Maternal history of type 2 diabetes is associated with diabetic nephropathy in type 1 diabetic patients


* Corresponding author.
E-mail address: s.hadjadj@chu-poitiers.fr (S. Hadjadj).

Abstract

Aims. – Insulin resistance is a key feature of type 2 diabetes. It is also involved in the development and progression of microvascular complications. We analysed the relationship between parental history of diabetes, insulin resistance and diabetic nephropathy (DN) and assessed the specific maternal and paternal influences of history of type 2 diabetes on DN in type 1 diabetic offspring.

Methods. – We recorded information regarding family history of type 2 diabetes and of cardiovascular disease in 160 consecutive, unrelated type 1 diabetic patients. Insulin resistance was assessed using a validated estimation of the glucose disposal rate (eGDR).

Results. – Type 1 diabetic patients with a maternal history of type 2 diabetes were more likely to be insulin-resistant ($P = 0.043$) and to have renal complications ($P = 0.0041$) than those from the reference group (without parental history of diabetes), while patients with a paternal history were not different from those from the reference group, regarding eGDR and DN. Time to development of abnormal albuminuria was significantly affected by maternal history of type 2 diabetes (log-rank = 12.66; $P = 0.0004$) and by familial history of premature cardiovascular disease (log-rank = 5.48; $P = 0.0234$). In multivariate analysis, a maternal history of type 2 diabetes was independently associated with nephropathy after adjustment for sex, diabetes duration and familial history of premature cardiovascular disease.

Conclusion. – Maternal history of type 2 diabetes is independently associated with DN in type 1 diabetic patients. This might suggest the transmission of a maternal trait related to microvascular complications, raising the hypothesis of imprinted genes predisposing to diabetic renal disease.
1. Introduction

Diabetic nephropathy (DN) is associated with an increased risk for renal failure and also for cardiovascular and all-cause mortality [1]. Insulin resistance is a key feature of types 2 diabetes, whereas type 1 diabetes is characterised by a lack of insulin due to an auto-immune process [2]. Several studies have reported a relationship between insulin resistance and the risk for renal complications in type 1 diabetic patients. This question was first examined 30 years ago with insulin tolerance test [3]. Cross-sectional and familial studies have shown that patients with microalbuminuria were more insulin-resistant than normoalbuminuric patients, using the glucose-clamp method [4,5]. Follow-up studies, some using an estimation of insulin resistance [6], have also shown a relationship between insulin resistance and the development or progression of DN [7–9]. Several large-scale multicentre studies have shown that familial insulin resistance segregated with DN in type 1 diabetic patients [10–12].

DN is a complex trait resulting from interactions between genetic, environmental and lifestyle factors. Recently a large-scale population analysis of familial clustering of DN in type 1 diabetes confirmed that inherited factors are important determinants of renal disease, and also stressed on the deleterious effect of parental type 2 diabetes [13]. However, the specific maternal and paternal influences on nephropathy remain largely unknown.

The aim of our study was therefore to assess a specific aggregation between maternal and paternal history of type 2 diabetes and DN in type 1 diabetic offspring.

2. Patients and methods

2.1. Patients

Unrelated type 1 diabetic patients consecutively seen at the Poitiers Diabetes Centre between January 2002 and January 2003 were included in the study. Ketosis-prone type 1 diabetic patients were diagnosed according to the ADA classification [2] using the following criteria [14]: age at onset lower than 40 years, and definitive insulin therapy within 1 year of diagnosis. Type 2 diabetes was diagnosed according to the ADA classification [2] using the following criteria: age at onset > 40 years, and no need for continuous insulin treatment for more than 2 years. If the diagnosis was unsure, diabetes was classified as undetermined. This study was conducted in agreement with the declaration of Helsinki.

2.2. Methods

Insulin resistance was assessed using an estimated glucose disposal rate (eGDR) developed by Williams et al. [6], modified for HbA1c as recently reported [15]. Office blood pressure (BP) was measured in a sitting position after 5 min rest using a mercury sphygmomanometer.

Type 1 diabetic patients were questioned regarding parental history using a structured questionnaire. The questions were directed to family history of diabetes and cardiovascular disease (hypertension, myocardial infarction, angina pectoris and stroke). Age at occurrence of myocardial infarction or angina pectoris and type of diabetes in parents were recorded. Premature coronary artery disease was defined as myocardial infarction and/or angina pectoris before the age of 55 and 65 years in men and women, respectively.

2.2.1. Classification of microangiopathy

Retinopathy was assessed by a trained ophthalmologist by means of direct ophthalmoscopy after pupillary dilation and fluorescein angiography when required. Retinopathy was staged according to Kohner’s classification [16]: absent, simple, pre-proliferative or proliferative retinopathy.

Nephropathy was assessed after carefully checking patient records to determine the urinary albumin excretion before the prescription of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Nephropathy was staged according to the urinary albumin excretion on sterile samples and creatinine clearance according to the Cockcroft formula [17]: normo-, micro-, and macroalbuminuria were defined as urinary albumin excretion less than 20/30, 20–300/300 mg/l/mg/24 h, and more than 200/300 mg/l/mg/24 h, respectively, in at least two out of the three sterile urine collections. Advanced nephropathy was defined as proteinuria with creatinine clearance < 60 ml/min according to the Cockcroft formula [17].

2.2.2. Biological determinations

The serum creatinine concentration was determined by use of a modified Jaffe method (Roche Diagnostics, Meylan, France). Total cholesterol, HDL cholesterol and triglycerides
were measured in the fasting state (Roche Diagnostics). Urinary albumin was measured by a nephelometric method on sterile urine (verified by the dipstick method).

HPLC was used to measure the concentration on blood samples collected on EDTA (ADAMS HA 8160 - Menarini Diagnostics - Florence - Italy). Normal values range from 4.0 to 6.0%.

2.2.3. Statistical analysis

Data are given as mean ± 1 S.D. or as median (interquartile ranges). Our statistical analyses were comparisons with the reference group—patients with no parental history of type 2 diabetes. Categorical variables were analysed with the chi-square test or with the Fisher’s exact test. Continuous variables were examined with unpaired t-test after log-transformation when required, or with Mann–Whitney tests if data were not normally distributed. Correlation between continuous variables was examined using the non-parametric Spearman test. Comparisons regarding waist circumference or waist to hip ratio were adjusted for sex. Multivariate analysis was performed using logistic regression analysis.

Longitudinal evaluation of the relationship between the development of abnormal albuminuria and familial history of type 2 diabetes, hypertension, cardiovascular disease was performed using Kaplan–Meier method with statistical significance assessed using the log-rank test. Time between diabetes onset and the development of microalbuminuria was considered, since 1989 (date of implementation of urinary albumin determination in our hospital). If DN was present before this date, time to the occurrence of abnormal albuminuria was chosen as the half time to the occurrence of DN. Patients not developing abnormal albuminuria were censored at end of the study.

A two-sided P value of 0.05 was considered to be statistically significant.

3. Results

3.1. Population’s characteristics

We studied a total of 160 patients, 82 females and 78 males (mean age 42 ± 13 years). The patients’ characteristics are summarised in Table 1. Renal complications were found in 39 patients (microalbuminuria in 16 cases, macroalbuminuria in 11 cases and advanced nephropathy in 12 cases). There was a weak correlation between daily insulin dose/body weight and eGDR (Rho = 0.174, P = 0.0415). We found that retinopathy was more frequent in patients with nephropathy than in those without. When we analysed only the 117 patients who had diabetes for more than 15 years, our results were unchanged (data not shown).

3.2. Parental history and DN

3.2.1. Parental history of diabetes

Forty-four patients had a parental history of diabetes: type 2 diabetes in 20 patients, type 1 diabetes in 19 patients and undetermined diabetes in five patients. Type 2 was present in 10 mothers and 10 fathers of type 1 diabetic patients. No type 1 diabetic patient had both parents affected. Our reference group—patients with no parental history of type 2 diabetes—was made of 140 subjects. Patients characteristics according to parental history of type 2 diabetes are summarised in Table 2.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Absent (n = 121)</th>
<th>Present (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 ± 13</td>
<td>44 ± 13</td>
<td>0.1521</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>59 (49)</td>
<td>19 (49)</td>
<td>0.9963</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>21 ± 13</td>
<td>27 ± 11</td>
<td>0.0107</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 4</td>
<td>25 ± 4</td>
<td>0.3411</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83 ± 11</td>
<td>86 ± 12</td>
<td>0.2324</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.86 ± 0.09</td>
<td>0.89 ± 0.09</td>
<td>0.0633</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 16</td>
<td>136 ± 20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>69 ± 9</td>
<td>75 ± 11</td>
<td>0.0040</td>
</tr>
<tr>
<td>Anti-hypertensive treatment: n (%)</td>
<td>28 (23)</td>
<td>25 (64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5 ± 1.4</td>
<td>9.0 ± 1.8</td>
<td>0.0428</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.93 ± 0.28</td>
<td>1.22 ± 0.33</td>
<td>0.0045</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.73 ± 0.24</td>
<td>1.64 ± 0.45</td>
<td>0.5400</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.01 ± 1.14</td>
<td>5.18 ± 1.34</td>
<td>0.3990</td>
</tr>
<tr>
<td>eGDR (mg/kg per min)</td>
<td>8.04 ± 2.17</td>
<td>5.96 ± 2.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of insulin injections per day</td>
<td>3.6 ± 0.9</td>
<td>3.5 ± 0.8</td>
<td>0.3780</td>
</tr>
<tr>
<td>Insulin dose (UI/kg per day)</td>
<td>0.70 ± 0.21</td>
<td>0.67 ± 0.27</td>
<td>0.3698</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>71 (63–79)</td>
<td>87 (70–121)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/l) #</td>
<td>4 (3–9)</td>
<td>168 (28–630)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage of retinopathy (1/2/3/4): n (%)</td>
<td>51(42%)/50(41%)/65%(14%)/1(11%)</td>
<td>5(13%)/13(33%)/3(7%)/18(46%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGDR: estimated glucose disposal rate. Stage of retinopathy: 1. absent; 2. simplex; 3. pre-proliferative; 4. proliferative. Data are mean ± S.D. or median (interquartile range) when specified #.

a Sex-adjusted P value.

b Patients on continuous subcutaneous insulin infusion were not considered in the analysis.
Table 2
Characteristics of type 1 diabetic patients, according to family history of type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>(A) No parental history</th>
<th>(B) Positive parental history</th>
<th>(C) Maternal history</th>
<th>(D) Paternal history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 ± 14</td>
<td>47 ± 10</td>
<td>47 ± 7</td>
<td>46 ± 13</td>
</tr>
<tr>
<td>Age at diabetes onset (years)</td>
<td>19 ± 11</td>
<td>21 ± 9</td>
<td>20 ± 7</td>
<td>21 ± 11</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>69 (49%)</td>
<td>9 (45%)</td>
<td>6 (60%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>124 ± 19</td>
<td>125 ± 13</td>
<td>121 ± 17</td>
<td>129 ± 6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71 ± 10</td>
<td>72 ± 9</td>
<td>71 ± 12</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 3.7</td>
<td>25.1 ± 4.1</td>
<td>23.3 ± 3.4</td>
<td>26.8 ± 4.2</td>
</tr>
<tr>
<td>Waist circumference (cm)a</td>
<td>83 ± 11</td>
<td>87 ± 12</td>
<td>81 ± 10</td>
<td>92 ± 13</td>
</tr>
<tr>
<td>Waist/hip ratioa</td>
<td>0.86 ± 0.10</td>
<td>0.88 ± 0.08</td>
<td>0.88 ± 0.05</td>
<td>0.88 ± 0.09</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.00 ± 0.57</td>
<td>1.08 ± 0.38</td>
<td>1.26 ± 0.42</td>
<td>0.89 ± 0.24</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.75 ± 0.46</td>
<td>1.54 ± 0.60</td>
<td>1.31 ± 0.71</td>
<td>1.76 ± 0.37</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.09 ± 1.14</td>
<td>4.81 ± 0.59</td>
<td>4.66 ± 0.59</td>
<td>4.95 ± 0.58</td>
</tr>
<tr>
<td>eGDR (mg/kg per min)</td>
<td>7.65 ± 2.30</td>
<td>7.03 ± 2.38</td>
<td>6.03 ± 1.98</td>
<td>8.15 ± 2.39</td>
</tr>
<tr>
<td>Patients with renal complications (%)</td>
<td>29 (21%)</td>
<td>10 (50%)</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
</tr>
</tbody>
</table>

eGDR: estimated glucose disposal rate; BMI: body mass index. SBP: systolic blood pressure; DBP: diastolic blood pressure.

a Sex-adjusted P value.

Patients with a parental history of type 2 diabetes were more likely to have DN (chi-square: 8.14; P = 0.0043) than those patients from the reference group, without parental history of type 2 diabetes. The direct comparison of type 1 diabetic patients with maternal vs. paternal history of type 2 diabetes found an increased risk of nephropathy in type 1 diabetic patients with maternal history of type 2 diabetes (chi² = 3.2; P = 0.07). Interestingly, patients with maternal history of type 2 diabetes were different from patients with paternal history, regarding eGDR, and risk for kidney disease. When we analysed only the 117 patients who had diabetes for more than 15 years, our results were unchanged (data not shown).

Conversely, a parental history of type 1 diabetes was not associated with nephropathy (chi-square: 2.24; P = 0.1342) or eGDR (P = 0.3120). Specifically, neither a maternal nor a paternal history of type 1 diabetes were associated with renal complications (data not shown).

3.2.2. Parental history of cardiovascular disease
Fifty-seven patients had a family history of cardiovascular disease: angina pectoris in 10 cases, myocardial infarction in 27, stroke in 4 and hypertension in 16. Family history of premature coronary artery disease was present in 13 patients.

Parents with type 2 diabetes were more likely to have premature coronary artery disease (chi-square: 5.59, P = 0.018). Patients with a family history of premature coronary artery disease had a lower eGDR than the others (6.10 ± 2.54 vs. 7.72 ± 2.28 mg/kg per min; P = 0.0157). There was an association of borderline statistical signification between renal complications and family history of premature coronary artery disease (chi-square: 3.64; P = 0.0564), but not of hypertension (P = 0.1010).

3.2.3. Parental history and development of nephropathy
Time to the development of abnormal albuminuria was significantly affected by parental history of type 2 diabetes (log-rank: 6.88; P = 0.0087) or parental history of premature coronary artery disease (log-rank: 5.48; P = 0.0234) but not by parental history of type 1 diabetes (log-rank = 1.97; P = 0.1601). Maternal history of type 2 diabetes was a significant risk factor for the development of abnormal albuminuria (log-rank: 12.66; P = 0.0004) while paternal history of type 2 diabetes was not (log-rank: 0.04; P = 0.84) (Figs. 1–3). Stratification on parental history of premature coronary artery disease did not affect the role of parental history of type 2 diabetes (log-rank: 9.40; P = 0.0022).

3.3. Multivariate analysis
Diabetes duration and a maternal history of type 2 diabetes were significant and independent risk factors for renal complication after adjustment for sex (Table 3). Introducing parental history of cardiovascular disease did not modify the results. When only patients with established or advanced nephropathy

![Renal event free survival](image)

Fig. 1. Kaplan–Meier curve: survival without development of abnormal albuminuria according to parental history of type 2 diabetes. Solid line (reference group), absence of and dashed line, presence of parental history of type 2 diabetes, respectively (log-rank: 6.88; P = 0.0087).
were considered, the result did no change (data not shown). When we analysed only the 117 patients who had diabetes for more than 15 years, our results were unchanged (data not shown).

4. Discussion

In this study, we confirmed that a parental history of type 2 diabetes was associated with a 2.5-fold greater risk for renal complications in type 1 diabetes index patients. In addition, maternal but not paternal history of type 2 diabetes segregated with renal disease in type 1 diabetes mellitus offspring. Using a complementary longitudinal approach, we showed that maternal history of type 2 diabetes was associated with a faster development of abnormal albuminuria which was not previously reported, to our knowledge. We also showed that the relationship between maternal history of type 2 diabetes and renal complications in type 1 diabetes persisted after adjustment on insulin resistance, assessed using estimated GDR.

Our data are in accordance with previous reports: 16% of our patients had a first-degree relative with type 2 diabetes, a very similar prevalence as reported by Roglic et al. [18] or Fagerudd et al. [19]. Our data also confirmed the association between family history of cardiovascular disease and nephropathy in type 1 diabetic patients [18,20–23], but also suggested that a parental history of type 2 diabetes was an independent risk factor for nephropathy, in accordance with studies from Finland [13,19], at variance with the study by Roglic et al. [18]. In our cohort, the odds ratio associated with a parental history of type 2 diabetes was approximately 2.5, in good accordance with the adjusted relative risk of 1.6 in the study by Harjutsalo et al. [13]. It was recently shown that a maternal history of type 2 diabetes (compared with a paternal history) was associated with a greater transmission of insulin resistance, in good accordance with our results [24].

The association between parental history of type 2 diabetes and DN in type 1 diabetic offspring was reported by Fagerudd et al. [19] and Harjutsalo et al. [13] but the specific analysis of maternal or paternal origin was not performed. The specific effect of maternal type 2 diabetes was mentioned in Pima Indians: maternal history of diabetes was associated with a greater prevalence of proteinuria in type 2 diabetic offsprings, even if adjustment for age, diabetes duration and gender abolished this effect [25]. Such an effect of maternal type 2 diabetes was not described before for type 1 diabetic patients.

The differential effect of maternal and paternal history of type 2 diabetes might be related to the maternal origin of mitochondria. With this regard, the transmission of maternal inherited diabetes due to mutations of mitochondrial DNA is unlikely, as it is associated with a very peculiar form of retinal involvement, not encountered in our patients [26]. The role of other unknown mitochondrial mutations leading to risk factors for nephropathy is purely speculative.

An alternative hypothesis is related to genomic imprinting, i.e. the differential expression of alleles, according to their maternal process [27]. Environmental factors particularly in utero could favour type 2 diabetes in mothers and imprint maternal genes involved in type 1 diabetes nephropathy.

Some imprinted genes are thus of particular importance such as those controlling body growth [28], as height is a risk factor for DN [1] or insulin resistance [29]. It was recently shown that a hyperglycaemic in utero environment could lead to pancreatic dysfunction [30]. Kidney function was not examined in this report. It can be hypothesised that subtle modifications during pregnancy can induce type 2 diabetes in future mother life and DN in type 1 diabetes affected offspring. Cur-
rently, the nature of these modifications is unknown. An abnormal in utero environment with increased levels of glucose or free fatty acid can be speculated.

It is important to mention some limitations of this study. This is a single centre study, with small numbers leading to a possible chance finding. However, this study specifically analysed maternal and paternal influences, at variance with other previous reports pooling fathers and mothers. We asked index patients to answer a structured questionnaire and thus we were not able to examine family members. A recall bias according to type 1 diabetic complications is possible but is particularly unlikely to differ according to paternal or maternal history of diabetes. We used a clinical definition to type diabetes in parents, which could lead to an overestimation of type 2 diabetes because of atypical presentation of autoimmune diabetes in parents of type 1 diabetes children [31]. However, the finding that insulin resistance was greater in index patients whose mothers had type 2 diabetes supports that our classification was correct. Our questionnaire was not designed to assess parental socio-economic data, which were shown to affect the risk for DN in type 1 diabetic offspring [32]. A selection bias in this cohort is questionable but unlikely, because patients were consecutively recruited and because our centre is in charge of a majority of type 1 diabetic patients in the region. Finally, the use of eGDR rather than the measurement of insulin resistance must be discussed. It was validated using glucose-clamp technique [6], but its value is still debatable in type 1 diabetic patients with established renal complications.

5. Conclusion

We found that a maternal history of type 2 diabetes was independently associated with renal disease in type 1 diabetic index patients. This point may be clinically important: a careful search for such a parental history is thus highly advised and peculiar preventive interventions, with ACE-inhibitors for example, could be imagined in type 1 diabetic offspring of type 2 diabetic mothers. Our results stimulate the search for familial traits independent from insulin resistance that predispose to renal complications in type 1 diabetic patients, with special emphasis on imprinted genes and epigenetic phenomena.

Acknowledgments

We thank all type 1 diabetic patients who participated in this study. The English of the text was checked by Alex Edelman and associates.

We thank Catherine Iste and Vanessa Laneuze for secretarial assistance and Elodie Rogeon and Fanny Abriat (Clinical Research Associates) for clinical help. The association GEMMS (Poitiers, France) is acknowledged for supporting this study.

References


