

**Long-term follow-up of OGTT-derived glucose tolerance, insulin secretion and insulin sensitivity indices in subjects with glucokinase mutations (MODY2)**

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*Running title:* Long-term follow-up of MODY2 subjects

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*Objective* – We investigated the natural history of 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 of indices 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  $6.9 \pm 3.2\%$  ( $m \pm SEM$ ), 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 glucokinase-related beta-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.

**M**aturity onset diabetes of the young type 2 (MODY2) is a familial form of hyperglycemia caused by heterozygous mutations in the gene encoding glucokinase (1). Hyperglycemia related to glucokinase 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 (IFG) or impaired glucose tolerance (IGT) and less than 50% of affected individuals have overt diabetes (1). In order to investigate the natural history of MODY2, and notably the factors associated with deterioration of hyperglycemia, we have analyzed retrospectively hospital records of 33 MODY2 subjects. We report an 11-year follow-up of glucose tolerance and of indices of insulin secretion and insulin sensitivity derived from oral glucose tolerance tests (OGTT).

## 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). The areas under the curve (AUC) relating glucose or insulin levels and time during the OGTT were calculated by the trapezoidal rule. Glucose tolerance was expressed as  $AUC_{\text{glucose}}$ . Variation of  $AUC_{\text{glucose}}$  between tests ( $\Delta AUC_{\text{glucose}}$ ) was computed as the difference between values at 2<sup>nd</sup> and 1<sup>st</sup> OGTTs, expressed as a percent of the value at 1<sup>st</sup> OGTT. Variations of other clinical and biological parameters between tests were calculated similarly. Indices of beta-cell function were computed as the ratios  $AUC_{\text{insulin}}/AUC_{\text{glucose}}$  and  $\Delta\text{Insulin}_{30-0\text{min}}/\text{Glucose}_{30\text{min}}$  (4). Insulin sensitivity was assessed by Matzuda's composite insulin sensitivity index (5). HOMA indices of beta-cell function (%B) and insulin sensitivity (%S) were also computed. Results are expressed as means  $\pm$  SEM.

## RESULTS

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

Although the average  $AUC_{\text{glucose}}$  was only mildly increased between tests (variation of  $6.9 \pm 3.2\%$ ), individual results of  $\Delta AUC_{\text{glucose}}$  were heterogeneous, ranging -20% to 61% (online appendix figure 2). To investigate parameters associated with  $\Delta AUC_{\text{glucose}}$  heterogeneity, we compared subjects whose glucose tolerance remained stable or had improved during follow-up to subjects whose glucose tolerance had deteriorated (online appendix table 2). Groups were defined by a  $\Delta AUC_{\text{glucose}}$  below or above the median of the distribution (4.69%), respectively. Subjects whose glucose tolerance deteriorated were older at the second OGTT ( $38 \pm 4$  vs  $27 \pm 4$  years,  $p=0.02$ ) and had a longer follow-up ( $14 \pm 2$  vs  $8 \pm 1$  years,  $p=0.007$ ).  $\Delta AUC_{\text{glucose}}$  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  $\Delta\text{HOMA}\%S$  during follow-up as compared to subjects whose glucose tolerance remained stable ( $-27 \pm 12\%$  vs  $18 \pm 15\%$ ,  $p=0.04$ ). They also showed a trend towards higher  $\Delta AUC_{\text{insulin}}$ . 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 ( $16\pm 10\%$  vs  $6\pm 10\%$ ,  $p=0.49$ ).

physical activity to avoid the development or aggravation of insulin resistance.

## **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 beta-cell defect, as insulin secretion in MODY2 subjects does not seem to aggravate substantially over time. However, if or when insulin resistance develops, the beta-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

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Table 1: Clinical and OGTT follow up in MODY2 subjects

	First OGTT	Second OGTT	p	R <sup>2</sup>	p*
Age (years)	21 ± 2	33 ± 3	<0.0001	-	-
BMI (kg/m <sup>2</sup> )	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 / DM (%)	30% / 33% / 37%	15% / 30% / 55%	0.23	-	-
Treatment: Diet/OHA (%)	100% / 0%	85% / 15% <sup>†</sup>	0.02	-	-
FPG (mM)	6.8 ± 0.2	7.1 ± 0.1	0.02	0.19	0.01
2h glucose (mM)	8.2 ± 0.4	9.0 ± 0.4	0.03	0.16	0.01
AUC <sub>glucose</sub> (mM.min)	1106 ± 34	1163 ± 31	0.06	0.25	0.002
Fasting Insulin (pM)	50 ± 7	60 ± 5	0.004	0.36	0.0001
2h Insulin (pM)	183 ± 25	195 ± 26	0.87	0.13	0.02
AUC <sub>insulin</sub> (pM.min.10 <sup>3</sup> )	24.05 ± 2.39	24.34 ± 1.96	0.60	0.42	<0.0001
AUC <sub>insulin</sub> /AUC <sub>glucose</sub> (pmol insulin / mmol glucose)	21.7 ± 1.9	21.0 ± 1.6	0.82	0.43	<0.0001
ΔIns <sub>30-0</sub> /Glu <sub>30</sub> (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 <sub>comp</sub>	6.38 ± 0.82	4.56 ± 0.38	0.01	0.45	<0.0001

Data expressed as Mean ± SEM (n=33). Statistics (p) are paired Student's t test on log-transformed data or Fisher's exact test (qualitative traits). R<sup>2</sup> are correlation coefficients of bivariate linear fit relating values at first and second OGTT with ad hoc statistics (p\*). ISI<sub>comp</sub> is expressed in arbitrary units. FPG: fasting plasma glucose; IFG: impaired fasting glucose; IFG-IGT: combined impaired fasting glucose and impaired glucose tolerance; DM: diabetes mellitus; OHA: oral hypoglycemic agents, (<sup>†</sup>) sulfonylurea (n=3), metformin (n=2); AUC: area under the curve. HOMA%B and HOMA%S were computed with the HOMA Calculator (v2.2) available at <http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/index.php>