Genetic Influences on Insulinemia in Normotensive Twins

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The aim of this study was to establish the contribution of genetic factors to the variance of plasma insulin concentration in healthy, normotensive twins. Seventeen pairs of monozygotic (MZ) and 17 pairs of dizygotic (DZ) twins were investigated. The test of genetic variance revealed a significantly larger within-pair variance of fasting plasma insulin (FPI) and a relative insulin resistance (RIR) in the DZ twins, in comparison with the MZ twins. Both FPI and RIR had a higher intraclass correlation coefficient in the MZ twins than in the DZ twins; the corresponding heritability estimates were 0.54 for FPI and 0.66 for RIR. Adjusting for age, gender, and body mass index did not affect heritability estimates for either FPI or RIR. Our data indicate that genetic factors are important determinants of insulinemia in normal subjects, independent of body mass index.

KEY WORDS: Insulin, insulin resistance, genetic, twins, blood pressure.
(amplified fragment length polymorphism [AMPFLP] and short tandem repeats [STR]). Any discordance in any genetic system was sufficient to classify the twins as dizygotic. Monozygotic and dizygotic twins were comparable for age, body mass index, and ambulatory blood pressure (Table 1). The study was approved by the ethics committee of the Faculty of Medicine, and all subjects gave their informed consent.

Fasting plasma insulin (FPI) was measured by immunossay (Abbott IMX, Abbott Diagnostika, Wiesbaden-Delkenheim, Germany). The relative insulin resistance (RIR) was assessed from the fasting insulin and glucose concentrations by the formula: 

$$RIR = \frac{FPI}{(22.5 \times e^{-0.48 \times glucose})}$$

Statistical Analysis The analysis of the twin data was performed as described by Christian. First, equality of means and total variances of the twin types were tested for each variable. Since the means and total variances were not associated with the twin type, the genetic variance could be tested by the F ratio of the within-mean squares of dizygotic and monozygotic twins. In each group of twins and for each variable, the mean of all subjects, the among-pair variance and the within-pair variance are reported. In addition, the intraclass correlation coefficients were calculated for MZ and DZ pairs. The heritability estimate (G) was:

$$G = \frac{2(r_{MZ} - r_{DZ})}{r_{MZ} + r_{DZ}}$$

where $$r_{MZ}$$ and $$r_{DZ}$$ are intraclass correlation coefficients for MZ and DZ twins respectively. The formula for estimating the proportion of variance attributable to common environment (C) was:

$$C = 2r_{DZ} - r_{MZ}$$

The residual proportion of the variance was estimated by $$S = 1 - G - C$$. Multiple regression analysis was performed to control for age, gender, and body mass index; residual scores were then submitted to genetic analysis.

RESULTS

For the fasting plasma insulin MZ and DZ twins were comparable for the mean values and among-pair variances (Table 2). The test of genetic variance revealed a significantly larger within-pair variance for the DZ twins in comparison to the MZ twins. The test of genetic variance was significant also for the relative insulin resistance (Table 2). The within-pair variance in DZ was over four times larger than for MZ twins. After adjustment for the body mass index, gender, and age, the test of genetic variance for both FPI and RIR remained significant (Table 2).

Table 3 shows intraclass coefficients for MZ and DZ twins. Both FPI and RIR had a higher intraclass correlation coefficient in the MZ twins than in the DZ twins; the corresponding heritability estimates were 0.54 for FPI and 0.66 for RIR. Adjusting for age, gender, and body mass index did not affect heritability estimates for either FPI or RIR (Table 3). The within-pair difference in RIR was not related to within-pair differences in 24-h SBP or DBP ($r = -0.28$ for SBP and $r = 0.36$ for DBP in MZ twins; $r = 0.09$ for DBP in DZ twins).

DISCUSSION

It has been proposed that insulin resistance, acting directly or indirectly through hyperinsulinemia, amplifies the genetic predisposition for hypertension and diabetes, leading to a clinically manifested pheno-

### Table 1. Clinical Characteristics of the Studied Subjects

<table>
<thead>
<tr>
<th></th>
<th>MZ Twins</th>
<th>DZ Twins</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.4 (4.7)</td>
<td>21.5 (5.7)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.5 (2.6)</td>
<td>21.4 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>24-h SBP (mm Hg)</td>
<td>117.1 (10.5)</td>
<td>114.4 (7.2)</td>
<td>NS</td>
</tr>
<tr>
<td>24-h DBP (mm Hg)</td>
<td>68.9 (5.1)</td>
<td>66.3 (6.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values presented as means (SD). MZ, monozygotic; DZ, dizygotic.

### Table 2. Mean Values and Mean Squares of Fasting Plasma Insulin and Relative Insulin Resistance

<table>
<thead>
<tr>
<th></th>
<th>Mean Squares</th>
<th>Test of Genetic Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Among-Pair</td>
</tr>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPI (mU/L)</td>
<td>7.8</td>
<td>8.3</td>
</tr>
<tr>
<td>RIR</td>
<td>1.70</td>
<td>1.73</td>
</tr>
<tr>
<td>Adjusted for age, gender, and body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPI (mU/L)</td>
<td>7.9</td>
<td>8.6</td>
</tr>
<tr>
<td>RIR</td>
<td>1.73</td>
<td>1.75</td>
</tr>
</tbody>
</table>

MZ, monozygotic; DZ, dizygotic; FPI, fasting plasma insulin; RIR, relative insulin resistance.
### Table 3. Intraclass Correlation Coefficients for Fasting Plasma Insulin and Relative Insulin Resistance

<table>
<thead>
<tr>
<th></th>
<th>MZ Intraclass r</th>
<th>DZ Intraclass r</th>
<th>Heteritability</th>
<th>Common Environment</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPI</td>
<td>0.85</td>
<td>0.58</td>
<td>0.54</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td>RIR</td>
<td>0.54</td>
<td>0.51</td>
<td>0.66</td>
<td>0.18</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted for age, gender, and body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPI</td>
<td>0.85</td>
<td>0.59</td>
<td>0.52</td>
<td>0.33</td>
<td>0.15</td>
</tr>
<tr>
<td>RIR</td>
<td>0.81</td>
<td>0.44</td>
<td>0.74</td>
<td>0.07</td>
<td>0.19</td>
</tr>
</tbody>
</table>

MZ, monozygotic; DZ, dizygotic; FPI, fasting plasma insulin; RIR, relative insulin resistance.

The link between insulin resistance and blood pressure is typically demonstrable in lean subjects, either normotensive or hypertensive, is heavily confounded by the presence of overweight, and shows an element of familial aggregation. Insulinemia and insulin resistance are more closely correlated with ambulatory blood pressure than with the commonly used office blood pressure. Several mechanisms have been proposed to explain the hypertensive effect of insulin, including the influence on renal sodium absorption, cation transport, proliferation of vascular smooth muscle cells, and the effects on the sympathetic nervous system. Ethnic differences, along with the longitudinal observations in normotensive individuals, prehypertensives, and in offspring of hypertensives, all point to an inherent link between insulin and blood pressure.

This study was undertaken to look for evidence that genetic factors influence insulinemia in normotensive subjects. We used two heritability estimates; one was based on the analysis of variance model, and the other on monozygotic and dizygotic intraclass correlations. The estimates of heritability by the two methods were in close agreement. Our data indicate that genetic factors are important determinants of the fasting plasma insulin and relative insulin resistance in normal subjects. The heritability estimates for both plasma insulin level and relative insulin resistance remained significant after correction for body mass index, suggesting that some factors besides body size must underlie intrapair aggregation of insulinemia in healthy twins. These results support the concept of genetic origin of insulin resistance.

It is well known that, in many individuals, insulin resistance and hyperinsulinemia do not cause hypertension. In the present study, we have not observed any significant correlation between within-pair differences of insulin and within-pair differences of ambulatory blood pressure. These observations suggest that, although genetic factors determine both diurnal blood pressure profile and insulinemia, those mechanisms are not necessarily interlinked, and the association between insulinemia and blood pressure is not a straightforward one.

This study was conducted in young normotensive subjects, and the relevance of these findings to hypertension could not be examined. One limitation of this study is that we measured only fasting insulin levels, which are merely a crude measure of insulin resistance. However, since hypertension and other cardiovascular complications believed to be associated with hypertension and hyperinsulinemia are the result of chronic changes, it is likely that estimates of insulin resistance reflecting these long-term changes are most beneficial in understanding these diseases. A measure of insulin resistance that probably reflects long-term adaptations is the fasting plasma insulin concentration. Furthermore, the fasting insulin concentration and relative insulin resistance index in young normal subjects significantly correlate with other estimates of insulin resistance.

In summary, genetic factors are important determinants of insulinemia in normotensive subjects. The genetic variance for insulinemia remains significant after adjustment for body mass index. Our results support the concept of genetic origin of insulin resistance.

**REFERENCES**

5. Pollare T, Lithell H, Bernc C: Insulin resistance is a


