Body mass, plasma leptin, glucose, insulin and C-peptide in offspring of diabetic and non-diabetic mothers

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Abstract

Objective: The aim was to investigate the relationship between body mass index (BMI), plasma leptin, glucose, insulin and C-peptide levels in the offspring of diabetic mothers (DM) and non-diabetic healthy mothers (HM).

Design: Seventy-two offspring (37 girls and 35 boys, age 4–20 years) of DM were investigated in a prospective study. Those 14–16 years old (Tanner stage II–IV) were compared with age-matched offspring of HM (33 girls and 33 boys).

Results: BMI strongly correlated with plasma leptin concentration in the offspring of both DM and HM children. There were higher BMI and plasma leptin and glucose levels in DM than in HM children. There was no difference in plasma insulin or C-peptide levels between HM and age-matched DM children. There was a highly significant positive correlation between plasma leptin and C-peptide in boys of DM.

Conclusions: The higher plasma leptin found in the offspring of DM reflects their higher BMI. A moderately high but still normal glycemia might be a preclinical sign of insulin resistance or other disturbance of glucoregulation.

Introduction

The offspring of diabetic mothers (DM) have a higher risk of complications in the neonatal period and at a later age (1, 2). The occurrence rate of postnatal disorders is strongly correlated with the level of diabetes care during pregnancy (3–5) and genetic background (6). The offspring of DM have a higher incidence of impaired glucose tolerance and elevated body mass index (BMI) and blood pressure (7–9) at the age of 20 years compared with the offspring of non-diabetic healthy mothers (HM). We have been following longitudinally the children of HM (10–12) and DM (13) in prospective studies. It was the aim of our present study to compare these two groups to evaluate the effect of maternal diabetes mellitus on the development of obesity, and plasma concentrations of leptin, glucose, insulin and C-peptide.

Subjects and methods

The study was approved by the ethical committee of the Medical Faculty, Comenius University in Bratislava. Informed consent was obtained from the children and their parents.

Subjects

Children of DM Mothers with type 1 and type 2 diabetes mellitus and gestational diabetes mellitus (GDM) were prospectively included in our study during gestation and their offspring regularly evaluated from birth (13). The present study comprises 72 offspring (37 girls and 35 boys), age 4–20 years (Table 1). For comparison with the offspring of HM, only age-matched DM children (14–16 years old, Tanner stage II–IV) were used (13 girls and 8 boys).

Children of HM A group of healthy children followed longitudinally from birth to study prospectively late effects of infant nutrition and age of weaning (11) served as the control group in this study. At the time of examination they were 14–16 years old (33 girls and 33 boys, Tanner stage II–IV).

BMI was calculated as body mass (kg)/height$^2$ (m).

Blood analysis

Blood was taken after overnight fasting at 0800 h. Plasma glucose was measured by the glucose oxidase method. Plasma C-peptide (IRMA; Immunotech, Prague,
Czech Republic, intra-assay coefficient of variation (CV) at various concentrations 4.1–5.1%, interassay CV 4.6–7.5%, sensitivity 0.02 ng/ml, insulin (RIA-SAx-Insulin 100, Saxoniae GMH, Germany, 2.8–3.3%, 3.6–4.8%, 4 pmol/l) and leptin (Linco Research Inc., St Louis, MO, USA, 3.4–8.3%, 3.0–6.2%, 0.5 ng/ml) were determined by commercial RIAs for human hormones.

Statistical analysis

Results are given as the means ± s.e. Comparison between groups was performed with unpaired Student’s t-test and by ANOVA followed by the Bonferroni test. Simple correlation analyses were performed comparing age, BMI, glucose and hormonal data. P < 0.05 was considered statistically significant.

Results

BMI

BMI increased with age in girls of DM; the correlation in boys did not attain statistical significance (Fig. 1). Overweight and obesity were most common at the age of 8–15 years (Fig. 1). Analysis of the effect of the type of maternal diabetes (Fig. 2, upper panel) showed a higher BMI in daughters of mothers with non-insulin-dependent diabetes (NIDDM) as compared with GDM. A similar tendency in boys did not reach statistical significance.

At puberty, the BMI in the offspring of HM and DM was significantly higher in DM girls than in age-matched HM girls (Fig. 3, upper panel). The difference in boys was at the borderline of statistical significance.

Leptin

Higher leptin levels in pubertal girls than in boys were found in HM offspring (Fig. 3, lower panel). A gender difference was not seen in the offspring of DM due to an elevated plasma leptin in boys which was significantly higher than that in HM boys. BMI strongly correlated with plasma leptin concentration in the offspring of both DM and HM (Fig. 4). The type of maternal diabetes (Fig. 2, lower panel) did not significantly affect plasma leptin in the offspring.

Glycemia, insulin and C-peptide

At the age 14–16 years, plasma glucose was higher in DM than in HM offspring (in girls 4.77 ± 0.15 vs 4.28 ± 0.10 mmol/l, n = 13 and 31 respectively, P < 0.02; in boys 4.76 ± 0.11 vs 4.24 ± 0.07 mmol/l, n = 8 and 33 respectively, P < 0.03). There was no difference in insulin and C-peptide plasma levels despite a higher plasma glucose in the DM group where all three parameters were available (Table 2).
Correlations

The correlation between leptin and insulin plasma levels was higher in girls than in boys (Table 3, all children are included). A highly significant positive correlation between plasma leptin and C-peptide was found in boys of DM in contrast to the other groups, where the correlation was not significant (Table 3).

Discussion

Previously we reported some changes (13) in the lipoprotein spectrum in this DM group, including markedly higher 'sinking pre-beta' lipoprotein and higher plasma thyroxine at 5 years of age. In the present study we have concentrated on the development of body mass, plasma leptin and glucoregulation parameters. The higher BMI in DM compared with age-matched HM offspring indicates a higher incidence of overweight and obesity in the former. As shown in Fig. 1, obesity was present at the age of 8–15 years. This might be a long-term consequence of maternal diabetes appearing at this particular age. On the other hand the absence of increased BMI in younger children might be due to improving care for DM. Continuation of our prospective study until the younger groups reach this age should help discriminate between these possibilities.

A disturbed BMI–leptin relationship could play a role in the higher incidence of obesity in the offspring of DM. Fasting plasma leptin strongly correlated with the BMI in both the DM and HM groups, thus excluding an impaired association between the two parameters. As expected (15), higher concentrations of plasma leptin were found in girls than in boys in the offspring of HM. This gender difference was not confirmed, however, in the offspring of DM. Plasma leptin in boys of DM was high enough to attain the level seen in non-obese girls. Although the high plasma leptin level in the DM offspring seems to reflect their higher BMI, the parameters of glucoregulation suggest the situation might be more complicated.

The offspring of DM had higher average glycemia than the control group of children of HM. Plasma insulin levels were similar in the HM and DM groups, suggesting insulin resistance in the latter. Since C-peptide levels did not unequivocally support this explanation (no evidence of increased insulin secretion in DM), an alternative explanation — different sensitivity of the insulin response to glucose stimulation — should also be considered. Leptin has an antidiabetic effect in rodents (16–18) achieved through both an insulin-independent and an insulin-sensitizing mechanism. If confirmed in humans, increased plasma leptin in the offspring of DM could also represent a compensatory mechanism in a preclinical disturbance of glucose metabolism. This possibility is supported by the analysis of a healthy population which revealed a negative correlation between plasma leptin and measures of insulin sensitivity (19) and the report that an insulin-resistant phenotype is associated with high serum leptin levels in the offspring of patients with NIDDM (20). The last authors (21) found defective insulin secretion in adult non-diabetic offspring of patients with type 2 diabetes mellitus and believe that latent autoimmune diabetes mellitus is a familial disease involving gene defects leading to a progressive beta-cell destruction.
Figure 3 BMI (upper panel) and plasma leptin (lower panel) of the offspring of HM and age-matched children of DM. Means ± s.e., n is given at the bottom.
Both plasma leptin and insulin concentrations increase with food intake. Moreover insulin increases expression of the gene for leptin biosynthesis (for review see 22). Although an inhibitory effect of leptin on insulin secretion in obese mice (23) and the insulin secretory response of human islets to high glucose (22) have been described, correlation analysis of our groups indicates that in vivo a positive interaction prevails. As recently reviewed (24), the interaction between leptin and insulin secretion is complex and its many aspects remain to be clarified. The higher correlation coefficient in girls has been already described (19, 25) and is of interest. It might result from the higher plasma leptin in girls, which makes the relationship more pronounced.

Insulin-dependent diabetes (IDDM) mothers, although clinically well controlled, gave birth to newborns with significantly higher levels of leptin and insulin (26). Moderate increases in circulating leptin were recently reported to decrease considerably the expression of the gene for its synthesis in adipose tissue (14). Whether such a mechanism could affect later regulation of these hormones remains to be explored.

In conclusion higher glycemia, BMI and plasma leptin were found in the offspring of DM at the age of 14–16 years compared with an age-matched control group. Their plasma leptin was closely related to BMI.

Table 2 Selected parameters of glucoregulation in the offspring of diabetic mothers.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Type</th>
<th>n</th>
<th>Glucose (mmol/l)</th>
<th>Insulin (pmol/l)</th>
<th>C-peptide (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>DM</td>
<td>5</td>
<td>4.79±0.16**</td>
<td>78.0±17.1</td>
<td>0.86±0.33</td>
</tr>
<tr>
<td></td>
<td>HM</td>
<td>32</td>
<td>4.24±0.07</td>
<td>74.7±6.8</td>
<td>1.18±0.10</td>
</tr>
<tr>
<td>Girls</td>
<td>DM</td>
<td>5</td>
<td>4.87±0.18*</td>
<td>118±29.9</td>
<td>1.26±0.12</td>
</tr>
<tr>
<td></td>
<td>HM</td>
<td>25</td>
<td>4.29±0.10</td>
<td>83.2±7.9</td>
<td>1.26±0.12</td>
</tr>
</tbody>
</table>

**P < 0.01 against HM boys; *P < 0.03 against HM girls.
Table 3  Intragroup correlation of certain parameters.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group</th>
<th>Leptin–C-peptide</th>
<th>Leptin–insulin</th>
<th>Leptin–glycemia</th>
<th>C-peptide–insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>DM</td>
<td>0.14</td>
<td>0.57***</td>
<td>−0.10</td>
<td>0.46**</td>
</tr>
<tr>
<td></td>
<td>HM</td>
<td>0.31</td>
<td>0.67***</td>
<td>0.02</td>
<td>0.67***</td>
</tr>
<tr>
<td>Boys</td>
<td>DM</td>
<td>0.72***</td>
<td>0.37</td>
<td>−0.04</td>
<td>0.40**</td>
</tr>
<tr>
<td></td>
<td>HM</td>
<td>0.17</td>
<td>0.30</td>
<td>0.17</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01; ***P < 0.001.

Acknowledgements

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References