Fetal exposure to maternal type 1 diabetes is associated with renal dysfunction at adult age

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**Objectives:** In animal studies, hyperglycemia during fetal development reduces nephron numbers. We tested if this observation translates into renal dysfunction in humans by studying renal functional reserve in adult offspring exposed *in utero* to maternal type 1 diabetes.

**Research design and methods:** We compared 19 non-diabetic offspring of type 1 diabetic mothers to 18 offspring of type 1 diabetic fathers (controls). Glomerular filtration rate ($^{51}$Cr-EDTA clearance), effective renal plasma flow ($^{123}$I-Hippurate clearance), mean arterial pressure, and renal vascular resistances were measured at baseline and during amino acid infusion, which mobilizes renal functional reserve.

**Results:** Offspring of type 1 diabetic mothers were similar to controls for age (27 (range 18-41) years), sex, body mass index (23.1± 3.7 kg/m$^2$), and birth weight (3288±550 vs 3440±489 grams). During amino acid infusion, glomerular filtration rate and effective renal plasma flow increased less in offspring of type 1 diabetic mothers than in controls: from 103 ± 14 to 111 ± 17 ml/min (+8±13%) vs from 108 ± 17 to 128 ± 23 ml/min (+19±7 %, p=0.009), and from 509 ± 58 to 536 ± 80 ml/min (+5±9%) vs from 536 ± 114 to 620 ± 140 ml/min, (+16±11 %, p=0.0035). Mean arterial pressure and renal vascular resistances declined less than in controls: +2±5 vs -2±3 % (p=0.019), and +3±9 vs -14±8 % (p=0.001).

**Conclusions:** Reduced functional reserve may reflect a reduced number of nephrons, undergoing individually hyperfiltration. If so, offspring of type 1 diabetic mothers may be predisposed to glomerular and vascular diseases.

A reduced number of nephrons may cause hypertension and favor renal and cardiovascular risks in humans (1). This assumption is supported by autopsy findings (2). In addition, birth weight is a determinant of nephron numbers in humans (3). In animal models, moderate hyperglycemia during pregnancy affects birth weight and nephron numbers in offspring (4), and favors the development of hypertension at adulthood (5). Also, angiogenesis impacts on kidney development (6, 7). In this respect, moderate hyperglycemia induces a defect in angiogenesis as reported in experimental conditions (8).

We hypothesized that the effects of moderate hyperglycemia on kidney development reported in animal studies might have clinical relevance in humans. Thus, we studied kidney function in subjects who had been exposed to hyperglycemia during their fetal development. For this purpose, we investigated as previously (9) adults whose mothers had type 1 diabetes at time of their conception and used as controls offspring of type 1 diabetic fathers to minimize potential genetic heterogenicity between groups. Type 1 diabetes as a source of hyperglycemia during fetal development also minimizes confounding factors associated with type 2 diabetes such as hypertension. Counting nephron numbers and/or visualizing glomerular size by non-invasive methods is not feasible in humans currently. Thus, we measured global kidney function at baseline and during vasodilatation produced by amino acid infusion, i.e., renal functional reserve. Reduction in renal functional reserve can be interpreted as reflecting a reduced surface available for filtration, suggesting that the number of functional nephrons is reduced. As a result, the global hemodynamic load provokes hyperfiltration at the single nephron level (1). This disturbance in renal hemodynamics was associated with renal and vascular diseases both in experimental models...
(1,4,5) and clinical settings (10, 11, 12, 13). We report here that renal functional reserve is reduced in offspring of type 1 diabetic mothers.

METHODS

Participants. Participants were direct offspring of type 1 diabetic subjects attending specialized clinics in 5 hospitals in France: Hôpital Saint-Louis, Hôpital Bichat – Claude Bernard, Hôtel-Dieu, all in Paris, Centre Hospitalier Universitaire in Poitiers, and Centre Hospitalier Sud Francilien in Corbeil Essonne.

We selected type 1 diabetic parents, then their offspring. Parents were with type 1 diabetes (as defined by the American Diabetes Association) for at least two years before offspring conception. Eligibility was possible if spouses had neither type 1, nor type 2 diabetes at time of study. Mothers were asked if they smoked during their pregnancies. Offspring were men or women aged 18 years or above, not pregnant at time of investigation for women, and had no diabetes. They were checked as having no immune marker of type 1 diabetes (anti-islet antibodies, antibodies against GAD, IA2, and IA2 beta, and anti-insulin antibodies). Chronic drug intake, acute infection, any chronic disease, and personal or family history of kidney disease, other than possible diabetic nephropathy in their diabetic parents were not allowed. Cases were offspring of type 1 diabetic mothers, and controls offspring of type 1 diabetic fathers.

Study design. The current study is part of a program investigating the physiological consequences of fetal exposure to maternal type 1 diabetes at adult age. We report here data on kidney function.

At first visit, plasma glucose, insulin, and glucagon concentrations were measured after an overnight fast on occasion of an Oral Glucose Tolerance Test. Renal volume was measured using ultra sounds. Urines were collected for albumin measurement during 2 hours before and after a 20-min exercise on ergocycle at an intensity of 80% maximal heart rate. Then, ambulatory blood pressures were monitored during the following 24 hours.

On a separate occasion, the participants brought 24-hour urines for albumin and sodium measurements, and their kidney function was investigated after an overnight fast. Glomerular Filtration Rate (GFR) and renal plasma flow were measured at baseline and during amino acid infusion using the renal clearances of two radiopharmaceuticals: \(^{51}\text{Cr-EDTA}\) (GE Health Care, France), as an estimate of GFR and \(^{123}\text{I-Hippurate}\) (Covidien Imaging, France), as of Effective Renal Plasma Flow (ERPF). A catheter was inserted in a forearm vein for infusion, and another one controlaterally for sampling. The subjects remained supine for one hour, after which blood was sampled for plasma renin and aldosterone measurements. They were given tap water (100 ml every 15 minutes) throughout study to induce a forced water diuresis (mean 10 ± 2 (SD) ml/min). Once diuresis was adequate, the participants received a primed infusion of both \(^{51}\text{Cr-EDTA}\) (bolus 1.8 MBq, then 0.9 MBq/hour) and \(^{123}\text{I-Hippurate}\) (bolus 4 MBq, then 1.5 MBq/hour) throughout study. Two hours were necessary to obtain a radioisotope plateau and to calculate baseline clearances of \(^{51}\text{Cr-EDTA}\) and \(^{123}\text{I-Hippurate}\) (baseline period). Aminoacids (Vamine 10%, Fresenius-Kabi, France) were infused at a rate of 5 mg/kg/min (previously reported as providing maximal renal vasodilatation (14)) afterwards for the following 90 minutes (stimulation period). Plasma and urine samples were processed to calculate urinary clearances of radiopharmaceuticals. Along the experiment, participants remained supine, except when they voided their bladder every 30 minutes for urinary sampling. Blood samples were collected for isotope counting and hematocrite every 30 minutes three times before the end
of each period. Mean Arterial Pressure (MAP) was recorded using an automatic device (Dinamap®, France).

All aspects of study were approved by the Ethical Committee of Paris Saint-Louis. Each participant gave a written informed consent to participate.

**Measurements.** Kidney volume was measured with ultrasounds (Siemens Elegra SSN 7083, Germany) using a previously published program (15).

Urinary albumin was measured using a nephelometric method (Behring test, Marburg, Germany, assay sensitivity 2 mg/l and intra- and inter-assay variability of 5 % and 7 %, respectively). Glucose was measured with glucose oxidase and insulin, glucagon, renin, and aldosterone with radioimmuno assays.

Isotope counting was performed using a gamma counter (1480 Wizard 3, PerkinElmer, USA).

**Calculations.** Renal clearances of isotopes were calculated as urine volume multiplied by urine isotope concentration, divided by plasma isotope concentration. The first 60 minutes of the basal period and the first 30 minutes of the stimulation period were not used for calculations, because steady state could not be assumed for plasma isotopes and amino acids. Thus, renal clearances of isotopes were calculated from the mean of the two measurements performed 30-min apart at the end of each period. The GFR and ERPF values were not corrected for body surface. Filtration fraction (FF) was calculated as GFR divided by ERPF. To yield MAP values, blood pressure were recorded every 5 minutes, and meant for each 30-minute clearance period. Renal Vascular Resistances (RVR) were calculated from MAP/(ERPF/(1 – hematocrite)). The mean intra-subject variability for the basal periods were 4.2% for GFR, 3.5% for ERPF, 4.3% for FF, 2.2% for MAP and 4.9% for RVR. For the stimulated periods, they were respectively 4.9% for GFR, 4.2% for ERPF, 3.9% for FF, 1.8% for MAP and 4.9% for RVR. The renal functional reserve was calculated as the percent change in each of the studied variables from the basal period to the stimulated one.

**Statistical analysis.** Data are presented as mean ± SD, median (range), or percentages. The primary end-point was the inter-group difference in GFR changes produced by amino acid infusion. The assumption was that a 20% increase in GFR (standard deviation 10%) would be observed during infusion in controls, and that the mean increase would be 50% less in offspring of type 1 diabetic mothers. With a type 1 error rate of 5%, 21 subjects per group were required to test the hypothesis with a 90% power. Because of technical reasons, only experiments performed in 19 cases and 18 controls could be analyzed.

Intra-group changes where analyzed by paired t-tests or signed Wilcoxon rank-sum tests, and inter-group comparisons by Welsh modified t-tests or Mann-Whitney tests. Parametric or nonparametric tests were chosen by assessing whether the data distribution was skewed or not. The correlation between renal hemodynamic changes and birth weight was assessed by Pearson correlation coefficient. The hypothesis of a different correlation in cases and controls was tested by an interaction test in a linear model. The threshold for p value significance was set at 5%.

Statistical analysis was performed using R 2.6.2 (The R Foundation for Statistical Computing, Vienna, Austria) statistical software.

**RESULTS**

Participants’ recruitment and characteristics: Among about 2000 type 1 diabetic subjects attending the 5 clinics, 102 were eligible, 83 agreed to contact their offspring, and 62 offspring agreed to participate to our program investigating the
physiological consequences of fetal exposure to maternal type 1 diabetes at adult age. Forty one subjects (21 cases, and 20 controls) agreed to undergo renal tests. They did not differ from the 21 other subjects. Four participants (two in each group) were excluded from analyses, because of technical reasons (they vomited during amino acid infusions).

The characteristics of the participants’ parents are given in Table 1. None of the mothers smoked during their pregnancies. The characteristics of participants are given in Table 2. There was no inter-group difference for age or sex distribution. As anticipated, gestational age at delivery was lower in cases than in controls. Conversely, birth weights did not differ. The birth weights did not differ after adjustment on gestational age: 3535 ± 516 g in cases vs 3404 ± 430 g in controls. The body mass indexes were identical. Fasting plasma glucose, insulin, and glucagon were similar and within normal range. One case and 2 controls displayed impaired glucose tolerance during Oral Glucose Tolerance Test. During exercise test, systolic/diastolic blood pressures increased similarly in the 2 groups: from 116±14/71±14 mmHg to 127±15/71±12 mmHg in cases, vs from 118±16/68±12 mmHg to 126±14/70±10 mmHg in controls. Urinary albumin excretions varied similarly: from 2 (range 2-20) to 35 (5-810) µg/min in cases vs from 2 (2-3) to 64 (4-312) µg/min in controls. The 24-hour ambulatory blood pressure were not different showing diurnal and nocturnal blood pressures respectively at 117±10/71±4 mmHg and 114±4/64±8 mmHg in cases and 118±8/72±7 mmHg and 113±8/66±7 mmHg in controls. Kidney volumes were similar in both groups (Table 2). No morphological anomaly was detected on the kidneys and urinary tracts during ultrasound examination.

Renal tests: Systolic blood pressures and urinary albumin excretions were slightly, but not statistically higher in cases than in controls. While urinary excretions of sodium and potassium, and plasma renin were similar between groups, plasma aldosterone was higher in cases than in controls. However, the plasma renin/aldosterone ratio was similar (Table 3).

The individual changes in renal parameters are given in Figure 1. While the baseline GFR values did not differ, they increased less in response to amino acids in cases compared to controls: from 102±14 to 111±17 ml/min (+8±13%, p=0.019) vs from 108±17 ml/min to 128±23 ml/min (+19±7%, p=0.002, inter-group difference p=0.009, Figure 1A). The ERPF did similarly: from 509±58 to 536±114 ml/min (+5±9%, p=0.016) vs from 536±114 to 620±140 ml/min (+16±11%, p=0.002 inter-group difference p=0.0035, Figure 1B). The baseline FF (0.20±0.03 in cases vs 0.21±0.03 in controls) were not altered: +3±8 (p=0.14) vs +3±11 % (p=0.26, inter-group difference p=0.029, Figure 1C). In cases, MAP varied from 88±6 to 91±8 mmHg (+2±5%, p=0.061), while they declined from 86±6 to 84±5 mmHg in controls (-2±3%, p=0.029, inter-group difference p=0.019, Figure 1D). Consequently, RVR in cases did not vary: from 0.113±0.015 to 0.110±0.017 mmHg/ml/min, (-3±9%, p= 0.1), while they declined from 0.106±0.024 to 0.091±0.019 mmHg/ml/min in controls (-14±8%, p=0.002, inter-group difference p=0.001, Figure 1E).

We examined the relationship between renal hemodynamic changes and birth weight. It was significantly different in cases compared to controls (p = 0.009): the relationship between changes in GFR during amino acid infusion and birth weight was highly significant in cases (r = 0.61, p = 0.006), while it was not in controls (r = -0.08, p=0.78, Figure 2). These analyses were not altered, when birth weight was adjusted on gestational age. The relationship was not different according to sex (p = 0.70). There was no
association between height and changes in GFR \(r: 0.27; 95\%CI – 0.06; 0.54, p = 0.11\).

**DISCUSSION**

We found that fetal exposure to maternal type 1 diabetes was associated with a reduced renal reserve in offspring of humans at adult age. Our results in humans are consistent with what has been observed in rats regarding the impact of moderate hyperglycemia during fetal development on adult kidney dysfunction (5). They suggest a reduced number of nephrons in offspring of type 1 diabetic mothers, even though the precise quantification was not performed, as non invasive methods are not currently available in humans. We recognize that a reduced functional reserve does not mean a reduced nephron number in absence of direct association in humans. However, a reduced functional reserve in humans indicates an already dilated renal vasculature resulting in global hyperfiltration, or an already established glomerular disease with reduced glomerular filtration rate (10). In type 1 diabetes, global hyperfiltration was reported by Mogensen and Christensen as predictive of clinical proteinuria (12), and Sackmann et al reported a reduced functional reserve both in normotensive, normoalbuminuric subjects with recent type 1 diabetes (those prone to nephropathy displaying global hyperfiltration), and in proteinuric subjects with long lasting type 1 diabetes (those with an already reduced GFR) (13). The participants with microalbuminuria studied by these authors were on ACE inhibitors, making data interpretation difficult, since ACE inhibitors can alter kidney function of such patients (16), and since renal functional reserve can be altered by these drugs (17). Studies conducted in animals (18,19) support the view that the glomeruli of subjects such those with reduced functional reserve undergo individual hyperfiltration, a hemodynamic condition that favors glomerulosclerosis, hypertension and high reno-vascular risk (1,11). The possibility that permanent hyperfiltration occurs within each nephron of the offspring of type 1 diabetic mothers is supported here by the lack of inter-group difference for baseline GFR, while the renal vasodilatation produced by amino acid infusion was severely reduced in cases, compared to controls. In rats, a reduced number of nephrons provoked by hyperglycemia during fetal development favors salt-sensitive hypertension at adult age (5). Salt sensitive hypertension was related to glomerular dysfunction in human studies (20). Here, we found no difference for blood pressures or urinary albumin excretions, but our study was not powered to find out such differences. Oppositely, a large prospective study in Denmark reported that offspring of type 1 diabetic mothers displayed elevated systolic blood pressures (21), although their kidney function was not studied. Also, Pima Indians with type 2 diabetes exposed in utero to maternal diabetes developed more frequently microalbuminuria and higher blood pressure than those who were not exposed (22). Thus, large-scale studies are now required on blood pressure and albuminuria of offspring of type 1 diabetic mothers. Note we did not replicate our initial findings regarding glucose tolerance in offspring of type 1 diabetic mothers (9). Since this earlier report, several public health interventions were efficient in France to reduce incidence of obesity and diabetes. The offspring we studied might have been especially sensitive to these measures (their mean BMI was 22.5 kg/m² thereby reducing their risk for glucose intolerance). Also, the present study was not sized to address the issue of glucose intolerance in the participants.

The role of birth weight on kidney function at adulthood must be delineated. Hughson et al (3) reported in an autopsy study an association between birth weight and glomerular number and size. Here, we
observed a positive correlation between renal functional reserve and birth weight in offspring of type 1 diabetic mothers, but not in their controls, despite similar birth weight. Thus, birth weight may influence kidney function at adulthood only in subjects exposed in utero to maternal diabetes. Moderate hyperglycemia during fetal development may be permissive for birth weight to impact on adult kidney function.

We studied offspring of type 1, rather than type 2 diabetic mothers (22), taking offspring of type 1 diabetic fathers as controls as we did earlier (9), to avoid confusion due to the genetic background of hypertension, a condition linked both to kidney disease and to type 2 diabetes. Thus, our study supports a direct impact of hyperglycemia, or its associated metabolic abnormalities (23-25) during fetal development on kidney dysfunction later in life.

We could not establish a relationship between the level of hyperglycemia during pregnancy and kidney dysfunction at adulthood. Uncontrolled hyperglycemia in type 1 diabetic mothers favors renal malformations (26). None of our participants had morphological kidney anomaly. The average term for delivery of type 1 diabetic mothers was 37 weeks (range 33-40) without frank macrosomia or microsomia, and birth weights were not different between groups, suggesting optimized blood glucose control. However, we could not quantify retrospectively the level of glycemic control attained during these pregnancies. Half of them occurred before 1980, a time when neither glycated hemoglobin nor self monitoring of blood glucose were available for diabetes care.

Hyperglycemia induces several biochemical and hemodynamic abnormalities (23-25) that may account for the renal changes reported here. In rats, exposure in utero to hyperglycemia and reduced nephron numbers in offspring (4) was associated with alterations of the expressions of IGFs and their receptors in fetal kidney (27). Alterations in angiogenesis may also be plausible. In the model of chicken chorioallantoid membrane, we did not find that high glucose levels altered the expression of several growth factors involved in angiogenesis, but increased apoptosis and decreased proliferation of endothelial cells occurred (8). Whether hyperglycemia during fetal development provokes epigenetic alterations leading to renal dysfunction at adulthood remains to be elucidated (28).

Plasma aldosterone was higher in cases than in controls, while plasma renin did not differ significantly. These data are exploratory, and they may be due to a type 1 error. However, such a figure is often encountered in people with a volume-dependent hypertension (29). We found no relationship between plasma aldosterone, renin, and sodium or potassium urinary excretions, or blood pressure values (data not shown). However, we did not measure extra-cellular volumes of the participants to this study, and sodium intake was not controlled. Further investigations are required in this respect. Interestingly, epigenetic modifications of the renin-angiotensin system were reported in experimental settings (30), and an inverse relationship was reported between birth weight and plasma aldosterone at adult age in humans (31).

In conclusion, this study supports that moderate hyperglycemia (or its related metabolic alterations) during fetal development may alter kidney function in human adults. As pregnancy is now frequent in type 1 diabetic women, we will have to pay attention on the renal and vascular status of their offspring at adulthood.

Author Contributions: Charbel Abi Khalil researched data, contributed to discussion, wrote manuscript, reviewed manuscript; Florence Travert researched data, contributed
to discussion, reviewed manuscript; Sabrina Fetita researched data, contributed to discussion; François Rouzet researched data, reviewed manuscript; Raphaël Porcher researched data, contributed to discussion, reviewed manuscript; Jean-Pierre Riveline researched data; Samy Hadjadj researched data, contributed to discussion, reviewed manuscript; Etienne Larger researched data, contributed to discussion, reviewed manuscript; Ronan Roussel contributed to discussion, reviewed manuscript; Patrick Vexiau contributed to discussion; Dominique Le Guludec researched data, reviewed manuscript; Jean-François Gautier researched data, contributed to discussion, wrote manuscript, reviewed manuscript; Michel Marre researched data, contributed to discussion, wrote manuscript, reviewed manuscript.

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Figure 1: Kidney function of offspring of type 1 diabetic mothers (cases, left) and of offspring of type 1 diabetic fathers (controls, right) in basal conditions and during infusion of amino acids (stimulated). Data are given as median values with box plots and individual values. Panel A: changes in Glomerular Filtration Rate (GFR), intra-group changes in cases: +8±13%, p=0.019 and in controls: +19±17%, p=0.002, inter-group comparison: p=0.009; panel B: changes in Effective Renal Plasma Flow (ERPF), intra-group changes in cases: +5±9%, p=0.016 and in controls: +16±11%, p=0.002, inter-group comparison: p=0.0035; panel C: changes in Filtration Fraction (FF), intra-group changes in cases: +3±8%, p=0.14 and in controls: +3±8%, p=0.26, inter-group comparisons: p=0.92; panel D: changes in Mean Arterial Pressure (MAP), intra-group changes in cases: +2±5%, p=0.061 and in controls: -2±3%, p=0.029, inter-group comparison: p=0.019; panel E: changes in Renal Vascular Resistances (RVR), intra-group changes in cases: -3±9%, p=0.1 and in controls: -14±8%, p=0.002, inter-group comparison: p=0.001.

Figure 2: Relationship between birth weight and GFR relative changes during test in offspring of type 1 diabetic mothers (left panel) and of type 1 diabetic fathers (right panel). Solid lines represent the regression lines and dashed lines the 95% prediction intervals. Pearson correlation coefficient in offspring of type 1 diabetic mothers: r=0.61 (p=0.006); in offspring of type 1 diabetic fathers: r=-0.08 (p=0.76).

REFERENCES


Table 1. Characteristics of the parents of participants:

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetic Mothers (n=19)</th>
<th>Type 1 Diabetic Fathers (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (years)</td>
<td>53 (50 – 65)</td>
<td>55 (45 – 65)</td>
</tr>
<tr>
<td>Age at diabetes onset (years)</td>
<td>12 (4 – 24)</td>
<td>16 (3 - 33)</td>
</tr>
<tr>
<td>Age at offspring conception (years)</td>
<td>28 (19 – 35)</td>
<td>29 (25 - 41)</td>
</tr>
<tr>
<td>Number of patients with nephropathy</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

Data are given as median (range) values. Nephropathy was defined as present or past clinical proteinuria.

Table 2. Characteristics of the participants (part one).

<table>
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<th>Offspring of type 1 diabetic fathers (n=18)</th>
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</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>5/14</td>
<td>9/9</td>
<td>0.18</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>24 (18 - 41)</td>
<td>25 (18 - 37)</td>
<td>0.96</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)*</td>
<td>37 (33 - 40)</td>
<td>40 (37 - 40)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Birth weight (grams)*</td>
<td>3200 (2750-4270)</td>
<td>3300 (2700-4540)</td>
<td>0.29</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>22.6 (17.9-29.9)</td>
<td>22.4 (19-27.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mmol/L)†</td>
<td>4.5 (0.4)</td>
<td>4.5 (0.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>Fasting Plasma Insulin (µU/mL) †</td>
<td>5.0 (1.6)</td>
<td>4.6 (2.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>Fasting Plasma Glucagon (pg/mL) †</td>
<td>130.4 (28.1)</td>
<td>151.1 (41.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Kidney Volume (mL) †</td>
<td>Right Kidney 157.0 (35.5)</td>
<td>165.0 (42.2)</td>
<td>0.65</td>
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<tr>
<td></td>
<td>Left Kidney 155.9 (34.0)</td>
<td>151.1 (18.6)</td>
<td>0.71</td>
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Data are given as counts, median (range) [*], or mean (standard deviation) [†].

Table 3: Characteristics of the participants at the time of renal tests (part two).

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<th>Offspring of type 1 diabetic mothers (n=19)</th>
<th>Offspring of type 1 diabetic fathers (n=18)</th>
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<tr>
<td>Systolic BP/Diastolic BP (mmHg)*</td>
<td>118 ± 6/72 ± 7</td>
<td>114 ± 7 /70 ± 8</td>
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<tr>
<td>Urinary Sodium (mmol/24 hours)*</td>
<td>136 ± 78</td>
<td>131 ± 66</td>
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<tr>
<td>Urinary Potassium (mmol/24 hours)*</td>
<td>82 ± 58</td>
<td>72 ± 54</td>
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<tr>
<td>Urinary Albumin (mg/24 hours) †</td>
<td>9 (5 to 14)</td>
<td>5 (4 to 8)</td>
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<tr>
<td>Plasma Renin (pg/ml) †</td>
<td>7 (3 to 78)</td>
<td>7 (3 to 26)</td>
<td>0.75</td>
</tr>
<tr>
<td>Plasma Aldosterone (pg/ml) †</td>
<td>109.6 (56.5 to 138)</td>
<td>63.1 (35.8 to 83)</td>
<td>0.036</td>
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<tr>
<td>Renin/Aldosterone ratio†</td>
<td>0.15 (0.01 to 0.78)</td>
<td>0.15 (0.02 to 0.29)</td>
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Data are mean ± SD [*], or median (range) [†].
Fig 1A:

**GFR (ml/min)**

<table>
<thead>
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<td>50</td>
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**Offspring of type 1 diabetic mothers**

**Offspring of type 1 diabetic fathers**

Fig 1B:

**ERPF (ml/min)**

<table>
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<tr>
<td>900</td>
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**Offspring of type 1 diabetic mothers**

**Offspring of type 1 diabetic fathers**

Fig 1C:

**FF**

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</table>

**Offspring of type 1 diabetic mothers**

**Offspring of type 1 diabetic fathers**
Fig 1D:

Offspring of type 1 diabetic mothers

Offspring of type 1 diabetic fathers

MAP (mmHg)

Basal Stimulated

70 80 90 100 110

MAP (mmHg)

Basal Stimulated

70 80 90 100 110

Fig 1E

Offspring of type 1 diabetic mothers

Offspring of type 1 diabetic fathers

RVR (mmHg/ml/min)

Basal Stimulated

0.050 0.075 0.100 0.125 0.150

RVR (mmHg/ml/min)

Basal Stimulated

0.050 0.075 0.100 0.125 0.150

Fig 2

Offspring of type 1 diabetic mothers

Offspring of type 1 diabetic fathers

GFR relative changes (%)

Birth weight (g)

GFR relative changes (%)

Birth weight (g)