Original Article: Metabolism

Combined association of maternal and paternal family history of diabetes with plasma leptin and adiponectin in overweight Hispanic children


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Accepted 12 June 2008

Abstract

Aims To investigate the importance of a maternal and paternal family history of Type 2 diabetes and their combined association with plasma leptin and adiponectin levels in overweight Latino children with a family history of Type 2 diabetes (T2DM);

Methods This cross-sectional study investigated the combined association of a maternal and paternal family history of T2DM with leptin and adiponectin in 175 overweight Latino children (age 11.1 ± 1.7 years). All subjects had a family history of T2DM. Plasma adiponectin and leptin levels, body fat measured by dual-energy X-ray absorptiometry, Tanner stage, age and insulin sensitivity were assessed.

Results After adjustment for age, gestational diabetes, insulin sensitivity and body fat, a combined maternal and paternal family history of T2DM was associated with higher leptin concentrations (P=0.004) compared with a maternal or paternal family history alone. This association was most pronounced at Tanner stage 1 (P for interaction family history × tanner stage = 0.022). The presence of a combined maternal and paternal family history of T2DM accounted for 4% (P = 0.003) of the variation in leptin concentrations. No such combined association was observed for adiponectin levels.

Conclusions Maternal and paternal family history of T2DM may have an additive impact on leptin, but not on adiponectin levels independent of adiposity and insulin sensitivity in overweight Latino children. This may contribute to a further clinically relevant deterioration of metabolic health in this population.


Keywords adiponectin, leptin, diabetes

Abbreviations AIR, acute insulin response; CV, coefficient of variation; DI, disposition index; FSIVGTT, frequently sampled intravenous glucose tolerance test; GCRC, General Clinical Research Center; SI, insulin sensitivity; T2DM, Type 2 diabetes; USC, University of Southern California

Introduction

Adipose tissue has characteristics similar to endocrine organs. It secretes hormones affecting glucose metabolism and insulin sensitivity such as leptin and adiponectin [1]. Leptin acts to reduce food intake and increase energy expenditure [2]. In adults, levels of circulating leptin are directly proportional to total fat mass [3] and are negatively associated with insulin sensitivity [4,5]. Conversely, adiponectin decreases insulin resistance by stimulating glucose uptake and fatty acid oxidation in skeletal muscle [6,7]. We recently showed that leptin and adiponectin were independently associated with insulin sensitivity in overweight Hispanic adolescents [8].

Leptin levels increase before puberty and trigger the onset of puberty in humans [9]. In children approaching puberty, leptin
levels are closely related to luteinizing hormone and follicle-stimulating hormone, and leptin is therefore an important facilitator in the early phases of human puberty [9,10].

In adults, a family history of Type 2 diabetes (T2DM) is associated with higher concentrations of circulating leptin [11–13] and lower concentrations of circulating adiponectin [14–18]. In most studies, this association was independent of adiposity. In offspring of parents with T2DM, future risk of diabetes is higher in those with maternal history compared with those with paternal history [19]. However, to our knowledge no information is currently available on the association of maternal vs. parental family history of T2DM with leptin and adiponectin levels, nor has any study addressed this question in an adolescent population.

Therefore, the aim of the present study was to investigate the importance of a maternal and paternal family history of T2DM and their combined association with plasma leptin and adiponectin levels in overweight Latino children with a family history of T2DM. The hypothesis was that children with both a maternal and paternal family history of T2DM have higher leptin and lower adiponectin levels than children with a family history of T2DM in one parent’s family, either maternal or paternal. We also hypothesized that a maternal family history of T2DM may be more important than a paternal family history.

Participants and methods

Study design

For the present study, a cross-sectional subgroup of 175 subjects was used based on the availability of leptin and adiponectin data measured at entry into the Study of Latino Adolescents at Risk (SOLAR) Diabetes Project. Detailed study descriptions have been published previously [20]. Participants were recruited from the East and Central Los Angeles County. Participants were included with an age of 8–13 years, a body mass index ≥85th percentile for age and sex according to the Centers for Disease Control and Prevention, a Latino ancestry (all four grandparents Latino by parental self-report); and absence of diabetes, determined by an oral glucose tolerance test using a dose of 1.75 g of glucose per kg body weight (Hologic QDR 4500W; Hologic, Bedford, MA, USA). Central fat distribution was measured directly by magnetic resonance imaging at the Los Angeles County/USC Imaging Science Center. A single-slice axial TR 400/16 view of the abdomen at the level of the umbilicus was analysed for cross-sectional area of adipose tissue using a General Electric 1.5 Sigma LX-Echospeed device with a General Electric 1.5-T magnet (Waukesha, WI, USA).

After an overnight fast, the FSIVGTT was performed to determine insulin dynamics. A topical anaesthetic (EMLA cream; AstraZeneca, Wilmington, DE, USA) was applied to the antecubital area of both arms and an hour later a flexible intravenous catheter was inserted into both arms. Two fasting blood samples, at −15 and −5 min, were pooled for determination of basal glucose and insulin values. At time zero, glucose (25% dextrose; 0.3 g/kg of body weight) was administered intravenously. Blood samples were then collected at the following time points: 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, 120 and 180 min [21,22]. Insulin (0.02 U/kg of body weight; Humulin R—regular unmodified insulin; Eli Lilly and Co., Indianapolis, IN, USA) was injected intravenously at 20 min. Plasma was analysed for glucose and insulin, and values were entered into the Mimmod Millennium 2003 computer program (version 5.16; Richard N. Bergman, University of Southern California, Los Angeles, CA, USA) for determination of insulin sensitivity (SI), the acute insulin response (AIR = insulin area under the curve above basal for the first 10 min of the FSIVGTT) and the disposition index (DI = product of AIR and SI as a measure of pancreatic β-cell function) [22]. Blood samples from the FSIVGTT were centrifuged immediately to obtain plasma, and aliquots were frozen at −70°C until assayed. Glucose was assayed in duplicate on a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument, Yellow Springs, OH, USA) using the glucose oxidase method. Insulin was assayed in duplicate using a specific human insulin enzyme-linked immunosorbent assay kit from Linco Research (St Charles, MO, USA). Plasma adiponectin was measured using radioimmunoassay kits (Linco Research) with an intra-assay coefficient of variation (CV) of 3.9% and an interassay CV of 8.5%. For plasma leptin, radioimmunoassay kits were used (Linco Research) with an intra-assay CV of 3.9% and an interassay CV of 8.5%.

Statistical analysis

All data are reported as mean ± SE. Statistical analyses were performed using spss 11 (SPSS Inc., Chicago, IL, USA). Baseline characteristics of boys and girls were compared using Student’s

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r-test or \( \chi^2 \) test. Variables not normally distributed (adiponectin, leptin, SI, DI, AIR, total fat mass and lean body mass) were log transformed before performing statistical analyses.

ANOVA models were used to estimate the cumulative association of family history of T2DM on plasma adiponectin and leptin levels as dependent variables. Family history of T2DM was modelled in two ways: first, a model was encoded including (i) one parent’s family, either maternal or paternal family history, or (ii) both, maternal and paternal family history. Next, to test whether maternal and paternal family history of T2DM had differential associations with plasma adiponectin and leptin, another model was performed encoding (i) maternal family history, (ii) paternal family history, and (iii) both maternal and paternal family history. Maternal family history of T2DM is defined as the presence of T2DM in a member of the mother’s family (siblings and parents of the mother, or the mother herself). Consistently, paternal family history of T2DM is defined as presence of T2DM in the father’s family (siblings and parents of the father, or the father himself). The same models were performed for maternal or paternal diabetes without considering other family members. All models were adjusted for gender, Tanner stage, gestational diabetes of the mother while carrying the participant, age, and percentage body fat and an interaction term for Tanner stage and gender. Analyses were repeated with and without inclusion of family history. \( R^2 \) change is given for the inclusion of family history. For leptin, models were performed stratified by gender and adjusted as mentioned above. In figures, estimated geometrical means are given stratified by gender and Tanner stage for gestational diabetes, age, and percentage body fat.

**Results**

General characteristics of the study population are shown in Table 1. Due to the inclusion criteria, all subjects had a family history of T2DM. A maternal family history was reported by 47%, a paternal family history by 24% and a combination of maternal and paternal family history of T2DM accounted for 4% (P = 0.003). A maternal family history or the father himself). The same models were performed for maternal or paternal diabetes without considering other family members. All models were adjusted for gender, Tanner stage, gestational diabetes of the mother while carrying the participant, age, and percentage body fat and an interaction term for Tanner stage and gender. Analyses were repeated with and without inclusion of family history. \( R^2 \) change is given for the inclusion of family history. For leptin, models were performed stratified by gender and adjusted as mentioned above. In figures, estimated geometrical means are given stratified by gender and Tanner stage for gestational diabetes, age, and percentage body fat.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Boys (n = 101)</th>
<th>Girls (n = 74)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.2 ± 0.2</td>
<td>11.1 ± 0.2</td>
<td>0.704</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.2 ± 0.5</td>
<td>28.7 ± 0.6</td>
<td>0.435</td>
</tr>
<tr>
<td>Body mass index percentile</td>
<td>97.1 ± 0.3</td>
<td>97.4 ± 0.3</td>
<td>0.449</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>37.6 ± 0.7</td>
<td>40.0 ± 0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Subcutaneous fat (cm²)</td>
<td>330 ± 15</td>
<td>357 ± 16</td>
<td>0.239</td>
</tr>
<tr>
<td>Visceral fat (cm²)</td>
<td>47 ± 2</td>
<td>50 ± 2</td>
<td>0.457</td>
</tr>
<tr>
<td>SI ((10^{-4})min/mlU)‡</td>
<td>2.37 ± 0.14</td>
<td>1.88 ± 0.15</td>
<td>0.104</td>
</tr>
<tr>
<td>Plasma leptin (µg/l)</td>
<td>23.2 ± 1.1</td>
<td>31.1 ± 1.5</td>
<td>0.533</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/l)</td>
<td>10.2 ± 0.3</td>
<td>10.0 ± 0.4</td>
<td>0.220</td>
</tr>
<tr>
<td>Gestational diabetes (%)</td>
<td>19</td>
<td>23</td>
<td>0.579</td>
</tr>
<tr>
<td>Family history of Type 2 diabetes</td>
<td>0.375</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal only (%)</td>
<td>43</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Paternal only (%)</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Both (%)</td>
<td>33</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

*Data are mean ± SE, and %.
†Students t-tests and \( \chi^2 \) test used to compare differences between male and female patients.
‡SI, insulin sensitivity.

Neither plasma leptin nor plasma adiponectin concentrations were associated with the occurrence of gestational diabetes.

**Leptin**

Plasma leptin during puberty increased with age in girls but not in boys (age \( \times \) gender interaction, \( P = 0.005 \), Fig. 1), but no significant interaction for family history \( \times \) gender was observed.

In analyses adjusted for age, gender, gestational diabetes and SI, a combined maternal and paternal family history of T2DM was associated with higher plasma leptin (\( P = 0.044 \)) compared with a history of T2DM in only one parent’s family. After additional adjustment for body fat, the association between a combined maternal and paternal family history of T2DM and plasma leptin was limited to Tanner stage 1 (\( P = 0.004 \), P for interaction family history \( \times \) tanner stage = 0.022; Fig. 2). No significant differences were observed between maternal only and paternal only family history of T2DM. The combination of maternal and paternal family history of T2DM accounted for 4% (\( P = 0.003 \)) of the variation in leptin concentrations. The association between leptin concentrations and combined family history of T2DM was not affected by additional adjustment for visceral and subcutaneous fat. If only the history of T2DM for first-degree relatives (mother and father together) was included in the model, no association with combined maternal and paternal family history was observed, suggesting that general family history of T2DM is important for the strength of this association compared with family history in first-degree relatives alone.

**Adiponectin**

Adiponectin decreased with age in boys and girls (\( r = -0.231, P = 0.002 \), Fig. 1). Maternal and paternal family history of T2DM
T2DM did not have a significant association with plasma adiponectin levels (Fig. 3). Combined maternal and paternal history of T2DM for first-degree relatives was also not associated with plasma adiponectin levels. No gender or Tanner stage interactions were observed.

**Discussion**

The major finding of the present study is that in overweight Hispanic children a combined maternal and paternal family history of T2DM is associated with higher leptin levels compared with a family history of diabetes in the maternal or paternal side alone. This association was independent of adiposity. No such association was observed for plasma adiponectin levels.

**FIGURE 1** Serum leptin and adiponectin by age in overweight Hispanic boys (n = 101) and girls (n = 74).

**FIGURE 2** Plasma leptin in overweight Hispanic children (n = 175) with maternal (mat) or paternal (pat) family history (FH) of Type 2 diabetes. Data are estimate marginal means ± SE adjusted for age, body fat, gestational diabetes and insulin sensitivity. The interaction term for type of family history × Tanner stage, P < 0.022.

**FIGURE 3** Plasma adiponectin in overweight Hispanic children (n = 175) with maternal (mat) or paternal (pat) family history (FH) of Type 2 diabetes. Data are estimate marginal means ± SE adjusted for age, body fat, gestational diabetes and insulin sensitivity. The interaction term for type of family history × Tanner stage, P < 0.427.
Several studies have shown that a family history of T2DM is associated with higher circulating leptin levels [11–13]. Recent data from the Quebec family study suggest that genetic variation at the fat mass and obesity associated (FTO) locus contributes to the aetiology of obesity, insulin resistance and increased plasma leptin levels [23]. Several polymorphisms in the leptin gene affect the receptor binding activity of the protein [24] and secretion by adipose tissue. For example, a polymorphism in the promoter region of the human leptin gene has been associated with T2DM or impaired glucose metabolism [25]. This polymorphism increases leptin protein expression and secretion [26]. Another polymorphism, located in an exonic region of the leptin gene, has been associated with glucose homeostasis in response to exercise [27] and circulating leptin levels [28]. However, the association between the polymorphism and leptin levels was not consistent in different studies [29,30]. The association with a combined maternal and paternal family history of T2DM supports the hypothesis of a hereditary link between leptin and diabetes risk.

Other mechanisms explaining the association with a family history of diabetes could be related to epigenetic effects that are associated with both family history of T2DM and leptin [31]. Fetal programming by maternal diabetes is unlikely to be the cause of the association, because all results were adjusted for gestational diabetes.

Hormonal changes during puberty result in gender-specific differences in levels of leptin levels; oestrogen is known to stimulate and testosterone to suppress leptin secretion [32]. Jansson et al. have shown that leptin levels were only higher in male subjects with a family history of diabetes, but not in female subjects, suggesting a pronounced gender difference in the association between family history of diabetes and leptin levels [11]. In our study, however, no significant interaction was observed between gender and family history of T2DM, suggesting that gender differences in leptin levels did not affect the association between family history and leptin.

In the present study, a combined maternal and paternal history of T2DM was associated with leptin independent of the adjustment for adiposity. In analyses additionally adjusted for adiposity, the association was stronger in participants with a maternal family history of T2DM, female subjects, suggesting a pronounced gender difference in leptin that may occur during puberty. We have recently shown in a longitudinal study of the same cohort that the association between a maternal family history of T2DM and insulin dynamics becomes more pronounced during growth [33]. Longitudinal studies on the association between family history and leptin and adiponectin levels during growth will be necessary to demonstrate whether this is similar for leptin and adiponectin.

In conclusion, a combination of a maternal and paternal family history of T2DM is associated with higher leptin levels independent of adiposity and SI in overweight Latino children compared with a maternal or paternal family history alone. No such association was observed for adiponectin.

Competing interests
Nothing to declare.

Acknowledgement
This study was supported by the NIH Grant R01 DK 59211, the General Clinic Research Center (GCRC) and the National Center for Research Resources Grant M01 RR 00433 as well as an American Diabetes Association, Mentor-Based Postdoctoral Fellowship 2005 (awarded to M.I.G.). C.K. was supported by a training grant of the USC Center for Transdisciplinary Research on Energetics (NCI Grant 1U54CA116848-01), L.A.K. and J.N.D. by American Diabetes Association (Mentor-Based Postdoctoral Fellowship) grant under the direction of M.I.G., C.K.R. by a National Institute on Aging Training Award (5 T32 AG000093-24), C.M.T-C. was supported by a minority supplement grant under the direction of M.I.G. (3R01DK59211–06S1). We are grateful to the project managers, Quintilia Avila and Christina Ayala, and to the nurses and nutrition staff at the USC-GCRC.

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