440 subjects, who form the basis of this report.

Group means for baseline variables in converters to hypertensive versus nonconverters and means were computed by analysis of variance. Initial models included conversion status and ethnicity as grouping variables. All first-order interactions (e.g., conversion status × ethnicity) were nonsignificant, suggesting that the effects of the prehypertensive state were similar in the two ethnic groups. Therefore, to increase statistical power and simplify the presentation, subsequent analyses are presented with the ethnic groups pooled and conversion status as the only grouping variable (Table 1). Since both hypertension incidence and cardiovascular risk factors are related to age, BMI, and body fat distribution, we controlled for the effect of these possible confounders in addition to sex and ethnicity by multiple linear regression (Table 2). Since both hypertension incidence and cardiovascular risk factors are related to age, BMI, and body fat distribution, we controlled for the effect of these possible confounders in addition to sex and ethnicity by multiple linear regression (Table 2). Table 3 shows group means according to conversion status for individuals who were nonobese (BMI less than 25 kg/m²) and normoglycemic (2-hour glucose less than 7.8 mmol/l) at baseline. Triglyceride, glucose, and insulin concentrations were log transformed to take account of skewness and kurtosis. Fasting insulin concentrations (pmol/l) were divided into tertiles based on the distribution in the entire population: tertile 1, less than 57.6; tertile 2, 57.6-95.0; and tertile 3, more than 95.0. The mean ± SD for these tertiles were 37.4±11.5, 71.1±10.0, and 169.9±44.7 pmol/l, respectively. BMI (kg/m²) was divided into approximately equal thirds: less than 25, 25-30, and more than 30. The mean ± SD for these three categories were 22.1±2.0, 27.1±1.4, and 34.4±4.1, respectively. The incidence of hypertension in the highest category of these variables was compared with the incidence in the lower two categories using the relative risk. The χ² test was used to test the statistical significance of the relative risk. We also modeled hypertension incidence using multiple logistic models to control for age, ethnicity, and gender in analyses similar to those shown in Figures 1 and 2 and Table 4. Since the results of these were similar to the unadjusted results, we have elected to present the simpler unadjusted data.

Results

Characteristics of Prehypertensive Subjects

Table 1 shows mean levels of anthropometric variables and cardiovascular risk factors by conversion status. The sex and ethnic distribution did not differ significantly by conversion status. The 130 converters to hypertension were significantly older and more obese.
TABLE 1. Anthropometric Variables and Cardiovascular Risk Factors According to Conversion Status at Follow-up: Univariate

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Hypertension</th>
<th>Normotension</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>130</td>
<td>1,310</td>
<td></td>
</tr>
<tr>
<td>Mexican Americans (%)</td>
<td>58.8</td>
<td>59.4</td>
<td>0.704</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43.8</td>
<td>42.3</td>
<td>0.734</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.9±0.8</td>
<td>42.9±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7±0.4</td>
<td>25.9±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Centrality index</td>
<td>1.25±0.05</td>
<td>1.14±0.01</td>
<td>0.021</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)*</td>
<td>1.58±0.05</td>
<td>1.21±0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)*</td>
<td>5.63±0.09</td>
<td>5.32±0.02</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)*</td>
<td>3.62±0.08</td>
<td>3.14±0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)*</td>
<td>1.24±0.03</td>
<td>1.36±0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>122.5±1.2</td>
<td>109.0±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78.3±0.7</td>
<td>69.6±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)*</td>
<td>5.62±3.20</td>
<td>5.27±0.04</td>
<td>0.021</td>
</tr>
<tr>
<td>2-hr glucose (mmol/l)*</td>
<td>7.49±0.4</td>
<td>6.66±0.09</td>
<td>0.009</td>
</tr>
<tr>
<td>Glucose tolerance (%)</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>71.0</td>
<td>81.3</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>IGT</td>
<td>16.9</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>NIDDM</td>
<td>12.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>102.3±7.58</td>
<td>81.1±7.34</td>
<td>0.008</td>
</tr>
<tr>
<td>Follow-up variables</td>
<td>Systolic BP</td>
<td>137.5±20.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>78.8±11.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Centrality, ratio of subscapular-to-triceps skinfold; LDL, low density lipoprotein; HDL, high density lipoprotein; BP, blood pressure; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus.

*To convert triglyceride to milligrams per deciliter, multiply by 88.57. To convert cholesterol to milligrams per deciliter, multiply by 38.69. To convert glucose to milligrams per deciliter, multiply by 18.0.

Since age, obesity, and body fat distribution may confound the relation between conversion status and cardiovascular risk factors, we next performed multiple linear regression analyses, the results of which are shown in Table 2. The figures presented in this table represent differences between converters and nonconverters to hypertension. Positive differences indicate that converters had higher values, and negative differences indicate that nonconverters had lower values than converters. In model 1, we controlled for the effects of age, gender, and ethnicity. Converters to hypertension had higher baseline BMIs, centrality indexes, total and LDL cholesterol and triglyceride concentrations, systolic and diastolic blood pressures, 2-hour glucose and fasting insulin concentrations, and lower HDL cholesterol levels than subjects who remained normotensive. In the second model we adjusted for BMI and centrality index as well as age, ethnicity, and gender. After these further adjustments, the only differences that remained statistically significant were the higher baseline triglyceride concentrations and systolic and diastolic blood pressures and the lower baseline HDL cholesterol levels in converters compared with nonconverters. Since baseline obesity and body fat distribution are associated with baseline diastolic blood pressure, we also adjusted for diastolic blood pressure instead of obesity and body fat distribution. The results were virtually identical to those presented in model 2 (data not shown).

We also compared baseline levels of lipids and lipoproteins in nonobese, normoglycemic subjects (Table 3). Prehypertensive subjects who were lean and normoglycemic at baseline had significantly higher baseline levels of fasting insulin, triglyceride, LDL and total cholesterol, and systolic and diastolic blood pressure, and a more unfavorable body fat distribution than lean, normoglycemic subjects who remained normotensive at follow-up. As expected, there were no statistically significant differences in BMI or fasting glucose concentrations between the converters and nonconverters to hypertension. After adjustment for age and body fat distribution, converters still had significantly higher...
TABLE 2. Baseline Anthropometric Variables and Cardiovascular Risk Factors Between Converters and Nonconverters to Hypertension: Multivariate Analysis

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Adjusted for Age, ethnicity, gender</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>Adjusted for Age, ethnicity, gender, BMI, centrality</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td>1.62*</td>
<td>(0.8, 2.4)</td>
<td></td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Centrality</td>
<td></td>
<td>0.08†</td>
<td>(0.04, 0.12)</td>
<td></td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td></td>
<td>0.34†</td>
<td>(0.05, 0.63)</td>
<td>0.22‡</td>
<td>(0.05, 0.37)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td></td>
<td>0.29*</td>
<td>(0.05, 0.53)</td>
<td>0.10</td>
<td>(-0.05, 0.25)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td></td>
<td>0.36†</td>
<td>(0.11, 0.62)</td>
<td>0.12</td>
<td>(-0.18, 0.30)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td></td>
<td>-0.11‡</td>
<td>(-0.08, -0.14)</td>
<td>-0.08‡</td>
<td>(-0.02, -0.14)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td></td>
<td>11.5*</td>
<td>(9.54, 13.5)</td>
<td>8.8*</td>
<td>(6.7, 10.9)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td></td>
<td>8.1*</td>
<td>(6.7, 9.5)</td>
<td>7.3*</td>
<td>(5.8, 8.8)</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td></td>
<td>0.20</td>
<td>(-0.06, 4.69)</td>
<td>0.15</td>
<td>(-0.10, 4.49)</td>
<td></td>
</tr>
<tr>
<td>2-hr glucose (mmol/l)</td>
<td></td>
<td>0.70*</td>
<td>(0.12, 1.29)</td>
<td>0.46</td>
<td>(-0.20, 1.07)</td>
<td></td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td></td>
<td>35.9*</td>
<td>(23.1, 48.7)</td>
<td>25.2</td>
<td>(-0.41, 52.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean differences. BMI, body mass index; Centrality, ratio of subscapular-to-triceps skinfold; CI, confidence interval; LDL, low density lipoprotein; HDL, high density lipoprotein; BP, blood pressure.

*£<0.05, †<0.01, ‡<0.001.

To convert triglyceride to milligrams per deciliter, multiply by 88.57. To convert insulin to microunits per milliliter, multiply by 0.139. To convert cholesterol to milligrams per deciliter, multiply by 38.69. To convert glucose to milligrams per deciliter, multiply by 18.0.

triglyceride and total and LDL cholesterol concentrations, blood pressure, and insulin and lower levels of HDL cholesterol than subjects who remained normotensive at follow-up (data not shown).

Incidence of Hypertension According to Selected Risk Factors

Recently, Saad et al 41 have described a cross-sectional relation between insulin resistance and blood pressure in whites but not in Pima Indians or blacks. We therefore examined separately the relation of BMI, glucose tolerance and fasting insulin to the incidence of hypertension in Mexican Americans and non-Hispanic whites. These results are shown in Figure 1. In both ethnic groups, the incidence of hypertension increased significantly with obesity, higher insulin concentration, and poorer glucose tolerance. Subjects in the highest category of BMI had an increased incidence of hypertension relative to subjects in the lowest two categories (13.8% versus 6.3%, respectively; relative risk [RR]=

TABLE 3. Baseline Anthropometric Variables and Cardiovascular Risk Factors in Nonobese, Normoglycemic Subjects According to Conversion Status at Follow-up: Univariate Analysis

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Hypertensive</th>
<th>Normotensive</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>552</td>
<td></td>
</tr>
<tr>
<td>Mexican American (%)</td>
<td>59</td>
<td>61</td>
<td>0.835</td>
</tr>
<tr>
<td>Male (%)</td>
<td>46</td>
<td>39</td>
<td>0.622</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.2±1.6</td>
<td>41.6±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.4±0.3</td>
<td>22.2±0.1</td>
<td>0.572</td>
</tr>
<tr>
<td>Centrality</td>
<td>1.20±0.04</td>
<td>1.14±0.01</td>
<td>0.045</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>118.2±1.5</td>
<td>108.9±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.1±1.0</td>
<td>69.9±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose* (mmol/l)</td>
<td>5.12±0.22</td>
<td>4.91±0.06</td>
<td>0.091</td>
</tr>
<tr>
<td>Triglyceride* (mmol/l)</td>
<td>1.32±0.05</td>
<td>1.01±0.01</td>
<td>0.010</td>
</tr>
<tr>
<td>Total cholesterol* (mmol/l)</td>
<td>5.59±0.08</td>
<td>5.04±0.02</td>
<td>0.011</td>
</tr>
<tr>
<td>HDL cholesterol* (mmol/l)</td>
<td>1.33±0.03</td>
<td>1.44±0.01</td>
<td>0.018</td>
</tr>
<tr>
<td>LDL cholesterol* (mmol/l)</td>
<td>3.36±0.07</td>
<td>2.88±0.03</td>
<td>0.015</td>
</tr>
<tr>
<td>Fasting insulin* (pmol/l)</td>
<td>81.6±2.2</td>
<td>54.4±0.6</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Centrality, ratio of subscapular-to-triceps skinfold; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein.

*To convert triglyceride to milligrams per deciliter, multiply by 88.57. To convert cholesterol to milligrams per deciliter, multiply by 38.69. To convert glucose to milligrams per deciliter, multiply by 18.0. To convert insulin to microunits per milliliter, multiply by 0.139.
Subjects with NIDDM had an increased incidence of hypertension relative to subjects in the normal range, the cumulative effect of these changes in triglyceride concentrations is about 30%. It is striking in the lean, normoglycemic group where the difference in triglyceride concentrations is about 30%. It is between converters and nonconverters are even more consistent by BMI and fasting insulin concentrations (Figure 2). In nonobese subjects, the incidence of hypertension increased with baseline fasting insulin concentrations in a stepwise fashion. This relation was not consistently observed in the more obese subjects. In lean subjects the incidence of hypertension for those in the highest tertile of insulin concentration compared with those in the lowest two tertiles was 10.1% versus 4.5%, respectively (RR=2.24; p=0.032); in subjects with BMI between 25 and 30 kg/m² the incidence in corresponding categories was 15.0% versus 11.5%, respectively (RR=1.32; p=NS); and in obese subjects the incidence of hypertension in corresponding categories was 12.1% versus 17.3%, respectively (RR=0.70; p=NS). Thus, the effect of fasting insulin on the incidence of hypertension decreased with increasing obesity. Homogeneity of the effect of insulin in the three BMI categories was rejected by Woolfs test for heterogeneity (p=0.003). Similar results were observed using multiple logistic regression analysis with age, ethnicity, gender, obesity, fasting insulin, and obesity×insulin as independent variables. A significant interaction term (p=0.008) for obesity×insulin was obtained, further supporting the concept of a lessening effect of prior insulinemia on hypertension incidence with increasing degrees of obesity (data not shown). Also, the data in Figure 2 suggest that the effect of obesity on the development of hypertension occurs primarily in the low and moderate insulinemia categories but not in the most hyperinsulinemic category.

Discussion

Williams et al have previously reported cross-sectional data indicating that subjects in whom hypertension develops at an early age have an increased frequency of lipid disorders ("familial dyslipidemic hypertension") and that a subset of these subjects has increased glucose and insulin concentrations. The present results extend these findings by showing that the metabolic abnormalities associated with the hypertensive state (increased triglyceride and decreased HDL cholesterol and increased glucose and insulin concentrations) actually precede the development of clinical hypertension. The differences between the prehypertensive subjects and those who remained normotensive are most striking for triglyceride concentration; prehypertensive subjects have obesity-adjusted triglyceride concentrations that are about 20% higher than control subjects (in contrast to differences of about 10% for the other lipid variables) (Table 1). These differences between converters and nonconverters are even more striking in the lean, normoglycemic group where the difference in triglyceride concentrations is about 30%. It should be noted, however, that this latter finding is based on only 27 converters to hypertension, and therefore larger studies will be needed to confirm these findings. Although the mean concentrations of lipids, lipoproteins, and glucose for both groups remain in the normal range, the cumulative effect of these changes in prehypertensive subjects could increase their atherogenic risk considerably.

Since the relative impact of insulin resistance may be greater in lean than in obese subjects, we also examined the incidence of hypertension stratified simultaneously by BMI and fasting insulin concentrations (Figure 2). In nonobese subjects, the incidence of hypertension increased with baseline fasting insulin concentrations in a stepwise fashion. This relation was not consistently observed in the more obese subjects. In lean subjects the incidence of hypertension for those in the highest tertile of insulin concentration compared with those in the lowest two tertiles was 10.1% versus 4.5%, respectively (RR=2.24; p=0.032); in subjects with BMI between 25 and 30 kg/m² the incidence in corresponding categories was 15.0% versus 11.5%, respectively (RR=1.32; p=NS); and in obese subjects the incidence of hypertension in corresponding categories was 12.1% versus 17.3%, respectively (RR=0.70; p=NS). Thus, the effect of fasting insulin on the incidence of hypertension decreased with increasing obesity. Homogeneity of the effect of insulin in the three BMI categories was rejected by Woolfs test for heterogeneity (p=0.003). Similar results were observed using multiple logistic regression analysis with age, ethnicity, gender, obesity, fasting insulin, and obesity×insulin as independent variables. A significant interaction term (p=0.008) for obesity×insulin was obtained, further supporting the concept of a lessening effect of prior insulinemia on hypertension incidence with increasing degrees of obesity (data not shown). Also, the data in Figure 2 suggest that the effect of obesity on the development of hypertension occurs primarily in the low and moderate insulinemia categories but not in the most hyperinsulinemic category.

Discussion

Williams et al have previously reported cross-sectional data indicating that subjects in whom hypertension develops at an early age have an increased frequency of lipid disorders ("familial dyslipidemic hypertension") and that a subset of these subjects has increased glucose and insulin concentrations. The present results extend these findings by showing that the metabolic abnormalities associated with the hypertensive state (increased triglyceride and decreased HDL cholesterol and increased glucose and insulin concentrations) actually precede the development of clinical hypertension. The differences between the prehypertensive subjects and those who remained normotensive are most striking for triglyceride concentration; prehypertensive subjects have obesity-adjusted triglyceride concentrations that are about 20% higher than control subjects (in contrast to differences of about 10% for the other lipid variables) (Table 1). These differences between converters and nonconverters are even more striking in the lean, normoglycemic group where the difference in triglyceride concentrations is about 30%. It should be noted, however, that this latter finding is based on only 27 converters to hypertension, and therefore larger studies will be needed to confirm these findings. Although the mean concentrations of lipids, lipoproteins, and glucose for both groups remain in the normal range, the cumulative effect of these changes in prehypertensive subjects could increase their atherogenic risk considerably.
It is interesting to compare these data on prehypertensive individuals with previous reports on the prediabetic state. In the Israeli Heart Study, the Dupont Study, the Rancho Bernardo Study, and the San Antonio Heart Study, cardiovascular risk factors including blood pressure, lipids, and lipoproteins were abnormal even before the onset of clinical diabetes. In the San Antonio Heart Study, this more adverse pattern of cardiovascular risk factors was seen even in prediabetic subjects who had completely normal glucose tolerance at baseline, indicating that this phenomenon is not merely a consequence of the fact that many prediabetics already have impaired glucose tolerance, a condition known to be associated with cardiovascular risk factors. Also, in the San Antonio Heart Study, adjustment for insulin, but not for obesity or body fat distribution, abolished the differences in atherogenic risk factors between prediabetic subjects and subjects who remained nondiabetic, highlighting the importance of hyperinsulinemia as a determinant of cardiovascular risk in the prediabetic state.

Although there are similarities between the prediabetic and the prehypertensive states, major differences also exist. In prediabetic subjects from the San Antonio Heart Study, insulin concentrations were twice as high as in subjects who remained normoglycemic. In contrast, the excess of insulin in prehypertensive subjects compared with normotensive subjects was only 26%. In prediabetic subjects, insulin concentrations remained significantly elevated even after adjustment for obesity and body fat distribution, whereas in the case of prehypertensive individuals, similar adjustments attenuated this difference to only 15%, which then became of only borderline statistical significance. In the prediabetic state, adjustment for the baseline insulin concentration abolished the differences in atherogenic risk factors between the converters and nonconverters, whereas in prehypertensive subjects, these differences were not abolished by such adjustment (data not shown).

Several factors may account for the differences in the effects of various metabolic precursors on hypertension and diabetes. First, hypertension is a heterogeneous disorder, and it is therefore quite possible that hyperinsulinemia plays an etiologic role in only certain subgroups of hypertensive patients. In support of this possibility is the present finding that insulin concentrations are related to the incidence of hypertension in lean but not in obese subjects (Figure 2). Thus, in the former subgroup, which accounts for 27% of future hypertensive subjects, hyperinsulinemia has a stronger predictive value and may, in fact, have a pathogenic significance in its own right. In more obese individuals, on the other hand, the mechanisms contributing to high blood pressure may be different than in lean subjects (e.g., hemodynamic adjustments to an expanded body mass). If this were the case, hyperinsulinemia would still accompany obesity, but would not contribute directly to high blood pressure, with the result that statistical adjustment for obesity would weaken any association between insulin and blood pressure. Two other observations are relevant in this context. One is that in metabolic ward studies, marked insulin resistance has been found in lean hypertensive patients compared with lean normotensive subjects, whereas among obese individuals the hyperinsulinemia(insulin resistance/hypertension association is much less marked. The other relevant observation is that the cross-sectional relation between insulin concentration and blood pressure is not observed in all populations. For example, it is much weaker in Pima Indians than in whites.

As noted previously, Saad et al have shown that insulin resistance as measured by the euglycemic clamp is related to blood pressure in whites but not in blacks or Pima Indians. Since Pima Indians are much more obese than whites, they may be less likely to manifest the hyperinsulinemia(insulin-resistant form of hypertension, assuming this form is more characteristic of lean hypertensive subjects. Falkner et al found an association between insulin resistance and mild hypertension in young, lean blacks. The blacks in this study were much less obese than those in the study by Saad et al (BMI, 24 versus 31 kg/m², respectively).

Several mechanisms have been proposed for the effect of insulin on blood pressure, including effects on the sympathetic nervous system, proliferation of vascular smooth muscle cells, cation transport, and renal sodium reabsorption. However, conflicting data also exist. Laakso et al have shown that insulin may lead to vasodilation (rather than vasoconstriction) in men. Hall et al have shown no increase in mean arterial blood pressure after 7 days of insulin infusion into dogs. Anderson et al have shown that short-term insulin infusions (2 hours) raise catecholamines but not blood pressure in normotensive men. The effect of chronic hyperinsulinemia (i.e., lasting years), however, is unknown.

It is possible that in certain groups (e.g., obese individuals, Pima Indians), the relation between insulin sensitivity and blood pressure may be weaker. This possibility is supported by data from the Pima Indian and Mexican American populations, both of which have high rates of non-insulin-dependent diabetes, hyperinsulinemia, and insulin resistance, but paradoxically lower prevalences of hypertension. Whereas the relation between

Table 4. Distribution of Subjects by Baseline Body Mass Index and Glucose Tolerance Status and Hypertension Status at Follow-up

<table>
<thead>
<tr>
<th>Status at follow-up</th>
<th>BMI status at baseline</th>
<th>Nonobese (BMI &lt; 25 kg/m²)</th>
<th>Obese (BMI ≥ 25 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>and diabetic status at baseline</td>
<td>and diabetic status at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NI</td>
<td>IGT</td>
</tr>
<tr>
<td>Normotensive</td>
<td></td>
<td>552 (44%)</td>
<td>44 (4%)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td>27 (22%)</td>
<td>4 (3%)</td>
</tr>
</tbody>
</table>

The number of subjects is lower in this table than in Tables 1 and 2 because data on 2-hour glucose is missing in 77 subjects. BMI, body mass index; NI, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus.
insulin level and blood pressure is minimal in Pima Indians,\textsuperscript{41,42} both cross-sectional\textsuperscript{43} and the present prospective data (Figure 1) indicate that the strength of this association is as great in Mexican Americans as it is in non-Hispanic whites. Perhaps this difference between Pima Indians and Mexican Americans may relate to the fact that, although the two populations share native American ancestry, Mexican Americans have a greater than 50% white genetic admixture.\textsuperscript{44} Moreover, Mexican Americans, although they are more obese than non-Hispanic whites, are much less obese than Pima Indians. Again, since insulin resistance may be a more important determinant of hypertension in lean than in obese subjects,\textsuperscript{18,22-44} this relation may be more difficult to demonstrate in the very obese Pima population than in the less obese Mexican Americans. A third possibility for the relatively small difference in insulin concentrations between converters to hypertension and nonconverters is that only fasting levels are available from our 1979–1982 survey. In our later survey (1984–1988), both fasting and 2-hour insulin concentrations were measured, and the latter were more strongly correlated with blood pressure than the former, at least cross sectionally.\textsuperscript{16} Follow-up of the 1984–1988 cohort, however, has not yet been completed. On the other hand, we were able to document a strong relation between fasting insulin and future diabetes,\textsuperscript{46} indicating that the weaker relation reported here is probably not due to insensitivity of our assay for fasting insulin.

In summary, we have shown that the cluster of cardiovascular risk factors (atherogenic lipid and lipoprotein profile, glucose intolerance, and hyperinsulinemia) that have traditionally been associated with hypertension actually precede the development of the hypertensive state. Furthermore, the increased atherogenic state in confirmed prehypertensive subjects is not solely explained by their greater overall adiposity, body fat distribution, or baseline blood pressure. Neither can these changes be ascribed solely to the deleterious physiological effects of the hypertensive state itself. We have also shown that hyperinsulinemia is more marked in lean prehypertensive subjects, in whom it may have pathogenic significance.

References
Haffner et al

Risk Factor Clustering in Prehypertensive Individuals

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Clustering of cardiovascular risk factors in confirmed prehypertensive individuals.
S M Haffner, E Ferrannini, H P Hazuda and M P Stern

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