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Short communication

Maternal diabetes alters birth weight in glucokinase-deficient (MODY2) kindred but has no influence on adult weight, height, insulin secretion or insulin sensitivity

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Abstract

Aims/hypothesis. Altered fetal insulin secretion caused by fetal or maternal glucokinase mutations influence birth weight. Here, we attempt to answer two additional questions: firstly, whether this variation in birth weight (from low birth weight to macrosomia) has an effect on adult height or weight. Secondly, whether maternal hyperglycaemia during fetal life has an effect on metabolic phenotypes of the adult offspring.
Methods. We studied 447 family members from 37 MODY2 kindred, divided into four groups according to the presence or absence of a glucokinase mutation in the subject (S + or S–, respectively) and his/her mother (M + or M–). Birth weight data were obtained from a questionnaire sent to the mothers.
Results. Birth weight was reduced in the presence of a fetal mutation (M–S +) and increased in the presence of a maternal mutation (M + S–). These effects are additive as similar birth weights were observed in M + S + and M–S– offspring. Adult height, weight or body mass index (weight/height^2) were, however, similar in the four groups of subjects. Non-diabetic adult offspring, regardless of the glycaemic status of the mothers (M + S– or M–S–), had similar insulin secretion, insulin sensitivity, blood pressures and lipid profiles. These variables as well as the severity of hyperglycaemia were similar in adult M + S + and M–S + MODY2 subjects.
Conclusion/Interpretation. Maternal environment and fetal genotypes could alter growth in utero by changing fetal insulin secretion but these effects do not result in a persistent programming in latter life. [Diabetologia (2000) 43: 1060–1063]

Keywords MODY, glucokinase mutations, low birth weight, macrosomia, gestational diabetes, insulin secretion defect.

Maternal intrauterine environment and fetal genotypes influence size at birth and birth weight. It is well established that poor maternal nutrition is associated with reduced intrauterine growth and that maternal hyperglycaemia results in macrosomia. It was, however, recently observed that mutations in the glucokinase gene in the fetus result in reduced birth weight [1], probably by affecting insulin-mediated fetal growth [2]. Variations of birth weight and size at birth are associated with metabolic phenotypes late in life. Retrospective studies have shown low birth weight to be associated with insulin resistance and Type II (non-insulin-dependent) diabetes mellitus in adulthood [3]. It has been proposed that this association results from a metabolic adaptation to poor fetal nutrition [3] or a direct effect of fetal genes or both [2]. A maternal diabetic environment during fetal life, which is often associated with macrosomia, has, however, been reported in Pima Indians to predispose the offspring to diabetes late in life [4].

Glucokinase mutations cause maturity onset diabetes of the young Type II (MODY2), a familial auto-

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Abbreviations: MODY2, maturity onset diabetes of the young Type II; HOMA, homeostasis model assessment.

Table 1. Influence of maternal (M+) and fetal (S+) glucokinase mutation on childhood and adulthood height, weight and BMI

	M+S+	M–S+	M+S–	M–S–	*p*
Group 1: age 2–12 years (n = 85):					
Sex: male/female	14/9	9/9	13/13	8/10	0.75
Age (years)	8 ± 3 (9/4–12)	8 ± 2 (8/3–11)	9 ± 2 (10/5–12)	8 ± 3 (9/2–12)	0.57
Height (cm)	127 ± 16 (131/96–146)	127 ± 13 (126/100–150)	124 ± 18 (126/73–150)	125 ± 20 (130/85–149)	0.95
Weight (Kg)	26 ± 9 (26/15–47)	26 ± 7 (23/18–39)	24 ± 9 (22/8–50)	26 ± 9 (27/10–44)	0.92
BMI (Kg/m^2)	16.9 ± 2.8 (15.7/13.6–23.0)	16.1 ± 1.6 (15.8/14.0–19.9)	15.6 ± 2.5 (15.3/12.6–22.2)	16.3 ± 1.5 (16.0/13.8–19.8)	0.53
Group 2: age 13–24 years (n = 125):					
Sex: male/female	17/18	21/11	15/15	15/13	0.50
Age (years)	18 ± 3 (17/13–23)	18 ± 3 (19/13–23)	19 ± 4 (19/13–24)	18 ± 4 (19/13–23)	0.42
Height (cm)	166 ± 9 (164/147–182)	164 ± 12 (163/130–180)	169 ± 14 (170/135–194)	165 ± 10 (165/145–180)	0.43
Weight (Kg)	55 ± 9 (55/36–66)	53 ± 12 (55/25–73)	61 ± 14 (60/27–90)	56 ± 12 (55/36–88)	0.18
BMI (Kg/m^2)	20.0 ± 2.1 (19.9/14.6–23.4)	19.6 ± 2.6 (19.7/14.7–26.2)	21.0 ± 3.1 (20.9/14.8–28.4)	20.4 ± 2.6 (20.3/16.9–27.8)	0.33
Group 3: age 25–82 years (n = 237):					
Sex: male/female	32/53	38/33	24/18	17/22	0.11
Age (years)	45 ± 13 (41/25–80)	45 ± 11 (43/27–82)	43 ± 12 (42/25–71)	40 ± 10 (36/25–60)	0.07
Height (cm)	165 ± 10 (164/145–189)	166 ± 9 (166/150–183)	169 ± 9 (169/154–190)	168 ± 8 (168/154–188)	0.25
Weight (Kg)	64 ± 12 (62/36–106)	65 ± 12 (63/46–95)	70 ± 13 (69/49–108)	68 ± 15 (66/47–100)	0.19
BMI (Kg/m^2)	23.4 ± 3.5 (23.0/15.8–34.7)	23.3 ± 3.3 (22.8/18.3–32.9)	24.4 ± 3.7 (24.2/18.3–33.2)	23.8 ± 4.5 (23.0/17.3–32.7)	0.51

Data expressed as means ± SD (median/and range). Statistics are contingency-table chi-squared test (sex) and ANOVA

somal dominant form of hyperglycaemia with onset in the early years of life and high penetrance [5]. In MODY2 women, hyperglycaemia is always present during pregnancy. This makes MODY2 an attractive model for assessing the influence of maternal environment and its interaction with fetal genotype on anthropometric and metabolic phenotypes late in life, both in affected and unaffected offspring.

We attempt in this study to answer two questions: firstly, whether a variation in birth weight (from low birth weight to macrosomia) resulting from altered fetal insulin secretion caused by fetal and maternal genetic effects (glucokinase mutations) has an effect in the adult height or weight of offspring. Secondly, whether maternal hyperglycaemia during fetal life has an effect on the glucose tolerance, insulin secretion, insulin sensitivity, blood pressures and lipid profiles of the offspring late in life.

Subjects and methods

We have studied 447 family members from 37 MODY2 kindred of French ancestry [5]. Each of these subjects had either a mother or a father who carried a glucokinase mutation. Subjects were divided into four groups according to the presence of mutation in the subject and his/her mother: presence of the mutation in the mother and the subject (M + S + n = 143), absence of the mutation in the mother but presence in the subject (M–S + n = 121), presence of the mutation in the mother but absence in the subject (M + S– n = 98), and absence of the mutation in the mother and the subject (M–S– n = 85). Birth weight data were obtained for 143 subjects from a questionnaire sent to the mothers. Estimations of insulin secretion and insulin sensitivity were calculated from fasting plasma glucose and insulin concentrations with the homeostasis model assessment/continuous infusion of glucose with model assessment (HOMA/CIGMA) software [6]. Insulin was measured by a radioimmunoassay (SB-INSI-5, CIS-Bio, Gif-sur-Yvette, France) that cross-reacts ~ 22 % with intact proinsulin.

Data are expressed as means ± standard deviation. We used ANOVA for comparisons between groups. When this test was significant, comparisons between pairs were made using the Tukey-Kramer HSD test. Qualitative traits were analysed by chi-squared tests. We considered p values 0.05 or less to be statistically significant.

Results

Birth weight was available for 143 family members. It was lower in M–S + offspring (2990 ± 414 g) than in M + S + (3466 ± 429 g; $p < 0.0001$), M + S– (3754 ± 544 g; $p < 0.0001$) or M–F– (3391 ± 433 g; $p = 0.0011$) offspring. Birth weight was higher in M + S– than in M–S– offspring ($p = 0.014$) and similar in M + S + and M–S– offspring ($p = 0.88$). All comparison between pairs followed ANOVA with $p < 0.0001$.

To assess if these differences in birth weight are associated with differences in weight and height late in life, participants were sorted into three age groups: 2 to 12 years (n = 85), 13 to 24 years (n = 125) and 25 to 82 years (n = 237). No differences in height, weight or body mass index (BMI) were observed in the four groups of subjects in any of the groups (Table 1).

To assess the influence of diabetic maternal environment on metabolic phenotypes of adult offspring

Table 2. Influence of maternal (M+) and fetal (S+) glucokinase mutation on clinical and biological variables of adult offspring (Group 3: age 25–82 years)

	M+S+	M–S+	*p*	M+S–	M–S–	*p*
Subjects (*n*)	85	71		42	39	–
Glucose tolerance status: IFG-IGT/DM (%)	27%/73%	35%/65%	0.30	–	–	–
Age at diagnosis of hyperglycaemia (years)	33 ± 14	29 ± 10	0.05	–	–	–
Duration of hyperglycaemia (years)	12 ± 10	16 ± 11	0.02	–	–	–
Fasting glucose (mmol/l)	7.2 ± 1.0	7.2 ± 1.8	0.81	5.3 ± 0.5	5.1 ± 0.5	0.10
2-h glucose (mmol/l)	9.0 ± 3.2	9.3 ± 3.0	0.65	4.6 ± 1.4	5.1 ± 0.9	0.11
Fasting insulin (pmol/l)	50 ± 29	62 ± 40	0.07	57 ± 33	53 ± 36	0.72
Insulin secretion index: HOMA B (%)	69 ± 31	78 ± 34	0.23	112 ± 48	118 ± 56	0.67
Insulin sensitivity index: HOMA S (%)	56 ± 39	50 ± 39	0.41	52 ± 25	58 ± 30	0.45
Treatment: diet/OHA (%)	66%/34%	77%/23%	0.25	–	–	–
Systolic blood pressure (mm Hg)	127 ± 15	127 ± 14	0.97	126 ± 12	129 ± 13	0.39
Diastolic blood pressure (mm Hg)	74 ± 9	72 ± 11	0.48	72 ± 13	72 ± 11	0.91
Creatinine (μmol/l)	82 ± 15	83 ± 17	0.74	83 ± 21	81 ± 15	0.64
Triglycerides (mmol/l)	1.21 ± 0.88	1.14 ± 0.78	0.63	1.07 ± 0.52	1.23 ± 0.62	0.23
Total Cholesterol (mmol/l)	5.92 ± 1.05	5.70 ± 1.21	0.24	5.62 ± 1.03	5.60 ± 1.29	0.93
HDL Cholesterol (mmol/l)	1.51 ± 0.35	1.39 ± 0.38	0.03	1.40 ± 0.36	1.44 ± 0.43	0.61
LDL Cholesterol (mmol/l)	3.86 ± 0.91	3.77 ± 1.02	0.56	3.74 ± 0.88	3.59 ± 1.13	0.54
Apo A1 (mg%)	176 ± 29	165 ± 0.32	0.04	170 ± 31	167 ± 30	0.71
Apo B (mg%)	122 ± 32	117 ± 36	0.42	115 ± 28	118 ± 36	0.73
Lp(a) (mg%)	24.1 ± 15.7	21.2 ± 15.1	0.32	29.0 ± 24.8	32.7 ± 32.3	0.64

Data expressed as means ± SD. Statistics are contingency-table chi-squared test (qualitative data) and ANOVA. *p* values refer to comparisons of M+S+ vs M–S+ subjects and M+S– vs M–S– subjects. 2-h glucose are values during an oral glucose tolerance test; other biological variables are fasting values. IFG, IGT and DM: impaired fasting glucose, impaired glucose tolerance and diabetes mellitus, respectively. OHA: oral hypoglycaemic agents. HOMA B and HOMA S: Homeostasis Model Assessment of insulin secretion and insulin sensitivity, respectively [6]

we compared clinical and biological variables in adult non-diabetic and in diabetic subjects who had a mother or a father with diabetes (Table 2). Fasting and 2-h glucose concentrations, fasting insulin concentrations, HOMA insulin secretion and insulin sensitivity indexes, blood pressures and extended lipid profiles were similar in non-diabetic M + S– and M–S– subjects. These variables as well as the glucose tolerance status were similar in M + S + and M–S + MODY2 subjects.

Discussion

We confirmed in this large panel of French MODY2 families that birth weight is reduced in the presence of a fetal glucokinase mutation and increased by the presence of a maternal glucokinase mutation [1]. These two effects are additive as shown by the similar weight of M + S + and M–S– offspring. Low birth weight in M–S + offspring could have resulted from fetal hypoinsulinaemia due to the glucokinase mutation and fetal macrosomia in M + S– offsprings might have resulted from fetal hyperinsulinaemia in response to maternal hyperglycaemia. The normal birth weight of M + S + offspring could be related to the inability of the glucokinase-deficient fetal pancreas to increase insulin secretion proportionally to the maternal hyperglycaemia, the two opposing effects on fetal insulin secretion cancelling each other out.

Despite these differences in birth weight, no differences in height, weight or BMI were observed in the four groups of subjects analysed in three age groups, pre-adolescence (younger than 13 years), adolescence and young adulthood (13 to 24 years) and adulthood (older than 24 years). This postnatal realignment of weight in M + S– (catch-down) and M–S + (catch-up) offspring is in agreement with observations that after birth, when the effects of maternal uterine environment are no longer present, a large proportion of babies show early postnatal catch-up or catch-down growth in weight as they move towards their genetic growth trajectory [7]. In M + S– offspring it is the maternal hyperglycaemia which drives the hyperinsulinaemia. Despite the insulin secretion defect, M–S + subjects maintain, however, relatively normal insulin concentrations throughout the day at the expense of hyperglycaemia [8]. Our data contrast with those from other studies showing that babies born to Type II diabetic mothers remain fat [9, 10]. These data might, however, be biased by some of the studies having included young Type II diabetic mothers who were themselves obese and thus the fatness in the offspring might have been genetically determined. Noteworthy is that MODY2 is not associated with obesity and the BMI of affected and unaffected adult women in these kindred is 22.1 ± 3.6 and 22.1 ± 3.3 Kg/m^2 ($p = 0.97$), respectively.

It has been suggested that diabetes during pregnancy predisposes the offspring to diabetes in late

life [4]. In the polygenic forms of Type II diabetes this predisposition might, however, be related to the effects of the diabetic environment in utero, to the sharing between mother and offspring of a polygenic diabetic background or to an interaction between both. Our data do not support the hypothesis of a direct effect of a maternal diabetic environment. Non-diabetic subjects, regardless of the glucose tolerance status of the mothers (M + S– or M–S–), had similar glucose and insulin concentrations, insulin secretion and insulin sensitivity indexes, blood pressures and extended lipid profiles. Moreover, these variables, as well as the severity of hyperglycaemia were similar in affected M + S + and M–S + MODY2 subjects. This suggests here again that the diabetic maternal environment did not result in either insulin resistance or beta-cell dysfunction in the adult offspring. Late effects of an interaction between the diabetic maternal environment and a polygenic diabetic background on these variables in the offspring cannot, however, be excluded from our data.

In kindred with glucokinase mutations we observed that the fetal and maternal mutations can alter birth weight by decreasing or indirectly increasing fetal insulin secretion, respectively. Neither of these effects persist, however, into adult life as neither maternal nor fetal mutations alter the adult height or weight of offspring. In addition, the maternal hyperglycaemia during fetal life does not have an effect of the glucose tolerance, insulin secretion, insulin sensitivity, blood pressure and lipid profile of the offspring late in life. We conclude that maternal environment and fetal genotypes could alter growth in utero by changing fetal insulin secretion but these effects do not result in a persistent programming in later life.

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