Maternal but Not Paternal Association of Ambulatory Blood Pressure With Albumin Excretion in Young Offspring With Type 1 Diabetes

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OBJECTIVE — Familial predisposition to hypertension has been associated with the development of diabetic nephropathy in adults, but there are limited data in adolescents. Our aim was to assess whether parental ambulatory blood pressure (ABP) was associated with ABP and albumin excretion in young offspring with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Twenty-four-hour ABP monitoring was performed in 509 young offspring (mean ± SD age 15.8 ± 2.3 years) with type 1 diabetes, 311 fathers, and 444 mothers. Systolic (SBP) and diastolic blood pressure (DBP) measurements during 24 h, daytime, and nighttime were calculated. Three early morning urinary albumin-to-creatinine ratios (ACRs), A1C, and anthropometric parameters were available for the offspring.

RESULTS — All paternal ABP parameters, except for nighttime SBP, were independently related to the offspring’s ABP (24-h SBP 𝜒 = 0.18, 24-h DBP 𝜒 = 0.22, daytime SBP 𝜒 = 0.25, daytime DBP 𝜒 = 0.23, and nighttime DBP 𝜒 = 0.18; all 𝑃 < 0.01). Maternal 24-h DBP ( Potion = 0.04), daytime DBP ( Potion = 0.04), and nighttime SBP ( Potion = 0.001) were related to the corresponding ABP parameter in the offspring. Significant associations were found between the offspring’s logACR and maternal ABP. The association with 24-h DBP ( Potion = 0.16, Potion = 0.02), daytime DBP ( Potion = 0.16 Potion = 0.02), and nighttime DBP ( Potion = 0.15 Potion = 0.03) persisted even after adjustment for the offspring’s ABP. Mothers of offspring with microalbuminuria had higher ABP than mothers of offspring without microalbuminuria (all 𝑃 < 0.05).

CONCLUSIONS — In this cohort, parental ABP significantly influenced offspring blood pressure, therefore confirming familial influences on this trait. In addition, maternal ABP, particularly DBP, was closely related to ACR in the offspring, suggesting a dominant effect of maternal genes or an effect of the intrauterine environment on microalbuminuria risk.

Microalbuminuria remains the best predictive marker for the development of overt diabetic nephropathy and represents an independent risk factor for cardiovascular disease (CVD) (1). Evidence indicating that the risk for the development of microalbuminuria and diabetic nephropathy is partly genetic and may relate to the inheritance of genes associated with CVD is accumulating (2). Several studies have shown familial aggregation of renal disease in type 1 diabetes (2,3), and a family history of hypertension, dyslipidemia, insulin resistance, type 2 diabetes, or a cluster of these cardiovascular risk factors has been associated with an increased risk of diabetic nephropathy (2,4).

In particular, several lines of evidence have highlighted the fact that predisposition to hypertension might be a risk factor for the development and progression of diabetic nephropathy in individuals with type 1 diabetes (4–8), and, therefore, the inheritance of blood pressure–related genes might also contribute to abnormal albumin excretion and renal damage. Parental hypertension has been associated with changes in renal hemodynamics (9) and with the development of diabetic nephropathy in individuals with type 1 diabetes (5–8). However, the relationship between family history of hypertension and albuminuria has not been confirmed in all studies (10) and in the majority of studies, confirmation has been based on a single blood pressure assessment in the parents (7,8) or on a questionnaire-based history of parental hypertension. In addition, the effect of parental blood pressure, as was that of other heritable factors, has been mainly investigated in adults with diabetes, whereas it has been seldom studied in children and adolescents (11,12).

Understanding the role of such a familial/genetic effect of blood pressure on renal disease would be particularly important in adolescents with type 1 diabetes, who represent a vulnerable group at risk of vascular complications (13). In particular, the identification of familial/genetic factors predisposing to diabetic nephropathy and the understanding of their interplay with glycemic control and the hormonal and metabolic changes of puberty could help in identifying subjects at higher risk for diabetes complications, who therefore require more intensive treatment to prevent them. The aim of the present study was to assess whether parental ambulatory blood pressure (ABP) was related to variations in the same trait and in albumin excretion rates in young
offspring with childhood-onset type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — The study population was composed of young people with type 1 diabetes and their parents recruited in the Nephropathy Family Study (NFS). The NFS was set up in 2000 as part of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes Inflammation Laboratory: Genetic Resource Investigating Diabetes (GRID) study (14). Between 2000 and 2005, 1,066 subjects, aged 10–16 years, who had developed type 1 diabetes before the age of 16 years, were recruited throughout four English regions (East Anglia, Birmingham, Bristol, and Oxford) for detailed phenotypic and genetic study of the early pathogenesis of microalbuminuria. Subjects with insulin-treated diabetes due to other pathological conditions were excluded. Similarly, children with chronic renal disease or other chronic diseases, which are likely to affect renal function, were excluded. The median duration of follow-up is currently 2.6 (interquartile range 1.8–3.8) years.

The longitudinal study schedule comprised annual collection of three consecutive early-morning urine specimens for centralization of measurement of the albumin-to-creatinine ratio (ACR) and blood samples for measurements of A1C. Annual assessments also included measurements of height and weight. Parents of the NFS children were also recruited, and they underwent clinical assessment, including height and weight.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was performed in a subgroup of offspring and parents from the NFS. Specifically, it was done in 509 children, 311 fathers, and 444 mothers, for a total of 250 complete trios.

Ethics approval was obtained from the regional ethics committee, with written consent from the parents and assent from the children.

**24-h ABPM**

Each child and parent was fitted with a portable noninvasive oscillometric recorder (DiaSys Integra II, Novacor, Rueil-Malmaison, France). The validity of measurements with this monitor was confirmed previously (15). An appropriate cuff size was fitted on the basis of the arm circumference of each subject and applied on the nondominant arm. ABPM was performed during a normal day with typical activities, but subjects were asked to avoid vigorous exercises and to keep their arm relaxed during each daytime inflation. A measurement was automatically repeated if values were outside the following intervals of measurement validity: systolic blood pressure (SBP) <30 mmHg; diastolic blood pressure (DBP) <30 and >150 mmHg; heart rate <35 and >250 bpm; pulse pressure <10 and >150 mmHg at SBP <120 mmHg; and pulse pressure <15 and >150 mmHg at SBP >120 mmHg. Furthermore, all subjects were asked to record in a diary the time they went to bed and the time they awoke, as well as exercise periods and quality of their sleep.

Blood pressure readings were obtained at 30-min intervals during the daytime (0700–2200) and at 60-min intervals during the nighttime (2200–0700). At the end of the ABPM, the monitor was downloaded to a personal computer equipped with DiasySoft software for analysis of the measurements. All readings taken during 24 h were used to calculate mean 24-h SBP and DBP whereas mean daytime and nighttime SBP and DBP were calculated based on the awake and asleep periods, calculated from diary times. To characterize the circadian blood pressure rhythm, the percentage of the nocturnal fall in SBP and DBP was calculated using the formula: daytime SBP [or DBP] − nighttime SBP [or DBP]/daytime SBP [or DBP] × 100.

Patients were classified as dippers if their daytime SBP and/or DBP decreased by at least 10% during the night; all other subjects were classified as nondippers.

Hypertension in the parents was defined as current use of antihypertensive medication or an elevated ACR, defined as 24-h blood pressure >135/85 mmHg (15). Hypertensive fathers and mothers were excluded from all analyses, apart from those assessing prevalence of hypertension.

**Albumin and creatinine**

All urine samples were assessed centrally in a single reference laboratory. Samples were stored at −70°C before analysis. Albumin was measured centrally by a double-antibody enzyme-linked immunosorbent assay method. The within- and between-assay coefficients of variation (CV) were 6 and 12%, respectively. Creatinine was initially measured using a modified Jaffe method (Unimate 7; Roche Diagnostic Systems, Basel, Switzerland) on a Cobas Mira (Roche Diagnostic Systems) automated spectrophotometer (CV 2% at 2.2 mmol/l) and, more recently, by stable isotope dilution electrospray mass spectrometry-mass spectrometry (14).

**A1C**

All samples were analyzed centrally in Cambridge on a TOSOH G7 analyzer (Tosoh Bioscience, Redditch, U.K.), using high-performance liquid chromatography and absorbance change detection and Diabetes Control and Complications Trial–aligned methods. The normal range was 4.9–6.3%, and the CVs were 4.8 and 6.6% at A1C levels of 5.5 and 10.1%, respectively.

**Calculations**

ACR was summarized as the geometric mean of three consecutive early morning urine samples and log-transformed for analyses. Microalbuminuria was defined as an ACR between 3.5 and 35 mg/mmol in male patients and between 4.0 and 47 mg/mmol in female patients in two of three consecutive early morning urine collections during an annual assessment (corresponding to an overnight albumin excretion rate between 20 and 200 μg/min) (13). The mean of all A1C measurements for the offspring collected from the time of recruitment in the study until the last visit was calculated and included in the analyses.

**Statistical analyses**

Analyses were performed using SPSS for Windows (version 16.0; SPSS, Chicago, IL). Data are summarized as means ± SD or median (interquartile range) unless otherwise specified. Nonnormally distributed variables, such as ACR, were log-transformed before analysis. Age and sex adjustments for blood pressure were performed by calculating residuals. Comparisons between different groups were performed by unpaired t tests, whereas comparisons across categories were made using χ² or Fisher exact tests. Multiple regression analysis was applied to test the independent association between parental ABP and offspring ABP and albumin excretion, with adjustment for other confounding variables. For this analysis, data are expressed as the regression coefficient β. P < 0.05 was taken as significant for all analyses.

**RESULTS** — ABPM was performed in 509 children, 311 fathers, and 444 mothers, for a total of 295 matched father–offspring pairs, 411 matched mother–
Maternal ABP and offspring albumin excretion

Table 1—Multiple regression analysis: independent effect of parental ABP on the offspring’s ABP

|                  | Fathers |                  | Mothers |                  |
|------------------|---------|------------------|---------|------------------|
|                  | Model 1 | Model 2†         | Model 1 | Model 2†         |
|                  | $R^2$   | $R^2$            | $\beta$ | $P$ value        |
|                  |         |                  |         |                  |
| 24-h SBP         | 0.115   | 0.149            | 0.18    | 0.005            |
| 24-h DBP         | 0.119   | 0.166            | 0.22    | 0.001            |
| Daytime SBP      | 0.073   | 0.134            | 0.25    | <0.001           |
| Daytime DBP      | 0.055   | 0.106            | 0.23    | 0.001            |
| Nighttime SBP    | 0.114   | 0.195            | 0.04    | 0.5              |
| Nighttime DBP    | 0.136   | 0.108            | 0.18    | 0.005            |

Dependent variable: offspring’s ABP. *Model 1: independent variables are child’s age, sex, A1C, and BMI SD score. †Model 2: as for model 1 plus parental ABP parameter.

The association between parental blood pressure and ACR in the offspring was further investigated by comparing parents of offspring who developed microalbuminuria (both persistent and transient cases of microalbuminuria were considered) during the study period with parents of offspring who remained normoalbuminuric. Specifically, 38 fathers of patients with microalbuminuria (MA+) were compared with the remaining 212 fathers of patients with normoalbuminuria (MA−). Fathers of MA+ patients were similar in age, height, weight, and BMI compared with fathers of MA− patients (supplementary Table 2). There was no significant difference in any ABPM parameter between the two groups (Fig. 1). Similarly, the nocturnal fall in blood pressure (SBP fall [MA+ vs. MA− group] 15.2 ± 7.6 vs. 14.3 ± 7.3%, P = 0.4; DBP fall 15.2 ± 8.2 vs. 16.3 ± 8.4%, P = 0.4) and the percentage of hypertensive fathers was not different between the two groups (MA+ vs. MA− group 41.7 vs. 30.9%, P = 0.4).

Mothers of MA+ patients were similar in age, height, weight, and BMI compared with mothers of MA− patients.

Parents’ ABP and offspring’s microalbuminuria status

The association between parental blood pressure and ACR in the offspring was further investigated by comparing parents of offspring who developed microalbuminuria (both persistent and transient cases of microalbuminuria were considered) during the study period with parents of offspring who remained normoalbuminuric. Specifically, 38 fathers of patients with microalbuminuria (MA+) were compared with the remaining 212 fathers of patients with normoalbuminuria (MA−). Fathers of MA+ patients were similar in age, height, weight, and BMI compared with fathers of MA− patients (supplementary Table 2). There was no significant difference in any ABPM parameter between the two groups (Fig. 1). Similarly, the nocturnal fall in blood pressure (SBP fall [MA+ vs. MA− group] 15.2 ± 7.6 vs. 14.3 ± 7.3%, P = 0.4; DBP fall 15.2 ± 8.2 vs. 16.3 ± 8.4%, P = 0.4) and the percentage of hypertensive fathers was not different between the two groups (MA+ vs. MA− group 41.7 vs. 30.9%, P = 0.4).

Mothers of MA+ patients were similar in age, height, weight, and BMI compared with mothers of MA− patients.
Parental blood pressure could contribute to the risk of diabetic nephropathy in offspring through an effect on the offspring’s blood pressure and/or through other mechanisms (4). However, previous studies have not always included adjustments for offspring blood pressure. Where these adjustments were made, as in the EURODIAB study (4), the association between parental hypertension and albuminuria in the offspring was attenuated and lost statistical significance, suggesting that most of the influence of parental blood pressure is mediated through an effect on the offspring’s blood pressure. In the present study, we also found that after adding the offspring’s blood pressure into the regression model, there was an attenuation of the effect of the intrauterine environment on the risk of microalbuminuria in the offspring. The stronger association we found between maternal ABP and ACR in the offspring might be related to a dominant influence of maternal genes. Mitochondria-specific genes could be potential candidates (16), but imprinted genes, in which only the maternal allele is expressed, might be also implicated in the predisposition to microalbuminuria in the offspring.

Whereas familial predisposition to hypertension may indicate a genetic effect, the potential contribution of environmental and behavioral components also needs to be considered (21,22). The effects of the intrauterine environment might contribute to the stronger influence of maternal blood pressure on albumin excretion (21). However, a greater postnatal sharing of environmental factors between mothers and offspring than between fathers and offspring might also explain the stronger maternal influence (22).

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Maternal ABP and offspring albumin excretion

The present study is one of the few reports on the role of parental blood pressure in albumin excretion in a cohort of young offspring with type 1 diabetes. Previously, the effect of familial factors on the risk of developing diabetes complications in the offspring has been assessed mainly in adults, with only a few investigations including young people with diabetes. Rudberg et al. (11) found that a family history of hypertension and CVD was associated with an increased prevalence of microalbuminuria in a cohort of 300 offspring with type 1 diabetes. In an early report from the Oxford Regional Prospective Study, there was no effect of parental absolute ABP values or of parental hypertension on albumin excretion in young offspring with type 1 diabetes (12). The different findings of the latter study compared with those of the present study might be related to differences in the ages of the populations studied or differences in the ACR range between the two studies.

In our study, as in previous studies (4), the association between parental blood pressure and albumin excretion in the offspring was weak, suggesting that, even though there is an effect of parental blood pressure, this is likely to be just one of several factors implicated in the complex pathogenesis of diabetic nephropathy. This assumption is supported by the observation that the presence of a clustering of several CVD risk factors in the parents has a stronger effect on the risk for diabetic nephropathy in the offspring than the heritability of a single factor, such as hypertension alone (2).

A stronger effect of parental blood pressure emerged from studies in which the offspring had a more advanced stage of diabetic nephropathy, characterized by clinical proteinuria (7). Therefore, it could be argued that the effect of parental blood pressure might become more evident with further follow-up of our cohort and when more individuals with persistent microalbuminuria or macroalbuminuria are identified.

In summary, in the present study we found that in a cohort of young people with childhood-onset type 1 diabetes, parental ABP significantly influenced the offspring’s blood pressure, therefore confirming a familial influence on this trait. Of particular interest was the finding that maternal, but not paternal, ABP was closely related to albumin excretion and the presence of microalbuminuria in the offspring, suggesting a dominant effect of maternal genes or an effect of the intrauterine environment on the offspring’s risk of developing diabetic nephropathy.

These findings underline the importance of considering familial factors, in particular blood pressure, when one is estimating the renal risk in young offspring with diabetes. The identification of familial risk factors predisposing to nephropathy could help in identifying subjects at higher risk for diabetes complications, who might require more intensive treatments, including antihypertensive drugs, to prevent diabetic micro- and macrovascular complications.

Acknowledgments—The NFS is funded by the Juvenile Diabetes Research Foundation (JDRF), Wellcome Trust, and Diabetes UK. M.L.M. is the recipient of a European Society for Pediatric Endocrinology (ESPE) research fellowship (sponsored by Novo Nordisk AS) and an ESPE Visiting Scholarship.

No other potential conflicts of interest relevant to this article were reported.

We acknowledge the study field workers, pediatricians, physicians, and diabetes nurse specialists involved in the NFS, JDRF, Wellcome Trust, the National Institute for Health Research Cambridge Comprehensive Biomedical Research Centre and Novacor U.K. We thank John Todd and Jason Cooper from the JDRF/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, U.K.

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