Parental History of Diabetes Is Associated with Increased Cardiovascular Risk Factors

Steven M. Haffner, Michael P. Stern, Helen P. Hazuda, Braxton D. Mitchell, Judith K. Patterson, and Eleuterio Ferrannini

Serum insulin concentrations are higher in persons with a positive parental history of diabetes than in persons without such a history. Since hyperinsulinemia is associated with both an increased prevalence of hypertension and an atherogenic pattern of serum lipids and lipoproteins, we hypothesized that among nondiabetic persons, a parental history of diabetes would be associated with an atherogenic pattern of cardiovascular risk factors. In the San Antonio Heart Study, a population-based study of cardiovascular disease and diabetes, we examined 549 nondiabetic persons with a parental history of diabetes and 1167 nondiabetic persons without such a history. Compared to persons without a parental history of diabetes, those with such a history had a more atherogenic pattern of cardiovascular risk factors, including higher body mass index, higher systolic and diastolic blood pressures, higher serum insulin and triglyceride concentrations, and lower levels of high density lipoprotein cholesterol. After adjustment for serum insulin concentration, body mass index, and waist-to-hip ratio, the differences in lipids, lipoproteins, and blood pressure between the two parental history groups were no longer statistically significant. Since persons with a parental history of diabetes are more likely to be prediabetics, the present results suggest that prediabetics have an increased risk of coronary heart disease even before they become diabetic. This phenomenon may help explain why the duration of clinical diabetes is only weakly associated with the risk of coronary heart disease as much as, if not more than, the duration of the subsequent diabetes itself. (Arteriosclerosis 9:928–933, November/December, 1989)
in nondiabetic persons with a parental history of diabetes, a population enriched with prediabetic individuals, than in persons without such a history. We further hypothesized that the differences in the pattern of CHD risk factors would be due to differences in obesity and insulinemia.

**Methods**

The San Antonio Heart Study is a population-based study of diabetes and cardiovascular risk factors in Mexican American and non-Hispanic white men and women, ages 25 to 64. Detailed descriptions of the study design, sampling procedures, response rates, and field procedures have appeared elsewhere. The present report is restricted to persons studied in Phase II of the San Antonio Heart Study (1984 to 1988), since postglucose load, serum insulin concentrations were measured only in this phase. Furthermore, these analyses are restricted to Mexican Americans, a population at high risk for NIDDM, since the nondiabetics in this population are likely to include a large number of persons with a parental history of diabetes and, hence, a large number of prediabetic persons. The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All persons studied gave informed consent.

Blood specimens were drawn after a 12-hour fast for determination of plasma glucose, serum insulin, and lipid and lipoprotein concentrations. A 75 g glucose-equivalent load (Koladex or Orangedex, Custom Laboratories, Baltimore, MD) was then administered in the morning, and blood specimens were drawn after 30, 60, and 120 minutes for determination of plasma glucose and serum insulin. The methods for determining the glucose and insulin levels and lipid and lipoprotein levels have been described previously.

The systolic (first phase) and diastolic (fifth phase) blood pressures were measured to the nearest even digit with a random-zero sphygmomanometer (Hawksley-Gelman, London, UK). Three readings were recorded for each individual, and the average of the second and third reading was used as the patient’s blood pressure. Waist circumference was measured at the level of the umbilicus and hip circumference, at the level of the greater trochanter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The ratio of waist-to-hip circumference (WHR) was chosen as a measure of upper body adiposity. The patients were asked what their weight was at age 20, and weight change was calculated as the current measured weight minus the self-reported weight at age 20.

Diabetes mellitus was diagnosed according to the National Diabetes Data Group as modified for epidemiologic studies. Since this report is concerned with the parental history of diabetes as it relates to cardiovascular risk factors among nondiabetics, 289 persons who met the above criteria for diabetes were excluded, leaving 1716 nondiabetic patients. These persons were asked whether their father or mother had diabetes. If at least one parent had diabetes, the parental history of diabetes was considered to be positive.

The group means were computed by two-way analysis of covariance with parental history of diabetes and gender as the grouping variables (SAS) (Table 1). In the analyses presented in Table 2, the equality-of-slopes assumption (e.g., that the effect of insulin concentration on triglyceride concentration was the same in both parental history categories) was met (p>0.20). Triglyceride levels were log-transformed to improve skewness and kurtosis. They were then back-transformed to their natural units for presentation in Tables 1 and 2. Since the standard errors for log-transformed variables are asymmetric about the mean, 95% confidence intervals (CI) are presented for triglyceride levels.

**Results**

Mean age did not differ among the categories of parental history of diabetes (p=0.813). Table 1 shows the age-adjusted mean levels of current weight, weight at age 20, weight change since age 20, height, BMI, WHR, lipids and lipoproteins, systolic and diastolic blood pressures, glucose, and insulin according to parental history of diabetes and gender. For all variables, persons with a parental history of diabetes had a more atherogenic pattern of risk factors than did persons without such a history, although for WHR, height, and total and low density lipoprotein (LDL) cholesterol, these differences were not statistically significant. The difference between the two parental history groups was most marked for 2-hour insulin levels, systolic blood pressure, history of hypertension, and serum triglyceride levels. Since, as previously noted, insulin levels, BMI, and WHR are themselves related to lipids, lipoproteins, and blood pressures, we adjusted for these factors in addition to age (Table 2). After these additional adjustments, the differences in lipids, lipoproteins, and blood pressure were no longer statistically significant between parental history categories. The 2-hour insulin concentration and BMI were significantly associated with all of the risk factors, and WHR is associated with all except total and LDL cholesterol and hypertension prevalence. Adjustment for 2-hour insulin concentrations alone also abolished the differences in risk factors between parental history categories (data not shown).

**Discussion**

The present data show that nondiabetic persons with a parental history of diabetes are characterized not only by hyperinsulinemia but also by a more atherogenic pattern of cardiovascular risk factors in comparison to nondiabetic persons without such a history. If hyperinsulinemia in nondiabetic persons is taken to indicate the presence of insulin resistance, the current results suggest that insulin resistance, elevated blood lipids, and elevated blood pressure co-segregate in the nondiabetic offspring of diabetic parents. In addition, both overall adiposity and unfavorable body fat distribution (both of which are associated with insulin resistance and hyperinsulinemia) also have a strong genetic component. Because a population of nondiabetic persons with positive parental histories of diabetes is likely to be enriched with prediabetic individuals, the increased atherogenicity of the prediabetic phase may make an important contribution to the subsequent risk of CHD even before overt diabetes...
whether a parental history of diabetes also carries the risk of subsequent hypertension remains to be established. Williams et al.47 have recently demonstrated that persons with a family history of hypertension also have a familial aggregation of lipid and lipoprotein disorders that especially affect the high density lipoprotein (HDL) and triglyceride components. Although insulin concentrations were not measured in this study, it is possible that hyperinsulinemia may underlie both hypertension and lipoprotein disorders in this population.

Our findings also indicate that hyperinsulinemia itself may account for the altered lipids, lipoproteins, and blood pressure. In fact, when the two parental history groups were compared after adjusting for insulin levels alone, the differences in blood pressure, triglyceride, and HDL cholesterol concentrations were considerably attenuated and no longer statistically significant. This finding is in accord with the known stimulatory action of insulin on triglyceride and hepatic very low density lipoprotein secretion.49 The fact that adjusting for insulin alone also reduced the difference in blood pressure values between the two groups is compatible with the hypothesis that hyperinsulinemia may be causally linked to hypertension.29

Insulin may contribute to hypertension in a number of ways. Hyperinsulinemia can raise blood pressure by increasing sodium re-absorption at the level of the proximal renal tubule48 and by activating the adrenergic nervous system.49 In tissue cultures, insulin has a direct atherogenic effect on the arterial wall.50 However, it cannot be excluded a priori that some primary pathophysiological process associated with hypertension can cause a secondary decrease in tissue responsiveness to insulin.

Table 1. Age-adjusted Mean Levels of Anthropometric Variables and Cardiovascular Risk Factors by Parental History of Diabetes and Gender

<table>
<thead>
<tr>
<th>Variables and risk factors</th>
<th>Absent (Men = 522)</th>
<th>Absent (Women = 645)</th>
<th>Present (Men = 212)</th>
<th>Present (Women = 337)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>41.4±0.4</td>
<td>41.9±0.4</td>
<td>40.8±2.0</td>
<td>41.7±1.6</td>
<td>0.329</td>
</tr>
<tr>
<td>Current weight (kg)</td>
<td>78.0±0.5</td>
<td>69.5±0.7</td>
<td>84.3±1.0</td>
<td>72.0±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight at age 20 (kg)</td>
<td>65.9±0.5</td>
<td>53.6±0.4</td>
<td>68.2±0.7</td>
<td>55.1±0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Current height (m)</td>
<td>1.70±0.03</td>
<td>1.57±0.02</td>
<td>1.70±0.04</td>
<td>1.57±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight change (kg) since age 20</td>
<td>14.2±0.6</td>
<td>16.0±0.5</td>
<td>16.0±0.9</td>
<td>16.8±0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6±0.2</td>
<td>28.3±0.2</td>
<td>29.0±0.4</td>
<td>29.2±0.3</td>
<td>0.066</td>
</tr>
<tr>
<td>WHR</td>
<td>0.936±0.003</td>
<td>0.833±0.003</td>
<td>0.942±0.005</td>
<td>0.834±0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>127</td>
<td>109</td>
<td>143</td>
<td>125</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>123,131</td>
<td>105,113</td>
<td>133,158</td>
<td>116,135</td>
<td>0.009</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>42.9±0.8</td>
<td>48.9±0.5</td>
<td>40.2±0.9</td>
<td>45.2±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL/TC</td>
<td>0.223±0.003</td>
<td>0.263±0.003</td>
<td>0.211±0.005</td>
<td>0.234±0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>Total C (mg/dl)</td>
<td>200±2</td>
<td>193±1</td>
<td>203±3</td>
<td>196±3</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>127±2</td>
<td>120±1</td>
<td>130±2</td>
<td>130±2</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>123±0.5</td>
<td>119±0.4</td>
<td>127±1.0</td>
<td>124±0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>74.1±0.4</td>
<td>70.7±0.3</td>
<td>76.3±0.6</td>
<td>72.5±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension prevalence</td>
<td>7.1%±1.1%</td>
<td>7.7%±1.0%</td>
<td>11.3%±1.8%</td>
<td>10.3%±1.9%</td>
<td>0.422</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>87.3±0.5</td>
<td>84.0±0.4</td>
<td>88.3±0.7</td>
<td>86.5±0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>2-hour glucose (mg/dl)</td>
<td>98.2±1</td>
<td>110.8±1</td>
<td>107.0±2</td>
<td>115.7±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml)</td>
<td>14.4±0.6</td>
<td>13.5±0.6</td>
<td>16.8±1.0</td>
<td>16.8±0.9</td>
<td>0.223</td>
</tr>
<tr>
<td>2-hour Insulin (µU/ml)</td>
<td>86±4</td>
<td>106±4</td>
<td>98±7</td>
<td>125±6</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Values are in given units±SE. Significance was determined by analysis of covariance.

*Not age adjusted.

BMI = body mass index, WHR = ratio of waist-to-hip circumference, HDL = high density lipoprotein, C = cholesterol, LDL = low density lipoprotein, TG = triglyceride, BP = blood pressure, CI = confidence interval.
Table 2. Mean Levels of Cardiovascular Risk Factors Adjusted for Age, BMI, WHR, and 2-hour Insulin Concentrations

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Parental history of diabetes</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
<td>P values</td>
<td>Gender</td>
<td>Parental history</td>
<td>Ins</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>152</td>
<td>123</td>
<td>148</td>
<td>126</td>
<td>0.0001</td>
<td>0.603</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>44.1</td>
<td>47.4</td>
<td>44.3</td>
<td>48.1</td>
<td>0.0001</td>
<td>0.967</td>
</tr>
<tr>
<td>HDL/total cholesterol</td>
<td>0.229</td>
<td>0.253</td>
<td>0.227</td>
<td>0.251</td>
<td>0.0001</td>
<td>0.388</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>200</td>
<td>194</td>
<td>194</td>
<td>197</td>
<td>0.004</td>
<td>0.219</td>
</tr>
<tr>
<td>LDL</td>
<td>127</td>
<td>120</td>
<td>128</td>
<td>123</td>
<td>0.001</td>
<td>0.339</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>123</td>
<td>118</td>
<td>123</td>
<td>115</td>
<td>0.0001</td>
<td>0.183</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>74.0</td>
<td>71.1</td>
<td>74.5</td>
<td>70.8</td>
<td>0.0001</td>
<td>0.345</td>
</tr>
<tr>
<td>Hypertension prevalence</td>
<td>7.2%</td>
<td>8.6%</td>
<td>8.2%</td>
<td>8.7%</td>
<td>0.976</td>
<td>0.716</td>
</tr>
</tbody>
</table>

BMI = body mass index, WHR = ratio of waist-to-hip circumference, Ins = insulin, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure.

In addition, consideration should be given to behavioral modifications that reduce insulinemia in persons with a parental history of diabetes. These lifestyle modifications might include weight reduction and physical activity programs, both of which improve insulin sensitivity.

References

8. Jarrett RJ. Type II (non-insulin-dependent) diabetes mellitus and coronary heart disease—chicken, egg or neither? Diabetologia 1984;26:99–102


Index Terms: coronary heart disease • lipids • lipoproteins • diabetes • insulin resistance • genetics
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