Long-Term Follow-Up of Oral Glucose Tolerance Test–Derived Glucose Tolerance and Insulin Secretion and Insulin Sensitivity Indexes in Subjects With Glucokinase Mutations (MODY2)

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OBJECTIVE — We investigated the natural history of glucokinase (GCK)-related maturity-onset diabetes of the young type 2 (MODY2), notably the factors associated with deterioration of hyperglycemia over time.

RESEARCH DESIGN AND METHODS — We report an 11-year follow-up of glucose tolerance and indexes of insulin secretion and insulin sensitivity derived from oral glucose tolerance tests in 33 MODY2 subjects.

RESULTS — The variation between tests of glucose tolerance (expressed as the area under the glucose curve) was 6.9 ± 3.2% (mean ± SEM), but individual results ranged from −20 to 61%. Deterioration of glucose tolerance between tests was associated with decreased insulin sensitivity, while insulin secretion remained stable.

CONCLUSIONS — Glucose tolerance can remain stable over many years in subjects with MODY2 due to the relative stability of the GCK-related β-cell defect. However, the development of insulin resistance may have an important role in the deterioration of the glucose tolerance and in the long-term evolution of the disorder.

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Maturity-onset diabetes of the young type 2 (MODY2) is a familial form of hyperglycemia caused by heterozygous mutations in the gene encoding glucokinase (GCK) (1). Hyperglycemia related to GCK mutations results from defects in glucose-stimulated insulin secretion (2) and hepatic synthesis of glycogen from glucose (3). The hyperglycemia of MODY2 is often mild. Most patients have impaired fasting glucose or impaired glucose tolerance, and <50% of affected individuals have overt diabetes (1). To investigate the natural history of MODY2, and notably the factors associated with deterioration of hyperglycemia, we retrospectively analyzed hospital records of 33 MODY2 subjects. We report an 11-year follow-up of glucose tolerance and of indexes of insulin secretion and insulin sensitivity derived from oral glucose tolerance tests (OGTTs).

RESEARCH DESIGN AND METHODS

— We studied 17 women and 16 men from 14 MODY2 kindred of French ancestry who had undergone two OGTTs with insulin measurement, spaced by at least 4 years. GCK mutations were confirmed by direct sequencing (online appendix Table 1 [available at http://dx.doi.org/10.2337/dc07-2017]). The area under the curve (AUC) relating glucose or insulin levels and the time during the OGTT was calculated by the trapezoidal rule. Glucose tolerance was expressed as $AUC_{glucose}$. Variation of $AUC_{glucose}$ between tests ($\Delta AUC_{glucose}$) was computed as the difference between values at the second and first OGTTs, expressed as a percent of the value at the first OGTT. Variations of other clinical and biological parameters between tests were calculated similarly. Indexes of β-cell function were computed as the ratios of $AUC_{insulin}$ to $AUC_{glucose}$ and $\Delta insulin_{30-0min}$ to $glucose_{30min}$ (4). Insulin sensitivity was assessed by Matzuda's composite insulin sensitivity index (5). Homeostasis model assessment (HOMA) indexes of β-cell function (%B) and insulin sensitivity (%S) were also computed. Results are expressed as means ± SEM.

RESULTS

— The average follow-up period, defined as the interval between OGTTs, was 11.0 ± 1.1 years (range 4.3–25.1). Clinical and OGTT data are shown in Table 1 and in online appendix Fig. 1. Both fasting and 2-h glucose levels were slightly but significantly increased in the second compared with the first OGTT. Indexes of insulin secretion were similar at the first and second OGTTs. Insulin sensitivity was significantly decreased at the second OGTT. All quantitative clinical or biological parameters were significantly correlated at the first and second OGTTs (Table 1).

Although the average $AUC_{glucose}$ was only mildly increased between tests (variation 6.9 ± 3.2%), individual results of $\Delta AUC_{glucose}$ were heterogeneous, ranging −20 to 61% (online appendix Fig. 2). To investigate parameters associated with $\Delta AUC_{glucose}$ heterogeneity, we compared subjects whose glucose tolerance remained stable or had improved during follow-up with subjects whose glucose tolerance had deteriorated (online appendix Table 2). Groups were defined by a $\Delta AUC_{glucose}$ below or above the median

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Table 1—*Clinical and OGTT follow-up in MODY2 subjects*

	First OGTT	Second OGTT	*P*	R^2	*P**
Age (years)	21 ± 2	33 ± 3	<0.0001	—	—
BMI (kg/m^2)	19.2 ± 0.5	22.3 ± 0.6	—	—	—
BMI (*Z* score)	−0.16 ± 0.15	0.08 ± 0.20	0.04	0.69	<0.0001
Hyperglycemic status: IFG/IFG-IGT/diabetes (%)	30/33/37	15/30/55	0.23	—	—
Treatment: diet/OHA (%)	100/0	85/15†	0.02	—	—
FPG (mmol/l)	6.8 ± 0.2	7.1 ± 0.1	0.02	0.19	0.01
2-h glucose (mmol/l)	8.2 ± 0.4	9.0 ± 0.4	0.03	0.16	0.01
$AUC_{glucose}$ (mmol/l glucose × min)	1,106 ± 34	1,163 ± 31	0.06	0.25	0.002
Fasting insulin (pmol/l)	50 ± 7	60 ± 5	0.004	0.36	0.0001
2-h insulin (pmol/l)	183 ± 25	195 ± 26	0.87	0.13	0.02
$AUC_{insulin}$ (pmol/l insulin × min × 10^3)	24.05 ± 2.39	24.34 ± 1.96	0.60	0.42	<0.0001
$AUC_{insulin}/AUC_{glucose}$ (pmol insulin/mmol glucose)	21.7 ± 1.9	21.0 ± 1.6	0.82	0.43	<0.0001
$\Delta Ins_{30-0}/Glu_{30}$ (pmol insulin/mmol glucose)	17.2 ± 1.9	16.3 ± 1.4	0.66	0.21	0.004
HOMA%B (%)	49 ± 3	52 ± 3	0.50	0.12	0.03
HOMA%S (%)	133 ± 12	101 ± 8	0.01	0.34	0.0002
ISI_{comp}	6.38 ± 0.82	4.56 ± 0.38	0.01	0.45	<0.0001

Data are means ± SEM unless otherwise indicated ($n = 33$). Statistics (*P*) are paired Student's *t* test on log-transformed data or Fisher's exact test (qualitative traits). R^2 are correlation coefficients of bivariate linear fit relating values at first and second OGTT with ad hoc statistics (*P**). ISI_{comp} is expressed in arbitrary units. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IFG-IGT, combined impaired fasting glucose and impaired glucose tolerance; OHA, oral hypoglycemic agents, †sulfonylurea ($n = 3$)/metformin ($n = 2$). HOMA%B and HOMA%S were computed with the HOMA Calculator (version 2.2) available at http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/index.php.

of the distribution (4.69%), respectively. Subjects whose glucose tolerance deteriorated were older at the second OGTT (38 ± 4 vs. 27 ± 4 years, $P = 0.02$) and had a longer follow-up (14 ± 2 vs. 8 ± 1 years, $P = 0.007$). $\Delta AUC_{glucose}$ correlated both with age at the second OGTT ($R^2 = 0.17$; $P = 0.01$) and with the duration of follow-up ($R^2 = 0.16$; $P = 0.01$). Subjects whose glucose tolerance deteriorated had a higher BMI increase during follow-up, but the differences were not statistically significant. However, insulin sensitivity was correlated with BMI at the second OGTT ($r^2 = 0.19$; $P = 0.01$).

Subjects whose glucose tolerance deteriorated showed significantly decreased ΔHOMA%S during follow-up compared with subjects whose glucose tolerance remained stable (−27 ± 12% vs. 18 ± 15%, $P = 0.04$). They also showed a trend toward higher $\Delta AUC_{insulin}$. These observations are best explained by a deterioration of insulin sensitivity between tests in the former group. The variation of HOMA%B index of insulin secretion between tests was not significantly different in the two groups of subjects (16 ± 10% vs. 6 ± 10%, $P = 0.49$).

CONCLUSIONS — This is the first systematic follow-up study of the natural history of MODY2. Our results suggest that glucose tolerance can remain stable over the course of many years in subjects with this form of diabetes. This may be related to the relative stability of the glucokinase-related β-cell defect, as insulin secretion in MODY2 subjects does not seem to aggravate substantially over time. However, if or when insulin resistance develops, the β-cell defect may prevent an adequate compensatory increase in insulin secretion, resulting in a deterioration of the glucose tolerance. We have previously documented that insulin resistance is frequent in subjects with MODY2 (6). Our present results suggest that it may have an important role in the deterioration of the glucose tolerance and in the long-term evolution of the disorder. These results contrast with those observed in MODY1 (HNF4A) and MODY3 (HNF1A), associated with a progressive decrease of insulin secretion and severe deterioration of hyperglycemia (7,8).

Insulin sensitivity is influenced by polygenic determinants interacting with multiple environmental factors. Putative unfavorable alleles are probably frequent in the general population, given the increasing worldwide prevalence of type 2 diabetes associated with changes in lifestyle. These unfavorable alleles could affect the clinical phenotype of MODY2 subjects. Their identification may provide a better understanding of the role of modifier genes in the clinical progression of monogenic types of diabetes. Regarding treatment, in most MODY2 cases, diet therapy satisfactorily controls blood glucose levels and no hypoglycemic medication is required (1). However, as for all patients with diabetes, subjects with MODY2 should be instructed not to gain excessive weight and to have a regular physical activity to avoid the development or aggravation of insulin resistance.

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