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The genetic abnormality in the beta cell determines the response to an oral glucose load

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Abstract

Aims/hypothesis. We assessed how the role of genes genetic causation in causing maturity-onset diabetes of the young (MODY) alters the response to an oral glucose tolerance test (OGTT).
Methods. We studied OGTT in 362 MODY subjects, from seven European centres; 245 had glucokinase gene mutations and 117 had Hepatocyte Nuclear Factor –1 alpha (*HNF-1α*) gene mutations.
Results. BMI and age were similar in the genetically defined groups. Fasting plasma glucose (FPG) was less than 5.5 mmol/l in 2 % glucokinase subjects and 46 % *HNF-1α* subjects ($p < 0.0001$). Glucokinase subjects had a higher FPG than *HNF-1α* subjects ([means ± SD] 6.8 ± 0.8 vs 6.0 ± 1.9 mmol/l, $p < 0.0001$), a lower 2-h value (8.9 ± 2.3 vs 11.2 ± 5.2 mmol/l, $p < 0.0001$) and a lower OGTT increment (2-h – fasting) (2.1 ± 2.3 vs 5.2 ± 3.9 mmol/l, $p < 0.0001$). The relative proportions classified as diabetic depended on whether fasting (38 % vs 22 %, glucokinase vs *HNF-1α*) or 2-h values (19 % vs 44 %) were used. Fasting and 2-h glucose values were not correlated in the glucokinase subjects ($r = –0.047$, $p = 0.65$) but were strongly correlated in *HNF-1α* subjects ($r = 0.8$, $p < 0.001$). Insulin concentrations were higher in the glucokinase subjects throughout the OGTT.
Conclusion/interpretation. The genetic cause of the beta-cell defect results in clear differences in both the fasting glucose and the response to an oral glucose load and this can help diagnostic genetic testing in MODY. OGTT results reflect not only the degree of hyperglycaemia but also the underlying cause. [Diabetologia (2002) 45: 427–435]

Keywords Maturity-onset diabetes of the young, MODY, hepatocyte nuclear factor-1 alpha, glucokinase, oral glucose tolerance test, genetics.

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Abbreviations: MODY, Maturity-onset diabetes of the young; OGTT, oral glucose tolerance test; *HNF-1α*, Hepatocyte Nuclear Factor –1 alpha; FPG, fasting plasma glucose; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; ADA, American Diabetes Association; WHO, The World Health Organisation

Diabetes is defined on the basis of both fasting glucose concentration and the glucose concentration 2 h following a glucose load. Recent revisions by the American Diabetes Association (ADA) and World Health Organisation (WHO) have put more emphasis on the fasting value as it is easier to ascertain [1, 2]. They both adopted a lower value for fasting samples but the WHO recommended continued use of the 2-h oral glucose tolerance test (OGTT) [2]. Numerous studies have been carried out comparing diagnosis according to the fasting and 2-h criteria in different ethnic and age groups [3–7]. In all data sets, fasting and 2-h glucose values are correlated but there is only moderate agreement between the fast-

ing and 2-h criteria for diabetes [7], with lower diagnostic rates using fasting alone compared to 2-h values. When subjects are defined as having diabetes or IFG/IGT on either fasting or 2-h values but not both, different patterns of cardiovascular and mortality risk have been defined in some studies [7, 8]. There have been no studies looking at the impact of using fasting and 2-h values in different subtypes of diabetes with distinct underlying causes.

It is now possible to define the molecular genetic cause in most cases of maturity-onset diabetes of the young (MODY). Mutations in five genes have been shown to cause MODY by resulting in beta-cell dysfunction: glucokinase, hepatocyte nuclear factor HNF-1α *HNF-4α*, *HNF-1β* and insulin promoter factor 1 (*IPF-1*) [9, 10]. Each gene has distinct clinical and physiological characteristics [9]. Glucokinase mutations are associated with stable, mild fasting hyperglycaemia throughout life as a result of reduced glucose sensing in the beta cell [9, 11]. Mutations in the transcription factors (*HNF-1α*, *HNF-4α*, *HNF-1β* and *IPF-1*) result in progressive beta-cell failure with impaired insulin secretion at high glucose concentrations [9, 12, 13]. Glucose concentrations are normal in early childhood and increase with age; this is mirrored by increasing treatment requirements and frequent microvascular complications [9].

It has been suggested that the molecular genetic cause of the hyperglycaemia altered the fasting and 2-h glucose values [14]. This study showed that subjects with genetic defects leading to insulin resistance had fasting values that were lower and 2-h values that were higher compared with a group of subjects with beta-cell dysfunction due to glucokinase mutations. The high fasting and relatively low increment (2-h minus fasting glucose) during an OGTT in glucokinase subjects was subsequently used as criteria for selecting women with gestational diabetes who were likely to have a glucokinase mutation [15]. There have been no large studies looking at the response to an OGTT in MODY or the impact of using fasting rather than 2-h glucose values.

We studied the OGTT glucose values of 362 MODY subjects from 7 European centres with mutations in the glucokinase and *HNF-1α* genes to establish whether the cause of the beta-cell defect alters the response to a glucose load.

Subjects and methods

Subjects. We studied 362 MODY family members with early onset (at least one family member diagnosed before 25 years of age), non-insulin-dependent diabetes inherited in an autosomal dominant pattern. In all subjects studied, mutations had been identified in either the glucokinase gene ($n = 245$) or the *HNF-1α* gene ($n = 117$). These subjects were from 7 European centres (UK ($n = 50$), France ($n = 154$), Sweden ($n = 56$, 43 Finnish subjects), Italy ($n = 51$), Norway ($n = 24$), Denmark ($n = 16$) and Spain ($n = 11$)). None of the subjects received pharmacological treatment for diabetes for at least 1 week prior to testing and none of the women were pregnant. When more than one eligible OGTT result was available, only the first test performed on that subject was recorded. Informed consent was obtained from subjects in each centre following approval from local ethical committees. Some of these subjects have previously been described [16–30].

Methods. OGTT were carried out after an overnight fast using an anhydrous glucose load of 75 g. For subjects under 42.9 kg, a glucose load of 1.75 g/kg was given. Plasma glucose results were analysed locally by glucose oxidase methods (all centres had comparable assays with a CV of < 1 % at 4. 9 mmol/l) and recorded at baseline, 30 min, 60 min, 90 min and 120 min when available. In all tests fasting and 2-h results were available and in 217 subjects values at all time points were available. In a subset of French subjects (glucokinase, $n = 79$; *HNF-1α*, $n = 10$), plasma insulin concentrations were analysed at baseline, 30, 60, 90 and 120 minutes following the glucose load using the insulin IMRA kit from Immunotech (Beckman Coulter, Fullerton, Calif., USA). The kit was calibrated against the international standard WHO 66/304 with a sensitivity of 3.73 pmol/l [31]. Insulin concentrations were not combined between centres due to differences in insulin assays in comparative tests.

Calculations. The OGTT (120 – 0 min) increment during the test was calculated by subtracting the fasting value from the one at 120 min. In the 217 tests where all time points were available, the single highest plasma glucose was defined as the 'peak value' and the area under the curve was calculated using the trapezoidal rule. Diabetic status was classified according to the fasting result (normal = < 6.1, impaired fasting glycaemia(IFG) = 6.1 – 6.9, diabetes = > 7.0 mmol/l) and the 2-h value (normal = < 7.8, impaired glucose tolerance (IGT) = 7.8 – 11.0, diabetes = > 11.1 mmol/l).

Statistical analyses. Data are given as means ± SD for normally distributed data. As the insulin data was skewed this was logarithmically transformed and the geometric means ± SD range calculated. We used the unpaired t test to compare means, chi-square (χ^2) test to compare group frequencies and Pearsons correlation coefficient to assess the correlation between continuous variables. Statistical analysis was by SPSS for Windows (Chicago, Ill., USA, Version 9). All tests were two-tailed and a p value of less than 0.05 was considered to be statistically significant.

Results

Clinical characteristics. The clinical characteristics of the subjects are shown in Table 1. The age and BMI of the subjects with glucokinase or *HNF-1α* mutations were similar.

OGTT Results. The OGTT results are shown in Fig. 1 and summarised in Table 1. The fasting plasma glucose (FPG) was higher in the glucokinase than in the *HNF-1α* subjects (6.8 ± 0.8 mmol/l vs 6.0 ± 1.9 mmol/l $p < 0.0001$). The FPG was less than 5.5 mmol/l in only 2 % of glucokinase subjects compared to 46 % of *HNF-1α* subjects ($p < 0.0001$).

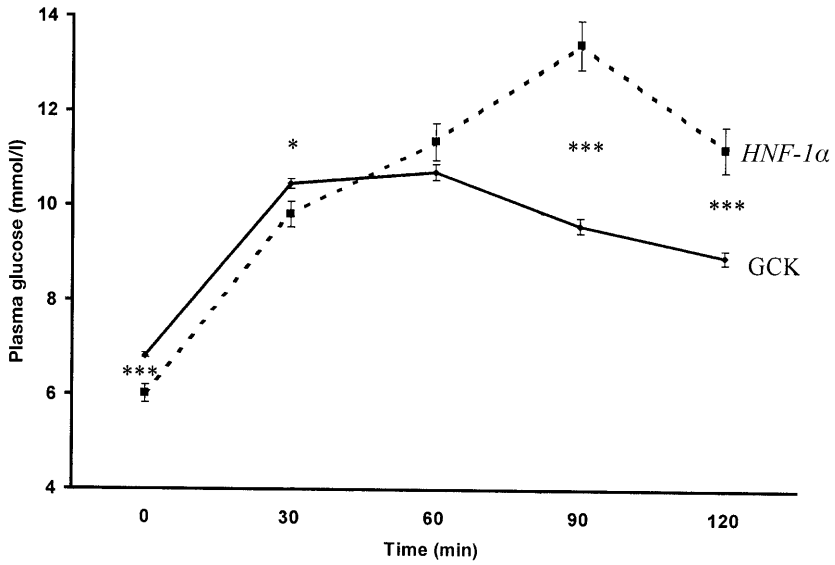


Fig. 1. Mean glucose concentration at five time points during an OGTT in subjects with glucokinase (—) and *HNF-1α* mutations (- - - -). SEM shown by bars. *** = $p < 0.0001$, * = $p < 0.05$

The 5 glucokinase subjects found to have a FPG of under 5.5 mmol/l were from 4 centres (Subject 1: Age 2 years, FPG 4.9 mmol/l; subject 2: 5 years, 4.4 mmol/l; subject 3: 7 years, 5.3 mmol/l; subject 4: 13 years, 5.4 mmol/l; subject 5: 59 years, 5.4 mmol/l). On repeat testing, subjects 1–4 were found to have a FPG > 5.5 mmol/l; subject 5 has not been re-tested.

Despite having a higher FPG, the 2-h values in glucokinase subjects were lower than *HNF-1α* subjects (8.9 ± 2.3 mmol/l vs 11.2 ± 5.2 mmol/l $p < 0.0001$).

The OGTT increment was lower in glucokinase subjects compared to *HNF-1α* subjects (2.1 ± 2.3 mmol/l vs 5.2 ± 3.9 mmol/l $p < 0.0001$). An increment of greater than 3.0 mmol/l was seen in 29.0% subjects with glucokinase but 66.7% subjects with *HNF-1α*. The interplay between the discriminatory values of a FPG of > 5.5 mmol/l and an increment of less than 3.0 mmol/l in the two genetic subtypes is shown in Fig. 2.

The plasma glucose concentrations differed significantly at all time points of the OGTT except 60 min (Fig. 1). The pattern of glucose response following oral glucose load varied; 84.4% glucokinase subjects had a peak glucose value at 30 or 60 min while 72.5% *HNF-1α* subjects peaked at 90 or 120 min. The peak glucose was lower in the glucokinase subjects (glucokinase 11.6 ± 2.3 mmol/l vs *HNF-1α* 14.5 ± 5.0 mmol/l, $p < 0.001$). The area under the curve was significantly lower in the glucokinase subjects (glucokinase ($n = 176$) 1153 mmol min /l vs *HNF-1α* ($n = 41$) 1413 mmol min /l, $p = 0.002$, equal variance not assumed).

Diagnosis using fasting and 2-h criteria. The relative proportion of subjects with the two genetic causes classified as normal glucose tolerance (NGT), impaired fasting glycaemia and impaired glucose tolerance (IFG/IGT) or diabetes depended on whether fasting or 2-h values were used (Table 2). When fasting glucose values were used glucokinase subjects were more likely to be diagnosed as diabetic than *HNF-1α* subjects (38% vs 22%, chi-square $p < 0.05$). Using classification based on the 2-h value,

Table 1. Subjects clinical characteristics and glucose values during OGTT for glucokinase (glucokinase) and *HNF-1α* subjects

	n (male)	Age (range)	BMI Kg/m^2 (range)	FPG mmol/l (SD)	2-h PG mmol/l (SD)	Incr mmol/l (SD)	Peak mmol/l (SD)
glucokinase	245 (125)	26.7 (2–79)	21.1 (13.8–40.9)	6.8 (0.8)	8.9 (2.3)	2.1 (2.3)	11.6 (2.3)
HNF-1α	117 (53)	26.7 (2–76)	22.0 (14.7–37.0)	6.0 (1.9)	11.2 (5.2)	5.2 (3.9)	14.5 (5.0)
p =	NS	NS	NS	0.0001	0.0001	0.0001	0.0001

All values are given as mean with SD or range shown. *FPG* mean fasting plasma glucose, *2-hr PG* mean 2-h plasma glucose, incr, increment (FPG subtracted from 2-h plasma glucose), peak, single highest value. (NS) = not significant

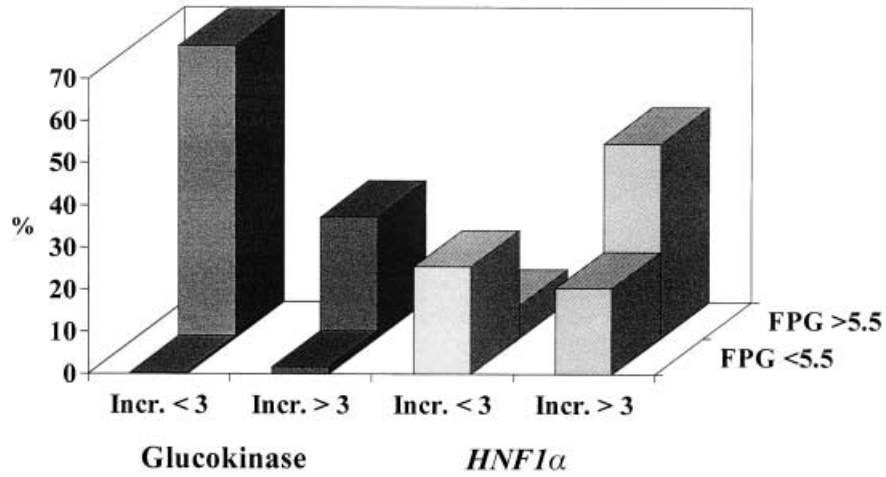


Fig. 2. Percentage of glucokinase subjects (■) and *HNF-1α* subjects (▒) with FPG above or below 5.5 mmol/l and an increment during the OGTT (120 min – 0 min) of above or below 3.0 mmol/l

HNF-1α subjects were more likely to be diagnosed diabetic (glucokinase 19% vs *HNF-1α* 44%, chi-square $p < 0.001$). Within glucokinase and *HNF-1α*, there was a significant difference between the proportion of subjects diagnosed as diabetic on FPG and 2-h values (chi-square glucokinase $p = 0.01$ *HNF-1α* $p < 0.001$). Of the 92 glucokinase subjects classified as diabetic on the FPG value, only 24 (26.1%) were also diabetic on the 2-h value. In contrast, of 26 *HNF-1α* subjects found to be diabetic on FPG, 23 (88.5%) were also classified diabetic at 2 h (chi-square $p < 0.001$).

Correlation between fasting and 2 h glucose. In glucokinase subjects there was no correlation between FPG and 2-h plasma glucose ($r = –0.047$, $p = 0.65$) (Fig. 3). However, in *HNF-1α* subjects, there was a strong correlation between FPG and 2-h plasma glucose ($r = 0.8$, $p < 0.001$) (Fig. 4).

Variation with age. The variation in FPG and 2-h plasma glucose in different decades is seen in Table 3. Both glucokinase and *HNF-1α* subjects show a statistically significant deterioration in FPG with age (glucokinase $r = 0.36$, $p = 0.01$ vs *HNF-1α* $r = 0.34$, $p = 0.01$). This would account for a 5% vs 11% (glucokinase vs *HNF-1α*) deterioration of FPG over

Table 2. Diabetic status on fasting and 2-h criteria

		Normal (%) (*n*)	IFG (%) (*n*)	IGT (%) (*n*)	Diabetes (%) (*n*)
Glucokinase	Fasting criteria	16.3 (40)	46.1(113)	–	37.6 (92)
	2-h criteria	28.2 (69)	–	52.6 (129)	19.2 (47)
HNF-1α	Fasting criteria	65.0 (76)	12.8(15)	–	22.2 (26)
	2-h criteria	31.6 (37)	–	24.8 (29)	43.6 (51)

IFG, impaired fasting glycaemia, IGT, impaired glucose tolerance

Table 3. FPG and 2-h plasma glucose in mmol/l (means ± SD) according to age band in subjects with glucokinase and *HNF-1α* mutations

		Age band (years)							
		0–10	11–20	21–30	31–40	41 –50	51–60	61–70	71–80
glucokinase	*n* =	48	66	27	41	24	19	7	4
	FPG	6.5 (0.7)	6.6 (0.6)	6.8 (0.7)	7.1 (0.9)	7.2 (0.8)	7.3 (1.0)	7.4 (1.0)	7.1 (1.9)
	2-h glucose	8.9 (1.8)	9.4 (1.9)	8.5 (1.8)	8.9 (2.8)	8.1 (2.2)	8.9 (2.8)	10.7 (4.7)	9.4 (1.9)
HNF-1α	*n* =	11	37	33	12	16	6	2	0
	FPG	4.6 (0.8)	5.6 (1.4)	5.9 (1.6)	6.4 (2.0)	7.4 (3.0)	7.0 (1.7)	7.1 (2.2)	–
	2-h glucose	6.7 (3.6)	10.6 (3.7)	11.4 (5.6)	10.3 (4.4)	14.5 (5.8)	12.7 (5.1)	20.4 (1.8)	–

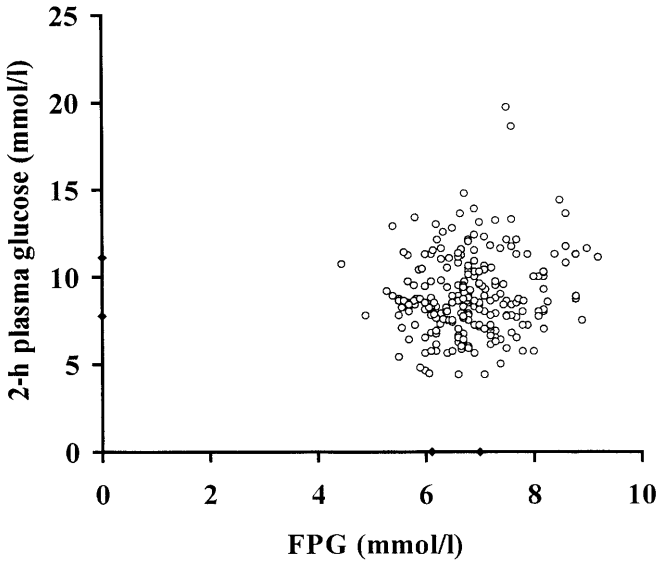


Fig. 3. 2-h plasma glucose against fasting plasma glucose in subjects with glucokinase mutations ($r = -0.047$, $p = 0.65$)

70 years (B = 0.006 mmol/l/year CI = 0.0125 – 0.019 vs B = 0.0446 CI = 0.022 – 0.068) which corresponds to a deterioration of 0.8 mmol/l compared with 3.3 mmol/l over a lifetime.

HNF-1α subjects show a deterioration in 2-h plasma glucose with age ($r = 0.32$, $p = 0.01$), but this is not seen in glucokinase subjects ($r = 0.03$).

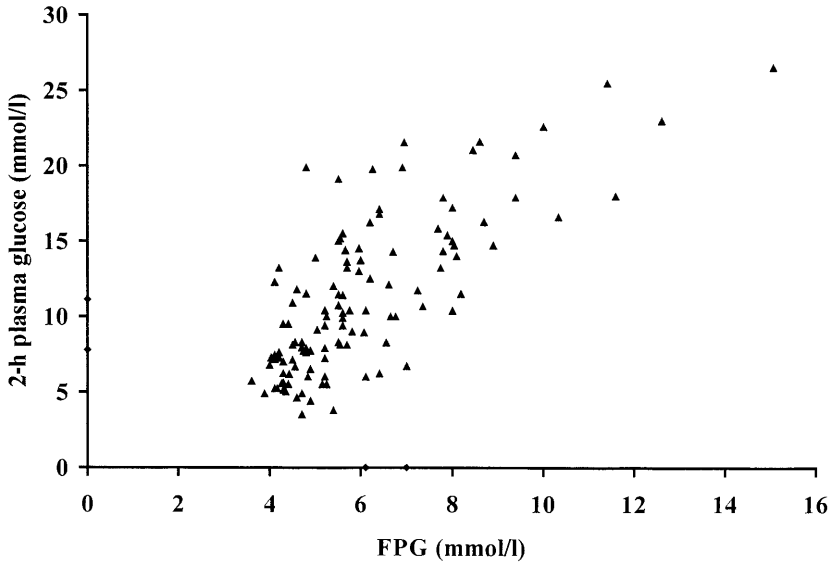
Table 3 illustrates that whilst the majority of glucokinase subjects of all ages have IFG or diabetes on fasting values, *HNF-1α* subjects under 20 years of age commonly have a normal FPG. Altogether 77.2% of subjects under 20 years of age with a glucokinase mutation have fasting hyperglycaemia or diabetes compared with 20.8% subjects with *HNF-1α* mutations ($p < 0.0001$).

Variation with BMI. There was no significant correlation between FPG or 2-h plasma glucose and BMI centile for age as shown in Table 4 (BMI centile calculated according to age and sex in subjects under 20 years of age and calculated at the age of 20 for those over 20 years of age [32]).

We assessed if there were differences in BMI or age between subjects who had diabetic (> 11.1 mmol/l) 2-h values compared to those who had a normal 2-h value (< 7.8 mmol/l). The glucokinase subjects were of similar BMI (22.0 vs 21.3 kg/m^2, $p = 0.4$; 2-h < 7.8 vs 2-h > 11.1 mmol/l) and age (32.2 vs 29.5 years, $p = 0.4$). In contrast the HNF-1α subjects with normal 2-h values were younger (22.2 vs 30.2 years, $p = 0.014$) than those who had a diabetic 2-h glucose and slimmer by absolute BMI (20.3 vs 22.4 kg/m^2, $p = 0.004$; 2-h < 7.8 vs 2-h > 11.1 mmol/l) but not centile BMI suggesting that this reflected the age difference.

Plasma insulin values. The results of plasma insulin concentrations in a subset of French patients are shown in Fig. 5. The geometric mean plasma insulin concentrations were higher throughout the OGTT in glucokinase subjects. This reached statistical significance at 0 and 120 min between glucokinase and *HNF-1α* patients (geometric mean (standard deviation range) 0 min, glucokinase 57.5 (31.7 – 104.3) pmol/l vs *HNF-1α* 30.1 (6.5 – 139.8) pmol/l, $p = 0.01$; 120 min, glucokinase 180.7 (75.1 – 435.0) pmol/l vs *HNF-1α* 91.3 (17.8 – 468.0) pmol/l, $p = 0.04$). There was no significant difference at 30, 60 or 90 min, although glucokinase subjects tended to have a higher geometric mean plasma insulin concentration (Fig. 5). The geometric mean peak insulin concentra-

Fig. 4. 2-h plasma glucose against fasting plasma glucose in subjects with *HNF-1α* mutations ($r = 0.8$, $p < 0.001$)



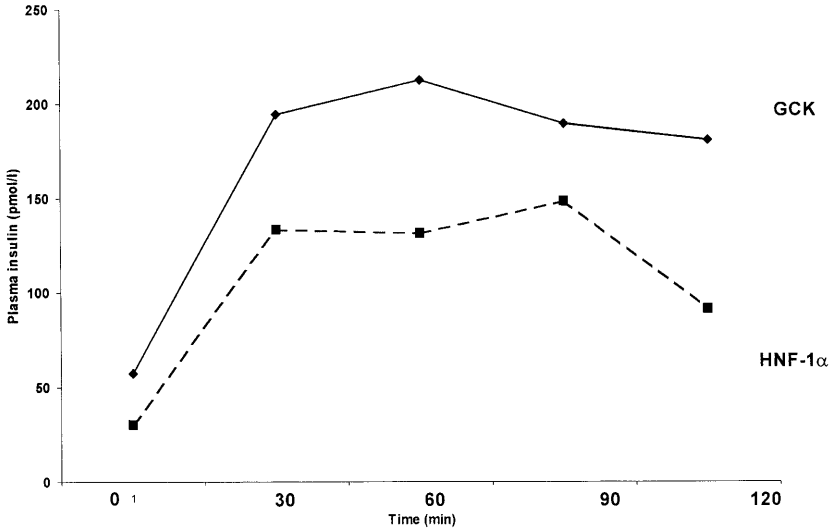


Fig. 5. Geometric mean plasma insulin concentrations (pmol/l) at 5 time points during an OGTT in subjects with glucokinase (—) and *HNF-1α* mutations (- - - -)

tion was higher in the glucokinase subjects (286.3 (150.1–546.3) pmol/l vs 196.2 (94.9 – 405.6) pmol/l) but this did not reach significance ($p = 0.08$).

Discussion

Studying a large number of MODY subjects has shown that there is a difference in fasting glucose and response to an oral glucose load in subjects according to the molecular genetic cause of their hyperglycaemia.

This data set represents the largest reported collection of MODY subjects, with subjects from all major European groups. As patients on insulin and oral hypoglycaemic medication were less likely to have undergone an OGTT, the subjects studied represent MODY subjects with relatively mild hyperglycaemia. This means that these subjects cannot be considered representative of all MODY subjects, particularly in patients with *HNF-1α* mutations where up to 74% of subjects are treated with insulin or oral agents [16]. This is less of an issue in glucokinase where less than 15% of subjects are treated with oral hypoglycaemic agents or insulin [16]. These results are representative of the clinical situations when subjects are likely to have an oral glucose tolerance test; eg. in family screening early in the course of a patients diabetes or when a diagnosis of diabetes is not certain.

Changes in the criteria for diagnosis of diabetes made by the ADA and WHO and the consequences for various populations have been reported widely in the literature [3–7]. This is the first report to examine the effect of these changes in a large series of subjects with different genetic causes. Our results show a clear difference between the proportion of glucokinase and *HNF-1α* subjects diagnosed as diabetic depending on whether the fasting or 2-h criteria are used, fasting plasma glucose values are used, this would diagnose diabetes in a higher proportion of glucokinase subjects than if 2-h OGTT values are used. To our knowledge, glucokinase subjects are the first group to be described where using the fasting value results in more subjects being diagnosed as diabetic than if 2-h values are

Table 4. Fasting plasma glucose and 2-h plasma glucose (mmol/l (SD)) according to BMI centile (calculated by age and sex)and classifying all those over 20 years by the 20 year centiles [32]. BMI equivalent to centile shown in 20 year adults are shown (male) and [female]

		BMI centile band			
	BMI centile (Male BMI) [Female BMI]	≤ 25 (< 20.4) [< 20.0]	25.1 –50 (20.5–22.0) [20.1–21.7]	50.1 – 75 (22.1–23.9) [21.8–23.6]	> 75 (> 24.0) > 23.7]
glucokinase	*n* =	36	51	42	75
	FPG	6.8 (0.7)	6.5 (0.6)	7.0 (0.9)	7.0 (0.9)
	2-h glucose	9.3 (2.5)	8.7 (2.4)	9.4 (1.9)	8.8 (2.5)
HNF-1α	*n* =	18	23	31	35
	FPG	5.0 (0.8)	6.3 (2.7)	6.0 (1.6)	6.3 (2.0)
	2-h glucose	8.9 (3.5)	12.4 (6.3)	11.6 (4.4)	11.4 (5.1)

Table 5. Practical recommendations for use of OGTT in guiding molecular genetic diagnostic testing and for the screening of family members in MODY

Factors favouring specific molecular genetic testing in families fitting clinical criteria of MODY	
Glucokinase	FPG > 5.5 mmol/l at all ages FPG raised from early childhood Small OGTT increment (< 3.0 mmol/l)
HNF-1α	FPG < 5.5 mmol/l in childhood Increase in FPG with age Large OGTT increment (> 3.0 mmol/l, especially when FPG < 5.5 mmol/l)
Recommendations for screening method for unaffected MODY family members	
Glucokinase	Fasting plasma glucose FPG < 5.5 mmol/l makes glucokinase mutation very unlikely
HNF-1α	Oral glucose tolerance test FPG often normal and 2-h glucose higher when mild hyperglycaemia

used. In contrast, in subjects with *HNF-1α* mutations, FPG alone would fail to detect 60 % of subjects found to be diabetic on 2-h OGTT values.

The fasting hyperglycaemia coupled with a small increment and relatively low 2-h glucose value observed in subjects with glucokinase mutations probably reflects their glucose sensing defect in pancreatic beta cells. The beta-cell defect causes a right shift in the dose response curve of glucose-induced insulin secretion but does not reduce the maximal insulin secretion [11]. Therefore when these subjects receive a large intravenous glucose bolus leading to a short-term glucose rise, the first-phase insulin response is still more or less preserved [33]. A 75 g oral glucose tolerance test also results in an early short-term glucose rise and hence early (30 min) insulin secretion will be relatively preserved as shown by the insulin values in a subset of patients (Fig. 5). The early peak insulin secretion will be reflected in a small rise in glucose values at 2-h of an OGTT.

In contrast to glucokinase subjects, *HNF-1α* subjects had a lower fasting glucose but had a larger glucose increase in response to an oral glucose load. This response is a reflection of the type of beta-cell dysfunction seen in *HNF-1α* mutation carriers [13] resulting in a blunted insulin secretion (Fig. 5). *HNF-1α* subjects who are not diabetic have a normal insulin secretion rate at normal glucose concentrations but do not appropriately increase their insulin secretion rate at plasma glucose concentrations above 8 mmol/l [13]. Therefore non-diabetic *HNF-1α* mutation carriers have adequate insulin secretion to maintain a fasting glucose but not sufficient to prevent the blood glucose rising in response to a glucose bolus. When *HNF-1α* subjects become overtly diabetic, there is reduced insulin secretion at all glucose concentrations and so fasting blood glucose is also raised [13].

One of the most interesting findings is the lack of correlation of the fasting and 2-h glucose values in subjects with glucokinase mutations. A striking and related observation is that neither age nor BMI differs between glucokinase subjects with a normal and diabetic 2-h glucose value. The reason for this is not clear but could be a characteristic of a glucose sensing disorder (see above). In large epidemiological studies it has been shown that subjects with a relatively high fasting glucose and relatively low 2-h glucose (ie. a similar pattern to glucokinase subjects) have relatively low rates of cardiovascular mortality [8]. It could well be that those individuals with a high fasting and relatively low 2-h glucose value in the general population have a different cause for their hyperglycaemia when compared to those with a low fasting and relatively high 2-h glucose. It would be interesting to see if subjects in large population surveys who have a diabetic fasting value but non diabetic 2-h value show the same lack of correlation between their fasting and 2-h glucose that we have described in glucokinase subjects. These subjects could share other characteristics with glucokinase subjects including a glucose sensing abnormality on physiological testing [11], normal lipid profile [34] and a relatively normal proinsulin/insulin ratio [35, 36].

Fasting blood glucose was 5.5 mmol/l or more in the vast majority of glucokinase patients at all ages and over 6.0 mmol/l in 77.2 % subjects under 20 years of age. This indicates that the glucokinase mutation subjects have a stable beta-cell defect which is present in utero, as shown by reduced insulin-mediated fetal growth and so have hyperglycaemia from birth which can be detected very early in life [18, 37]. There is a very small but significant deterioration in fasting glucose and beta-cell function with age which is at a similar rate to that seen in the non-diabetic family members [34]. Both fasting and 2-h values were lower in *HNF-1α* subjects below 20 years of age compared to subjects over this age. Altogether 46.2 % of all the *HNF-1α* subjects had a fasting glucose under 5.5 mmol/l, these were usually under 20 years of age. Only 20.8 % subjects under 20 years of age had a FPG over 6.0 mmol/l. The deterioration with age seen in FPG in *HNF-1α* is underestimated in our data set as most patients on treatment have not under gone an OGTT and the proportion of patients requiring treatment increases with age. Despite this, as in previous studies [36], there is a decline in FPG with age which reflects the progressive beta-cell failure resulting from *HNF-1α* mutations [9, 13].

The differences in FPG and response to an oral glucose load could be used to guide the practical management of subjects with MODY (Table 5) Table 5. In families with clinical features of MODY (early onset- < 25 years, non-insulin dependent diabetes and autosomal dominant inheritance), the OGTT response can help suggest a possible genetic

diagnosis. A glucokinase mutation is not very likely if a diabetic subject has had an FPG of under 5.5 mmol/l. Altogether 98 % of subjects with glucokinase had a FPG of greater than or equal to 5.5 mmol/l. Of 5 subjects with a FPG of less than 5.5 mmol/l, 4 subsequently had a higher value than this on repeat testing. Glucokinase mutations are usually associated with a persistently high FPG from early childhood and a small increase on OGTT, typically less than 3.0 mmol/l. The presence of raised fasting glucose and a small increase on OGTT has been successfully used for recognising subjects with gestational diabetes who have glucokinase mutations [15]. *HNF-1α* subjects are more likely to show a progression from NGT to IGT to overt diabetes. Although FPG could be normal, a large 2-h fasting increase is seen on OGTT, typically more than 3.0 mmol/l.

We recommend that a full OGTT be done when testing MODY family members at risk of carrying an *HNF-1α* mutations but for glucokinase families a fasting plasma glucose is adequate.

In conclusion, the response to an oral glucose load in these two genetic subtypes is markedly different. FPG and increment are good discriminators between the two groups and can be used to guide molecular genetic testing. An increased use of fasting rather than 2-h values will result in a greater number of glucokinase subjects and fewer *HNF-1α* subjects being defined as having diabetes which is not desirable as the incidence of microvascular complications is much higher in *HNF-1α* subjects [17, 38]. Glucokinase subjects are, to our knowledge, the first hyperglycaemic subjects described in which 2-h glucose is not correlated with FPG. We have shown that OGTT results reflect not only the degree of hyperglycaemia but also the underlying causes.

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