Low birth weight does not increase the risk of nephropathy in Finnish type 1 diabetic patients

Johan Fagerudd1,4, Carol Forsblom1,4, Kim Pettersson-Fernholm1,4, Markku Saraheimo1,4, Johan Waden1,4, Mats Ronnback1,4, Milla Rosengard-Barlund1,4, Clas-Goran af Bjorksten1,4, Lena Thorn1,4, Maija Wessman1–4 and Per-Henrik Groop1,4 on behalf of the FinnDiane Study Group

1Folkhsans Institute of Genetics, Folkhsans Research Center, 2Department of Clinical Chemistry, 3The Finnish Genome Center, University of Helsinki and 4Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, Helsinki, Finland

Abstract

Background. Low birth weight (LBW) has been linked to renal disease both in animal models and human studies. However, the role of birth weight in the development of diabetic nephropathy is unclear. We, therefore, studied the impact of birth weight on the development of diabetic nephropathy and other related traits, such as diabetic retinopathy and macrovascular disease, in Caucasian type 1 diabetic patients.

Methods. Data on size at birth were obtained from original birth certificates in 1543 Finnish patients with type 1 diabetes. The patients were divided into those with low (LBW; below the 10th percentile), normal (NBW; 11–90th percentile) and high birth weight (HBW; above the 90th percentile).

Results. Diabetic nephropathy was equally common in the groups with various birth weight (LBW vs NBW vs HBW: 21 vs 20 vs 17%, P = NS). End-stage renal disease (3 vs 5 vs 4%, P = NS), laser-treated retinopathy (31 vs 31 vs 31%, P = NS) and macrovascular disease (5 vs 5 vs 8%, P = NS) were equally prevalent in the various birth weight groups. The time from the onset of diabetes to the onset of diabetic nephropathy was similar irrespective of birth weight (log-rank test; P = NS).

Conclusions. Based on our cross-sectional data, LBW does not have an impact on the development of diabetic nephropathy, laser-treated retinopathy or macrovascular disease later in life in Caucasians with type 1 diabetes.

Keywords: albuminuria; diabetic nephropathy; intrauterine growth retardation; type 1 diabetes mellitus

Introduction

Small size at birth has been linked to an increased morbidity later in life. For instance, individuals with low birth weight seem to be at increased risk of cardiovascular disease, type 2 diabetes, elevated blood pressure and renal disease [1–3]. The mechanisms causing intrauterine growth retardation and impaired health in adulthood remain to be elucidated, but environmental as well as genetic factors are suggested to play a role [1,4].

Birth weight correlates with the number of nephrons in the groups with various birth weight (LBW vs NBW vs HBW: 21 vs 20 vs 17%, P = NS). End-stage renal disease (3 vs 5 vs 4%, P = NS), laser-treated retinopathy (31 vs 31 vs 31%, P = NS) and macrovascular disease (5 vs 5 vs 8%, P = NS) were equally prevalent in the various birth weight groups. The time from the onset of diabetes to the onset of diabetic nephropathy was similar irrespective of birth weight (log-rank test; P = NS).

Conclusions. Based on our cross-sectional data, LBW does not have an impact on the development of diabetic nephropathy, laser-treated retinopathy or macrovascular disease later in life in Caucasians with type 1 diabetes.

Keywords: albuminuria; diabetic nephropathy; intrauterine growth retardation; type 1 diabetes mellitus

Correspondence and offprint requests to: Per-Henrik Groop, MD, DMSc, Folkhsans Research Center, Biomedicum Helsinki (C318b), PO Box 63, FIN-00014, University of Helsinki, Finland. Email: per-henrik.groop@helsinki.fi

© The Author [2006]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org
differences between type 1 and type 2 diabetes. However, before further conclusions can be drawn, the role of size at birth in the development of diabetic kidney disease needs to be clearly defined.

The aim of the present study was, therefore, to assess the impact of birth weight on the development of diabetic nephropathy. In addition, we aimed to study the association between birth weight and other diabetic late complications, such as diabetic retinopathy and macrovascular disease, in a large sample of Finnish type 1 diabetic patients.

Subjects and methods

The Finnish Diabetic Nephropathy (FinnDiane) study is a nationwide, prospective, multicentre study that was initiated in November 1997. The primary aim is to identify genetic and environmental risk factors for diabetic nephropathy in type 1 diabetes. The patients are recruited from 20 university and central hospitals, from 23 local hospitals and from 16 primary healthcare centres. The study protocol is in accordance with the Declaration of Helsinki and it has been approved by the local ethics committee of each participating study centre.

The present study presents cross-sectional data from the baseline visit. All patients with a diagnosis of type 1 diabetes (E10 in ICD-10) attending the diabetic and renal out-patient clinics and dialysis units were asked to participate in the study in a consecutive manner when they visited the hospitals and the healthcare centres as part of their routine follow-up. Of the invited patients, 78% gave their informed consent. Based on medical records, the attending local physician completed a study form assessing diabetic micro- and macrovascular late complications. Furthermore, data on the mode of insulin therapy, daily insulin dose and other regular medication were obtained. The patients were asked to complete a questionnaire concerning place of birth, smoking habits, alcohol intake, educational level and social class.

For the present study, we selected all patients with an age at onset of diabetes \(<36\) years, with insulin therapy initiated within 1 year after diagnosis, and with their data entered into the FinnDiane database by 31 October 2002. Of the 3115 patients fulfilling these criteria, 2313 reported birth at a hospital. Of these, we were able to obtain a copy of the original birth certificate for 1966 patients. After exclusion of twin pregnancies \((n=23)\), the final data set consisted of 1543 patients with data on birth weight available. Of these, 1419 had complete data on birth weight, height and gestational age (calculated from the last menstruation before pregnancy).

Definitions of long-term complications

While the classification of other diabetic late complications was based on the study form completed by the attending physician, the degree of renal involvement was classified centrally. All available data on urinary albumin excretion rate (UAER) was extracted from local medical records. A patient was classified as having microalbuminuria or diabetic nephropathy if the criteria mentioned subsequently were fulfilled at any time point after the diagnosis of diabetes. Diabetic nephropathy was defined as a UAER exceeding \(200\) \(\mu\)g/min (overnight collections) or \(300\) mg/24 h (24 h urine collections), or as a urinary albumin/creatinine ratio in a spot sample exceeding \(25\) mg/mmol (male) or \(35\) mg/mmol (female), in two out of three consecutive measurements. The corresponding cut-off values for microalbuminuria were \(20\–200\) \(\mu\)g/min or \(30\–300\) mg/24 h for UAER, and \(2.5\–25\) mg/mmol (male) or \(3.5\–35\) mg/mmol (female) for the urinary albumin/creatinine ratio. Two UAER measurements within the normal range were required to classify a patient as normoalbuminuric. The renal status was considered unclassifiable if there was insufficient data on UAER, or if UAER was elevated due to reasons other than diabetes (pregnancy, non-diabetic kidney disease, duration of diabetes \(<3\) years). End-stage renal disease (ESRD), defined as renal replacement therapy due to diabetic nephropathy, was present in 74 patients.

Retinopathy was defined as a history of laser photocoagulation treatment. Manifestations of macrovascular disease (history of myocardial infarction, coronary revascularization procedure, stroke, amputation of a limb or peripheral arterial revascularization procedure) were combined to a single macrovascular end-point.

Other definitions

Current smoking was defined as regular cigarette smoking during the year prior to participation in the study. A patient was considered an ex-smoker if more than 1 year had elapsed since the cessation of smoking. Social class was defined as follows: I. upper white-collar workers, II. lower white-collar workers, III. skilled blue-collar workers, IV. unskilled blue-collar workers, V. farmers and VI. others.

Laboratory assays

Serum creatinine concentration (normal reference values: male \(<115\) \(\mu\)mol/l, female \(<100\) \(\mu\)mol/l) was measured centrally with a kinetic Jaffe reaction on a Hitachi 917 automated analyser. Data on the latest HbA\(_1c\) measurement were obtained from local medical records. All patients without ESRD \((n=1469)\) were asked to perform a 24 h urine collection for central measurement of UAER, and the data were obtained in 1312 patients (89%). Of patients with previously well-documented diabetic nephropathy, current UAER in this single measurement had regressed to micro- or normoalbuminuria in 32% of the patients. Correspondingly, 24% of the microalbuminuric patients had a current UAER in the normoalbuminuric range.

Other calculations

Creatinine clearance was estimated using the Cockcroft-Gault formula corrected for body surface area [10]. Whole-body insulin sensitivity was calculated using the estimated glucose disposal rate (eGDR) formula [11].

Statistics

In order to test whether low birth weight predisposes to diabetic complications, the patients were classified into those with low (below the 10th percentile; group I), intermediate
Birth weight diabetic nephropathy in type 1 diabetes

As presented in detail [7], the patients included in the present study (n = 1543) were younger, had a shorter duration of diabetes and a lower prevalence of both micro- and macrovascular complications than the patients without available data on birth weight (n = 1572).

The patients were divided into four groups based on birth weight percentiles. Perinatal and current characteristics are presented in Tables 1 and 2, respectively. Patients with a low birth weight had shorter gestational age and were also thinner since their ponderal index was lower. There was a positive correlation between birth weight and adult weight (R = 0.176, P < 0.001) and height (R = 0.230, P < 0.001). The HbA1c was slightly higher in patients with a birth weight in the 50–90th percentiles (group III) when compared with

### Table 1. Perinatal characteristics according to birth weight group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>P (df = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight percentile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>154</td>
<td>612</td>
<td>622</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Males [n; birth weight range (g)]</td>
<td>76 (1210–2930)</td>
<td>304 (2940–3570)</td>
<td>303 (3580–4220)</td>
<td>76 (4230–5400)</td>
<td></td>
</tr>
<tr>
<td>Females [n; birth weight range (g)]</td>
<td>78 (1580–2820)</td>
<td>308 (2830–3440)</td>
<td>319 (3450–4090)</td>
<td>79 (4100–4900)</td>
<td></td>
</tr>
<tr>
<td>Birth height (cm)</td>
<td>46.8 ± 1.9</td>
<td>49.7 ± 1.4</td>
<td>51.3 ± 1.3</td>
<td>53.1 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ponderal index (kg/m3)</td>
<td>25.1 ± 2.1</td>
<td>26.4 ± 2.0</td>
<td>28.1 ± 1.9</td>
<td>29.7 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational time (days)</td>
<td>263 ± 19</td>
<td>276 ± 13</td>
<td>280 ± 10</td>
<td>284 ± 9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P < 0.001 vs group I, bP < 0.001 vs group II, cP < 0.001 vs group III.

### Table 2. Current clinical characteristics according to birth weight group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>P (df = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>154</td>
<td>612</td>
<td>622</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Current age (years)</td>
<td>33 ± 9</td>
<td>33 ± 10</td>
<td>33 ± 10</td>
<td>32 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Age at onset of diabetes (years)</td>
<td>14 ± 8</td>
<td>14 ± 8</td>
<td>14 ± 8</td>
<td>14 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>19 ± 11</td>
<td>19 ± 11</td>
<td>19 ± 10</td>
<td>18 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 9</td>
<td>170 ± 9</td>
<td>172 ± 9</td>
<td>173 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.7 ± 13.1</td>
<td>71.6 ± 12.2</td>
<td>73.7 ± 13.1</td>
<td>75.3 ± 12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.8 ± 3.3</td>
<td>24.8 ± 3.4</td>
<td>25.0 ± 3.6</td>
<td>25.1 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.85 ± 0.08</td>
<td>0.86 ± 0.09</td>
<td>0.86 ± 0.08</td>
<td>0.86 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Manual worker (%)</td>
<td>50</td>
<td>56</td>
<td>52</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-hypertensive medication (%)</td>
<td>34</td>
<td>34</td>
<td>36</td>
<td>30</td>
<td>NS</td>
</tr>
<tr>
<td>ACE-inhibitor/AR-blocker (%)</td>
<td>29</td>
<td>28</td>
<td>29</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 16</td>
<td>131 ± 17</td>
<td>131 ± 17</td>
<td>128 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80 ± 10</td>
<td>79 ± 10</td>
<td>80 ± 10</td>
<td>79 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 ± 1.5</td>
<td>8.4 ± 1.5</td>
<td>8.6 ± 1.6</td>
<td>8.3 ± 1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Estimated creatinine clearance (ml/min/1.73 m2)</td>
<td>90 ± 26</td>
<td>95 ± 26</td>
<td>96 ± 29</td>
<td>97 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Proportion (%) with hyperfiltration (creatinine clearance ≥120 ml/min/1.73 m2)</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>88 (79–103)</td>
<td>87 (77–98)</td>
<td>87 (77–98)</td>
<td>85 (77–98)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary AER (mg/24h)</td>
<td>11 (6–65)</td>
<td>11 (7–40)</td>
<td>13 (7–71)</td>
<td>11 (6–37)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Patients with ESRD excluded; available in 1312 of the 1469 patients without ESRD. bP < 0.01 vs group I, cP < 0.05 vs group II. dP < 0.05 vs group I. eP < 0.05 vs groups I, II and IV.
Systolic blood pressure was higher and estimated creatinine clearance lower in patients with low compared with high birth weight.

In an analysis restricted to patients without ESRD, there was a weak positive correlation between birth weight and estimated creatinine clearance in adulthood (R = 0.076, P = 0.004).

The prevalence of diabetic long-term complications is presented in Table 3. There was no difference in the prevalence of the assessed micro- or macrovascular complications between any of the groups with various birth weights irrespective of the mode of comparison (low birth weight vs high, low vs rest, high vs rest, low and high vs intermediate). The eGDR, a surrogate measure of insulin sensitivity, did not differ between the groups. As depicted in Figure 1, a sex-stratified analysis revealed no significant differences in the prevalence of diabetic nephropathy in the groups with different birth weight in either males or females.

The impact of size at birth on the time of onset of diabetic nephropathy was further assessed using a Kaplan–Meier survival analysis (Figure 2). In this analysis, we found no evidence of an earlier onset of nephropathy in patients with low birth weight. A sex-stratified survival analysis revealed similar results in both males and females (data not shown).

We also used alternative definitions of intrauterine growth retardation (birth weight below 2500 g, a ponderal index in the lowest 10th percentile), but these analyses yielded similar results to those now presented.

Patients with a low birth weight had a shorter gestational age. As a birth weight of, for instance, 2500 g indicates intrauterine growth retardation in the full-term child, it reflects normal intrauterine growth in the pre-termly born individual. Therefore, in a logistic regression analysis, we assessed the odds ratio of diabetic nephropathy in the different birth weight groups after adjustment for gestational age. However, the analysis had no effect on the results (Table 4).

A power calculation was performed with patients with low birth weight (group I) vs those without (groups II–IV). Assuming that the prevalence of nephropathy in groups II–IV is 20% as observed, our sample size would have detected a prevalence of nephropathy of 30% in group I as statistically significantly higher (P < 0.05) with a power of 0.80.

### Discussion

This study found no impact of size at birth on the risk of diabetic nephropathy in patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (0–10)</th>
<th>Group II (10–50)</th>
<th>Group III (50–90)</th>
<th>Group IV (90–100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated UAER (%)</td>
<td>36</td>
<td>30</td>
<td>34</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetic nephropathy (%)</td>
<td>21</td>
<td>19</td>
<td>21</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>ESRD (%)</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Laser-treated retinopathy (%)</td>
<td>31</td>
<td>31</td>
<td>30</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Macrovascular disease (%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>eGDR (mg/kg/min)</td>
<td>6.8 (5.0–8.7)</td>
<td>6.7 (4.4–8.7)</td>
<td>6.8 (4.5–8.7)</td>
<td>7.6 (4.9–9.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3. Proportion of patients with diabetic nephropathy, laser-treated retinopathy, macrovascular disease and estimated glucose disposal rate according to birth weight

<sup>a</sup> Microalbuminuria, diabetic nephropathy and ESRD combined. <sup>b</sup> Diabetic nephropathy and ESRD combined. It was not possible to classify the renal status in 17 patients (11%) in group I, 77 patients (13%) in group II, 86 patients (14%) in group III and in 16 patients (10%) in group IV. Exclusion of these patients did not change the results.
with type 1 diabetes. Similarly, no association was observed between birth weight and laser-treated diabetic retinopathy or macrovascular disease.

Ots and colleagues [12] demonstrated that nephron mass (or number) is instrumental in the development of arterial hypertension and glomerular hyperfiltration by studying the effects of kidney transplantation in subtotally nephrectomized rats. In humans, a markedly reduced number of nephrons has been found in patients with primary hypertension [6]. Further evidence suggests an increased risk of progressive renal disease in diabetic subjects with only one kidney [13]. The link between a reduced number of nephrons, elevated blood pressure and progressive renal disease therefore seems irrefutable.

In a separate analysis of this cohort of type 1 diabetic patients, we recently reported an inverse relationship between birth weight and systolic blood pressure and pulse pressure [7]. In the present article, we found a weak positive correlation between weight at birth and adult glomerular filtration rate. It should be noted, however, that although the correlation was statistically highly significant, birth weight explained <1% of the variation in estimated adult creatinine clearance. Furthermore, as many of our patients had normal kidney function, the Cockcroft–Gault formula may be suboptimal in estimating kidney function. Nonetheless, elevated systemic blood pressure and impaired kidney function are well-recognized players in the vicious circle leading to progressive renal failure. The question arises: why was low birth weight not associated with an increased risk of overt diabetic nephropathy?

First, as already mentioned, although statistically significant, the effects of birth weight on both systemic blood pressure [7] and kidney function were not profound. In a process where the degree of chronic hyperglycaemia is fundamental [14], the derangements associated with size at birth may simply be too small to have any impact on the development of progressive renal damage.

Second, although intrauterine growth retardation is associated with a reduced number of nephrons at birth [5], birth weight must be viewed only as a surrogate marker for the nephron number.

Third, the underlying cause of small size at birth, whether genetic, environmental or a combination of these two, may be of crucial importance. Animal studies have shown that intrauterine growth retardation induced by environmental changes, such as protein or salt depletion during pregnancy, is associated with signs of renal impairment in the offspring [15,16]. In humans, retrospective studies have reported a link between low birth weight and later progressive renal damage or related traits, such as congenital renal failure [17], diabetic nephropathy [8,9], albuminuria [18] and ESRD of any cause [19]. These findings have been observational and the causes of the retarded growth in utero have not been possible to define.

Several of the positive associations have been found in populations with a high incidence of ESRD, such as type 2 diabetic Pima Indians [9], aborigines [18] and a population from the southeastern region of the USA [19]. Interestingly, the mean birth weight in these previous studies was lower (3.38 [9], 2.71 [18] and 3.25 kg [19], respectively) than in the present (3.51 kg). The genetic background of these populations is undoubtedly different from that of our Finnish type 1 diabetic population. However, the environment may also differ substantially. Of the patients in our study, 85% were born after 1960. After the decade following the Second World War, due to governmentally financed prenatal care readily available for all citizens, malnutrition during pregnancy has become extremely rare in Finland. This has led to an infant mortality rate that has been one of the lowest in the world during the last decades [20]. If fetal malnutrition is crucial in the aetiology of intrauterine growth retardation and subsequent renal failure, this environmental factor may simply not have been present to any significant degree in our population.

The cross-sectional study design has well-known limitations. Selective excess mortality may have diluted a true association between low birth weight and diabetic renal disease. However, to our knowledge, no prospective studies dealing with the impact of birth weight on diabetic or non-diabetic kidney disease are
so far available. The previous observations reporting an association between birth weight and diabetic renal disease were also cross-sectional, but of considerably smaller size [8,9]. In addition to size, our finding is strengthened by the fact that we have data on the time of (known) onset of diabetic nephropathy available. Notably, we found no evidence of an earlier onset of persistent proteinuria in patients with low birth weight.

In conclusion, our present findings do not support a role for low birth weight in the development of diabetic nephropathy or other diabetic late complications in Finnish type 1 diabetic patients. Although prospective follow-up studies are needed to fully define the role of size at birth in the pathogenesis of diabetic renal disease, it seems unlikely that low birth weight would be a clinically relevant risk factor for diabetic nephropathy in Caucasians with type 1 diabetes.


Conflict of interest statement. None declared.

References


Received for publication: 16.10.05
Accepted in revised form: 29.3.06