Diabetes in Hong Kong Chinese

Evidence for familial clustering and parental effects

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OBJECTIVE — To investigate transmission patterns of diabetes and their relationships with clinical characteristics in Hong Kong Chinese patients with late-onset (age ≥35 years) type 2 diabetes.

RESEARCH DESIGN AND METHODS — This study involved 2,310 patients consecutively selected from a hospital clinic–based diabetes registry. These patients all reported the diabetes status of their parents as well as siblings.

RESULTS — Approximately 36% of the 2,310 patients reported at least 1 affected parent or sibling (25 and 21% reported at least 1 diabetic parent and sibling, respectively). These patients, irrespective of their sex, were more likely to have a diabetic mother than a diabetic father (17 vs. 13% of the male patients and 18 vs. 9% of the female patients, P < 0.01). The male patients were more likely than the female patients to have a diabetic father (13 vs. 9%, P < 0.01). The female patients with a diabetic mother were found to have higher levels of plasma total cholesterol compared with the female patients with a diabetic father in multiple comparisons with adjustment for significance (5.56 ± 1.30 vs. 5.09 ± 0.95 mmol/l, P < 0.05). In 2-group comparisons, there was also evidence that the male patients with a diabetic father had higher BMI values than the male patients with a diabetic mother (25.9 ± 3.5 vs. 25.0 ± 3.5 kg/m², P < 0.05).

CONCLUSIONS — We found familial clustering of diabetes in the Hong Kong Chinese population as well as a significant maternal influence and a male sex–specific paternal effect. We suggest that both maternal and paternal factors may be implicated in the development of type 2 diabetes in the Chinese population.

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The prevalence of type 2 diabetes is increasing at an alarming rate among Chinese (1), and its development is believed to involve the interplay between genetic and environmental factors. It is now known that maturity-onset type 2 diabetes of the young (MODY), a subtype of type 2 diabetes, is an autosomal-dominant monogenic disease caused by a number of MODY genes (2). Specific mutations in the mitochondrial genome have been found to cause maternally inherited diabetes and deafness—another uncommon subtype of type 2 diabetes (3). However, the importance of these clearly identified genetic etiologies in the majority of type 2 diabetes remains unknown. Typical late-onset type 2 diabetes may be transmitted in major gene modes or more complex multigenic patterns (4,5). Moreover, evidence is emerging that patients with type 2 diabetes are more likely to have a diabetic mother than a diabetic father, suggesting that the segregation of the disease may also be affected by a maternal effect (6–8).

In the present study, we examined the segregation patterns of diabetes in 2,310 Hong Kong Chinese patients with late-onset (≥35 years of age at diagnosis) type 2 diabetes. The relationships between various transmission patterns and clinical and metabolic profiles were also examined.

RESEARCH DESIGN AND METHODS — The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Informed consent was obtained from each participant.

Subjects
Since 1995, the diabetes clinic at the Prince of Wales Hospital of Hong Kong Special Administration Region has adopted a structured diabetes care protocol and created a diabetes registry based on a modified Europe DIAB-CARE format (9). This database currently has 3,300 Chinese index patients diagnosed with type 2 diabetes (10). We randomly selected 2,310 late-onset patients who had reported the diabetes status of their parents as well as siblings for the study. These patients had 3.7 ± 2.6 (3.7 ± 2.6) siblings on average (exclusive of the index patients). None of them had classic type 1 diabetes, as indicated by the presence of ketoadipos or heavy ketonuria or a continuous requirement for insulin within year 1 of diagnosis. Late-onset type 1 diabetes was not specifically excluded, but positivity for antibodies against GAD was uncommon in our patients, even in those with early-onset (<35 years of age) type 2 diabetes (11,12). Therefore, latent autoimmune diabetes in adults is unlikely to play a major role in our population. In addition, we interviewed by telephone the parents of 18 randomly selected index patients, of whom 10 reported a diabetic mother, 6 reported a diabetic father, and 2 reported that both parents were affected, and found no false-positive reports.
Familial clustering and parental effects in type 2 diabetes

Table 1—Clinical and biochemical characteristics and the self-reported family history of diabetes of the 2,310 Chinese index patients with late-onset type 2 diabetes

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2,310</td>
<td>962</td>
<td>1,348</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.4 ± 11.2</td>
<td>58.1 ± 11.1</td>
<td>58.7 ± 11.0</td>
</tr>
<tr>
<td>Age of diagnosis (years)</td>
<td>52.1 ± 10.4</td>
<td>52.2 ± 10.4</td>
<td>52.0 ± 10.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 3.6</td>
<td>24.6 ± 3.5</td>
<td>24.8 ± 3.7</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.89 ± 0.07</td>
<td>0.91 ± 0.06</td>
<td>0.87 ± 0.07*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>8.91 ± 3.41</td>
<td>8.95 ± 3.53</td>
<td>8.87 ± 3.32</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>7.70 ± 1.88</td>
<td>7.81 ± 2.00</td>
<td>7.62 ± 1.79</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138 ± 21</td>
<td>136 ± 20</td>
<td>139 ± 22*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 ± 11</td>
<td>80 ± 11</td>
<td>78 ± 11†</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.48 ± 1.21</td>
<td>5.36 ± 1.26</td>
<td>5.56 ± 1.17*</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.25 ± 0.35</td>
<td>1.16 ± 0.33</td>
<td>1.32 ± 0.36*</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.45 ± 0.98</td>
<td>3.40 ± 0.95</td>
<td>3.49 ± 1.00*</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.4 (0.3–9.8)</td>
<td>1.3 (0.3–9.7)</td>
<td>1.4 (0.3–9.8)</td>
</tr>
</tbody>
</table>

Family history of diabetes (%)

- At least 1 affected core family member: 36.0%, 35.3%
- At least 1 affected sibling: 20.8%, 19.9%
- At least 1 affected parent: 24.5%, 23.7%
- With diabetic father: 10.7%, 9.3%
- With diabetic mother*: 17.6%, 17.7%
- With diabetic parents: 3.8%, 3.3%

Data are n, means ± SD, or medians (range). *P < 0.01; †P < 0.05; ‡ both male and female patients were more likely to have a diabetic mother or a diabetic father.

RESULTS—Compared with the male patients, the female patients had lower values of waist-to-hip ratio but higher levels of total, HDL, and LDL cholesterol (Tables 1 and 2). The patients who had at least 1 diabetic parent had younger age at diagnosis compared with the overall index patients (44 ± 8 vs. 52 ± 10 years, P < 0.01).

Approximately 36% of the patients reported at least 1 affected parent or sibling (25 and 21% reported at least 1 affected parent or sibling, respectively) (Table 1). All of our patients, irrespective of their sex, were more likely to have a diabetic mother than a diabetic father (17 vs. 13% of the male patients and 18 vs. 9% of the female patients, P < 0.01). The male patients were also more likely to have a diabetic father than the female patients (13 vs. 9%, P < 0.01) (Table 1). The female patients with a diabetic mother had higher plasma total cholesterol compared with the female patients with a diabetic father (5.56 ± 1.30 vs. 5.09 ± 0.95 mmol/l, P < 0.05; multiple comparisons) (Table 2). In 2 group comparisons, the male patients

Table 2—Clinical and biochemical characteristics of the male and female patients who reported either a paternal or maternal history of diabetes

<table>
<thead>
<tr>
<th>Parental diabetes</th>
<th>Male patients</th>
<th>Female patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paternal</td>
<td>Maternal</td>
</tr>
<tr>
<td>n</td>
<td>81</td>
<td>125</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.1 ± 9.9</td>
<td>51.6 ± 9.4</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>46.2 ± 8.1</td>
<td>45.6 ± 7.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 3.5*</td>
<td>25.0 ± 3.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.91 ± 0.06†</td>
<td>0.89 ± 0.05†</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>8.7 ± 2.9</td>
<td>9.1 ± 3.3</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>7.6 ± 1.7</td>
<td>8.0 ± 1.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134 ± 19</td>
<td>130 ± 19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81 ± 13</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.21 ± 0.88</td>
<td>5.38 ± 1.31</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.09 ± 0.28</td>
<td>1.14 ± 0.27</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.39 ± 0.81</td>
<td>3.38 ± 0.86</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.3 (0.4–7.8)</td>
<td>1.4 (0.4–8.2)</td>
</tr>
</tbody>
</table>

Data are n, means ± SD, or medians (range). The patients in the 4 groups had, on average, 4 siblings. *Compared with the male patients with a diabetic mother using 2-group t test, P = 0.02. Results from multiple comparisons using ANOVA (Dunn’s test, P < 0.05); †compared with the female patients; §compared with the female patients with a diabetic father; ‡ compared with the male patients.

Study design
All patients had fasted for ≥8 h before the first assessment in our clinic. Blood pressure was measured after they remained seated ≥5 min. Body measurements were taken when patients were standing with light clothing and no shoes. Waist circumference was taken as the minimum circumference between the umbilicus and iliac crest, and the hip circumference was taken as the widest circumference around the buttocks. Other clinical data, including the subjects’ family history of diabetes, were also taken. Plasma glucose and HbA₁c were measured using a glucose oxidase method (Diagnostic, Los Angeles, CA) and an automated ion-exchange chromatographic method (Bio-Rad, Hercules, CA; normal range 5.1–6.4%), respectively. Plasma levels of total cholesterol and triglyceride were assayed enzymatically using commercially available reagents (Centrichem Chemistry System; Baker, Allentown, PA). HDL cholesterol was determined after fractional precipitation with dextran sulfate-MgCl₂, and LDL cholesterol was calculated using Friedewald’s equation (13).

Statistical analysis
All data for continuous variables are expressed as means ± SD or medians (range). Students’ t test and Mann-Whitney U test were used for 2-group comparisons as appropriate. Analysis of variance (ANOVA) (Dunn’s test for adjustment for significance) was used for multiple comparisons. A χ² test was performed for analyzing proportions.
with a diabetic father were found to have higher BMI values than the male patients with a diabetic mother (25.9 ± 3.5 vs. 25.0 ± 3.5 kg/m², P < 0.05).

CONCLUSIONS — We have found evidence for a familial clustering of diabetes and a significant influence of maternal factors in Chinese patients with type 2 diabetes. There was also an association between parental history of diabetes and a younger age at diagnosis. All of these results are in keeping with previous findings in other populations (6–8,15). The maternal effect may reflect the impact of the intrauterine environment (16). Genetic defects such as mutations in mitochondrial genome (7) and other genetic factors that may allow low birth weight babies to survive may also be implicated (17). All of these factors may lead to an increased susceptibility to diabetes, especially in the presence of a sedentary and high-fat food–abundant lifestyle.

A paternal effect has been observed in type 1 diabetes (18). Our data (Table 1) and those from Young et al. (6)—that male Asian patients were more likely to have a diabetic father—suggest a male sex–specific paternal effect on the development of type 2 diabetes. Karter et al. (8) recently showed a maternal effect using an integrated database with 15,001 families from Asian, Pacific Islander, Hispanic, African-American, and non-Hispanic white communities. We noted that, among the siblings of the index patients with a diabetic father, the male patients had a higher rate of diabetes than the female patients (18 vs. 16%, P < 0.01). This supports our view of a male sex–specific paternal effect, although the finding was not highlighted in the report by Karter et al. (8). Environmental and societal factors such as male preferential feeding (19,20) may lead to a higher rate of diabetes in male subjects. However, genetic factors may contribute to the observed moderate excess of diabetic father–son pairs.

Our finding that the female patients with a diabetic mother had higher total plasma cholesterol than female patients with a diabetic father (Table 2) supports previously reported associations between a positive maternal history of diabetes and lipid profiles (21–23). However, the nature of this association remains to be clarified. The male patients with a diabetic father were found to have higher BMI than the male patients with a diabetic mother in 2–group comparisons, although this significance disappeared after adjustment for the P value using multiple comparisons (Table 2). Because of sex differences in the regulation of body morphology, sex-specific comparisons of anthropometric measurements have been recommended (24). Hence, our data suggest that more studies are required for a better view on the relationship between a positive paternal history of diabetes and BMI in male subjects.

We noted the concerns of possible bias in studies of this kind (8,25,26). Although we have no relevant data to address the bias issue, the sample size recorded in our diabetes registry was large, and the observed familial clustering of diabetes and maternal effect are in keeping with the findings in other populations (6–8).

In conclusion, we have documented the familial clustering of diabetes as well as a maternal influence and a male sex–specific paternal effect. We suggest that both maternal and paternal factors may be implicated in the development of type 2 diabetes in the Chinese population.

References


