Recognition and Management of Individuals With Hyperglycemia Because of a Heterozygous Glucokinase Mutation

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Glucokinase–maturity-onset diabetes of the young (GCK-MODY), also known as MODY2, is caused by heterozygous inactivating mutations in the *GCK* gene. *GCK* gene mutations are present in ~1 in 1,000 of the population, but most are not diagnosed. They are common causes of MODY (10–60%): persistent incidental childhood hyperglycemia (10–60%) and gestational diabetes mellitus (1–2%). GCK-MODY has a unique pathophysiology and clinical characteristics, so it is best considered as a discrete genetic subgroup. People with GCK-MODY have a defect in glucose sensing; hence, glucose homeostasis is maintained at a higher set point resulting in mild, asymptomatic fasting hyperglycemia (5.4–8.3 mmol/L, HbA_{1c} range 5.8–7.6% [40–60 mmol/mol]), which is present from birth and shows slight deterioration with age. Even after 50 years of mild hyperglycemia, people with GCK-MODY do not develop significant microvascular complications, and the prevalence of macrovascular complications is probably similar to that in the general population. Treatment is not recommended outside pregnancy because glucose-lowering therapy is ineffective in people with GCK-MODY and there is a lack of long-term complications. In pregnancy, fetal growth is primarily determined by whether the fetus inherits the *GCK* gene mutation from their mother. Insulin treatment of the mother is only appropriate when increased fetal abdominal growth on scanning suggests the fetus is unaffected. The impact on outcome of maternal insulin treatment is limited owing to the difficulty in altering maternal glycemia in these patients. Making the diagnosis of GCK-MODY through genetic testing is essential to avoid unnecessary treatment and investigations, especially when patients are misdiagnosed with type 1 or type 2 diabetes.

Heterozygous mutations in the glucokinase (GCK) gene were first recognized as a cause of maturity-onset diabetes of the young (MODY) in 1992 (1,2), and this led to the recognition that GCK-MODY is a discrete type of diabetes/hyperglycemia (2,3). Since then, GCK mutations have been described throughout the world and are routinely tested for in many countries.

This article reviews what is known about GCK-MODY, which is caused by heterozygous inactivating mutations. The emphasis is on clinical management including when to consider genetic testing, treatment requirements, complication risk, and the management of affected women in pregnancy.

Role of the GCK Enzyme in Humans

GCK is a glycolytic enzyme that is one of the four members of the hexokinase family. It catalyzes the conversion of glucose to glucose-6-phosphate, the first step of

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glucose metabolism in the β-cell and hepatocyte. GCK is a key regulatory enzyme in the pancreatic β-cell and has been referred to as the pancreatic β-cells' glucose sensor (4,5). The unique catalytic properties of GCK, which include a markedly lower affinity for glucose than other hexokinases and lack of significant feedback inhibition, mean the rate of glucose phosphorylation is proportional to the glucose concentration in the normal physiological range (5,6). GCK also plays a critical role in the liver and in neuronal cells involved in glucose regulation (7–9).

The key role of GCK is reflected in the physiology of people with GCK-MODY resulting from heterozygous inactivating *GCK* gene mutations. In GCK-MODY, the fasting glucose is raised, but the glucose is regulated at this higher level with first-phase insulin response maintained (10,11). Byrne et al. (12) demonstrated a clear defect in glucose sensing in GCK-MODY with reduced insulin secretion at a given glucose level compared with control subjects. Patients with GCK-MODY have also been reported to have reduced hepatic glycogen production and augmented gluconeogenesis after meals (13). There is also evidence from euglycemic clamps that subjects with GCK-MODY have reduced suppression of hepatic glucose production by physiological concentrations of insulin (14). This increased rate of gluconeogenesis is likely to contribute to hyperglycemia in GCK-MODY. Further support for this comes from a study that demonstrated decreased hepatic glucose cycling and abnormally high endogenous glucose production relative to plasma glucose concentrations in GCK-MODY individuals (13,15).

Heterozygous Inactivating *GCK* Gene Mutations Cause Mild Hyperglycemia Known as GCK-MODY

In individuals with GCK-MODY, glucose homeostasis is maintained at a higher set point, and affected people have mild, asymptomatic fasting hyperglycemia (5.4–8.3 mmol/L) and an HbA_{1c} ~5.8–7.6% (40–60 mmol/mol) (16). The mild hyperglycemia is present from birth (17) and shows only slight deterioration with age (similar to that seen in healthy people without diabetes) (18,19). The details of this phenotype follow.

GCK-MODY Differs Greatly From Other Subgroups of MODY

Mutations in the *GCK* gene were initially found using linkage in large MODY families in France (1) and England (2). After this initial gene identification, there has been considerable progress in defining the molecular genetic etiology of MODY (20–22). The other major molecular genetic causes of MODY are mutations in the transcription factors (hepatic nuclear factors [HNF]1A, -4A, and -1B). Patients with transcription factor MODY have a strikingly different diabetes phenotype compared with GCK-MODY: they are born with normoglycemia and develop diabetes in adolescence or as young adults, the diabetes progresses resulting in marked hyperglycemia, and there are increasing treatment requirements and risk of diabetes-associated complications. The mild hyperglycemia and distinct pathophysiology of people with GCK-MODY mean they are best considered as a discrete genetic subgroup, which is very different from other MODY subtypes (21).

Prevalence of GCK-MODY

Population Prevalence

Prevalence studies have been performed in selected groups with hyperglycemia (discussed below), but the whole population prevalence of GCK-MODY has recently been directly assessed in a single study. A prevalence of 1.1 in 1,000 (95% CI 0.3, 2.9) was found in a predominantly white European population (23).

GCK-MODY is underdiagnosed. Within the U.K., the prevalence data suggest that 60,000 people have GCK-MODY; however, only 1% of these have a genetic diagnosis (24). There are a number of reasons for the underdiagnosis of GCK-MODY. First, as it is asymptomatic and benign, in many people the hyperglycemia diabetes is not diagnosed. Second, many cases of GCK-MODY are misclassified as type 1 or type 2 diabetes or impaired fasting glucose (24). It is important to diagnose these patients correctly, as they may be taking unnecessary treatment and have been given the wrong advice about their condition (25). Finally, there are barriers to genetic testing: both a lack of knowledge of the condition by health care professionals and the cost of the genetic testing (£350 for *GCK* gene testing [Exeter Molecular Genetics Laboratory]). As the costs of DNA sequencing fall, one of the main barriers to genetic testing will be reduced.

Prevalence of GCK-MODY in MODY

GCK-MODY and HNF1A-MODY are the most common causes of MODY (21,22,24). The precise prevalence depends on the definition of MODY, how families are ascertained, and the criteria used to define affected status (e.g., fasting hyperglycemia vs. diabetes). Most large series suggest a prevalence of 10–60% in tightly defined MODY. The prevalence of GCK-MODY is reported as being higher in southern European countries (France, Spain, and Italy) (26–29) compared with northern European countries (U.K., Sweden, Finland, and Norway) (24,30,31). This high prevalence of GCK-MODY may reflect predominant ascertainment from pediatric rather than adult clinics. The high prevalence of GCK-MODY in a pediatric survey in Poland is consistent with this (32).

Most studies of GCK-MODY are in white European populations. *GCK* gene mutations have been described in other ethnic groups, but studies in this area are limited (33,34). The phenotype of GCK-MODY in far Eastern and South Asian populations appears similar to that seen in the U.K. population (35–39). There is no reason to suspect a different prevalence of GCK-MODY in non-European populations, though the differentiation from other forms of diabetes may be different given the higher prevalence of type 2 diabetes, particularly in black and South Asian populations (33–38).

Prevalence of GCK-MODY in Children and Adults With Incidental Hyperglycemia

GCK-MODY is a very common cause (23–65%) of incidental hyperglycemia in children, especially when the fasting glucose is persistently above 5.5 mmol/L (29,40–44). Awareness of such high GCK-MODY prevalence rates in children with mild fasting hyperglycemia will aid early, correct diagnosis and management. In contrast, GCK-MODY is rare in adults with mild fasting hyperglycemia. *GCK* gene mutations were found in 0.76% (5 of 798) nondiabetic adults aged 30–70 years (45). The discrepancy between childhood and adult prevalence of GCK-MODY in patients with hyperglycemia reflects the likelihood of an alternative diagnosis. In adults, hyperglycemia below the criteria for diabetes is common and reflects impaired glucose tolerance on a trajectory to type 2 diabetes, whereas in children this is very unusual (45).

Prevalence of GCK-MODY in Gestational Diabetes Mellitus

Pregnancy is a time when asymptomatic women are screened for hyperglycemia,

and so women with GCK-MODY may be detected as having gestational diabetes mellitus. Approximately 2% (range 0–6%) of women with a diagnosis of gestational diabetes mellitus have a heterozygous *GCK* gene mutation (23,34,46–53). The detection rate can be increased considerably by using additional criteria such as a normal BMI, a fasting glucose >5.4 mmol/L, fasting hyperglycemia outside pregnancy, and family history (23,34,46).

Clinical Phenotype, Presentation, and Differential Diagnosis of GCK-MODY

Correct identification of GCK-MODY is important, as treatment, follow-up, and prognosis are different from those of the more common forms of diabetes both during and outside pregnancy. (See below.)

Clinical Features of GCK-MODY

In keeping with the physiological role of GCK, the clinical features are limited to hyperglycemia. Heterozygous *GCK* gene mutations result in mild fasting hyperglycemia (5.4–8.3 mmol/L) and an HbA_{1c} ~5.8–7.6% (40–60 mmol/mol) (16). The fasting hyperglycemia is present from birth (17), and there is a mild deterioration in glycemia with age (19,54). Blood glucose in people in their eighth and ninth decade rarely exceeds 10 mmol/L (55). This slow deterioration in β-cell function over time reflects changes observed in the general population (16,19,55). The raised fasting glucose is not correlated with BMI (54) so occurs to a similar degree in both slim and obese individuals.

A key feature is that the glucose is regulated at its higher set point: this is shown by the limited excursions in blood glucose, with ~70% having a 2-h glucose increment ≤3 mmol/L during an oral glucose tolerance test (54,55). People with GCK-MODY also maintain their elevated fasting glucose by counterregulating at higher glucose values than normal control subjects (56). Hence, there are considerable homeostatic mechanisms maintaining the glucose at its elevated set point.

Presentation of GCK-MODY Is Usually Incidental

The mild hyperglycemia seen in GCK-MODY is below the renal threshold, and, hence, glycosuria and the consequent symptoms of polyuria, polydipsia, and weight loss are rarely seen, or if they are seen, they are not related to glycosuria. Presentation is therefore usually by the finding of a raised glucose incidentally or on screening of an asymptomatic individual. Diagnosis may be at any age and therefore may result from blood testing that is performed during hospital admissions for other conditions, health screening, or insurance medicals.

Women with GCK-MODY are often picked up in the widespread testing performed for gestational diabetes mellitus in pregnancy. (See below.)

Differential Diagnosis of GCK-MODY

Patients with GCK-MODY are often initially misdiagnosed as having early type 1 or type 2 diabetes. Clinical features are key in supporting or refuting the diagnosis of GCK-MODY (Table 1).

The tight regulation of glycemia in people with GCK mutations is one of the most useful features in the differential diagnosis. People with GCK-MODY have a fasting glucose between 5.4 and 8.3 mmol/L and HbA_{1c} between 5.8 and 7.6% (40–60 mmol/mol) (16). Therefore, a fasting plasma glucose and/or HbA_{1c} above or below these limits can be usefully used to exclude the diagnosis of GCK-MODY.

Table 1—Clinical features of GCK-MODY and differentiation from more common forms of diabetes

	GCK-MODY	Type 1 diabetes	Type 2 diabetes	Gestational diabetes mellitus	HNF1A/HNF4A–MODY
Diagnostic fasting glucose (mmol/L)	5.4–8.3	≥7.0	≥7.0	≥5.1*	≥7.0 once developed diabetes
Diagnostic HbA_{1c}, %	5.8–7.6	≥6.5	≥6.5	Not routinely used in diagnosis	≥6.5
Diagnostic HbA_{1c}, mmol/mol	40–60	≥48 (progressive)	≥48 (progressive)		≥48 (progressive)
OGTT	Increment typically (71%) <3.0 mmol/L	Increment typically >3.0 mmol/L	Increment typically >3.0 mmol/L	Increment typically (60%) <3.0 mmol/L	Increment typically (67%) >3.0 mmol/L
Prognosis	Stable; population risk of type 1 or type 2 diabetes	Progressive	Progressive	Normal glycemia postpartum; ↑ risk of type 2 diabetes	Progressive
Presenting features	Asymptomatic	Polyuria, polydipsia, weight loss	Polyuria, polydipsia but may be asymptomatic	Asymptomatic	Polyuria, polydipsia but may be asymptomatic
Age at diagnosis	When tested	Typically child or young adult	Typically middle- or old age	In pregnancy	Typically adolescent or young adult
Parental history	>50% (>95% if tested)	10–20%	~50% if diagnosed at <35 years old	~30%	90%
Obesity	As per normal population	As per normal population	Obesity is common	Typically overweight/obese	As per normal population
Treatment	None	Insulin	Diet, OHA, insulin	Diet, OHA, insulin	Diet, SU, insulin
C-peptide	Positive	Negative outside honeymoon	Positive	Positive	Positive
Pancreatic autoantibodies	Negative	Positive (80%)	Negative	Negative	Negative

OHA, oral hypoglycemic agent; SU, sulfonylurea. *World Health Organization fasting criteria (91).

Age at diagnosis may not be helpful: GCK-MODY is present from birth but may be diagnosed at any age. Although almost all people will have inherited the *GCK* gene mutation from an affected parent, they may not be diagnosed as having diabetes or known to have mild hyperglycemia, so there may not be a known family history. When suspecting a diagnosis of GCK-MODY in a child, testing HbA_{1c} and/or fasting glucose in both parents can be very helpful.

People with GCK-MODY can be differentiated from those with type 1 diabetes, as hyperglycemia is less severe, pancreatic autoantibodies are rare (57), and C-peptide is not low (58). People with GCK-MODY are usually less obese as well as less hyperglycemic than people with young-onset type 2 diabetes. A useful MODY probability calculator that models age at diagnosis, BMI, HbA_{1c}, family history, and treatment to provide a probability of the common forms of MODY can be found at http://diabetesgenes.org/content/mody-probability-calculator (59). HNF1A-MODY and HNF4A-MODY are much more rapidly progressive than GCK-MODY, and so symptomatic diabetes and marked hyperglycemia are common in these forms of MODY.

When to Consider Testing a Person for GCK-MODY

There are no defining clinical features of GCK-MODY, so testing is based on clinical likelihood. Individuals should only be tested when they have a fasting glucose consistently in the range 5.4–8.3 mmol/L or HbA_{1c} that remains between 5.8 and 7.6% (40–60 mmol/mol), but many people with glucose and HbA_{1c} values in this range will not have GCK-MODY. The probability that it is GCK-MODY greatly increases when patients are young (<30 years old) and nonobese and, hence, less likely to have type 2 diabetes/impaired glucose tolerance (Table 1). A first-degree family history of known GCK-MODY or mild hyperglycemia meeting GCK-MODY criteria (this often needs to be tested for) further increases the probability of GCK-MODY.

Molecular Genetic Diagnosis of GCK-MODY

A diagnosis of GCK-MODY can only be confirmed when molecular genetic testing identifies a heterozygous *GCK* gene mutation.

More than 600 different mutations have been identified throughout the 10 pancreatic β-cell exons of the *GCK* gene in >1,400 families (60). Almost all cases of GCK-MODY are due to missense (65%), nonsense, frameshift, or splice site mutations (61). Rare causes include *GCK* pancreatic islet promoter mutations (62) and partial and whole gene deletions (63,64). The majority (59%) of the mutations are reported as private (reported within one family) or novel (60). Although GCK-MODY is usually familial and characterized by autosomal dominant inheritance, de novo mutations occur but are rare, with only 14 cases reported (27,33,43,65–67). It is difficult to ascertain how many mutations are de novo, as asymptomatic parents are often not tested, but a systematic study found 4% (6 of 150), suggesting they may be more common than previously thought (67).

The vast majority of mutations that alter the structure of glucokinase are inactivating mutations that result in GCK-MODY. However, there are also polymorphisms without a phenotype and activating mutations affecting the coding region that result in hypoglycemia (60).

Functional Analysis of GCK Gene Mutations

Functional studies have been undertaken for a minority (~80 of 620) of the mutations causing GCK-MODY (60,61,68), demonstrating a spectrum of kinetic defects for these mutations. Importantly, subjects with GCK-MODY have a remarkably similar clinical phenotype irrespective of the severity of their mutation (54). There is considerable evidence that high glucose induces β-cell glucokinase by a posttranslational mechanism, which allows the wild-type allele to partly compensate for the mutant allele (69–71).

Recent work has shown that protein stability is the key determinant of enzyme function where there is residual kinetic function (68). These studies have provided important insights into the structure and regulation of glucokinase and can provide additional confidence in the interpretation of the significance of a genetic variant in glucokinase (72).

Diabetes-Related Complications Are Rare in People With GCK-MODY

Diabetes-related complications are rare in individuals with GCK-MODY (Table 2 and Fig. 1). Several studies have shown very low prevalence of diabetes-related complications in discrete cohorts of people with GCK-MODY (19,26–28,31,73). This is likely to be due to a number of factors: the hyperglycemia is mild, stable, and under homeostatic regulation; the hyperglycemia is often lower than the threshold above which the risk of diabetes complications increases (26); and people with GCK-MODY do not have the additional burden of the metabolic syndrome, with weight, lipid profile, and blood pressure being comparable with the general population (27,73).

Microvascular Complications

Table 2 shows the studies investigating microvascular complications in GCK-MODY. These show that diabetes complications in GCK-MODY are comparable with the healthy population and much less frequent than in those with type 2 diabetes. This is in keeping with the modest hyperglycemia in these people.

In the one large comprehensive, cross-sectional study of all diabetes complications in GCK-MODY patients, with a mean of 49 years of mild hyperglycemia, the only complication that was increased in GCK-MODY compared with healthy control subjects was background retinopathy (19). No patients with GCK-MODY were found to have proliferative or other sight-threatening retinopathy. Microalbuminuria was only found in 1% of GCK-MODY and 2% healthy control subjects.

Macrovascular Complications

Descriptions of macrovascular complications are rare in GCK-MODY. The few reports of patients with ischemic heart disease have been in older male patients, often with comorbid risk factors such as smoking (27,31,73).

The incidence of macrovascular disease (peripheral vascular, cardiovascular, and cerebrovascular disease) in GCK-MODY is likely to be similar to that of the general population and lower than in type 1 and type 2 diabetes. However, the modest sized, retrospective cross-sectional studies to date are limited in their power to determine differences in prevalence of macrovascular disease. The prevalence of macrovascular disease in an adult (mean age ~50 years) GCK-MODY cohort matched that of healthy control subjects but was much less than in those with type 2 diabetes of a similar age (GCK-MODY 4% vs. type 2 diabetes 30%; $P < 0.001$) (19). The low risk of cardiovascular disease may be augmented by the cardioprotective lipid profile seen in GCK-MODY (74).

Table 2—Published reports of the microvascular complications seen in GCK-MODY compared with healthy control subjects and subjects with type 2 diabetes

First author, year of publication	Complication	Subjects with GCK-MODY	Healthy control subjects	Subjects with type 2 diabetes
Steele, 2014 (19)	Proliferative retinopathy	0 (0/90)	0 (0/87)	10 (8/83)
	Any proteinuria including microalbuminuria	1 (1/97)	2 (2/89)	31 (25/80)
	Peripheral neuropathy	2 (2/93)	0 (0/89)	29 (24/83)
Sagen, 2008 (31)	Retinopathy	6 (3/56)	Not assessed	Not assessed
Costa, 2000 (28)	All	0 (0/12)	Not assessed	Not assessed
Velho, 1996 (26)	Proliferative retinopathy	3 (2/65)	Not assessed	23 (34/150)
	Any proteinuria	5 (4/78)	Not assessed	7 (11/166)
	Peripheral neuropathy	5 (5/96)	Not assessed	17 (36/212)
Page, 1995 (73)	Proliferative retinopathy	0 (0/17)	0	Not assessed
	ACR	No difference between case and control subjects		
	Peripheral neuropathy	No difference between case and control subjects		

Data are % (*n*/*n*).

Treatment in GCK-MODY

Treatment Is Not Effective or Needed in GCK-MODY

GCK-MODY cohorts show that most people with GCK-MODY are not treated with hypoglycemic agents. Approximately 20% of family members with GCK-MODY receive treatment, the vast majority of these being treated with oral agents (proportions on treatment out of the respective cohort: U.K. 1992, 3 of 14 [21%] [2]; France 1996, 44 of 189 [23%] [26]; Norway 2001, 15 of 56 [26%] [31]; and U.K. 2013, 168 of 799 [28%] [25]).

There is no evidence that pharmaceutical therapy in the doses used in GCK-MODY alters glucose control. In 799 U.K. GCK-MODY patients, there was no difference in the HbA_{1c} in GCK-MODY who were on or off treatment (6.5 vs. 6.4% [48 vs. 46 mmol/mol]) (25). In a longitudinal study, stopping pharmaceutical therapy in GCK-MODY patients did not result in a deterioration in glycemia (mean change in HbA_{1c} −0.06% [95% CI −0.27, 0.15], 0.68 mmol/mol [95% CI −2.97, 1.61]) (25). The lack of response reflects that glycemia is tightly regulated by homeostatic mechanisms in GCK-MODY that counteract the glucose-lowering effect of treatment (e.g., when subreplacement exogenous insulin doses are given, endogenous insulin secretion is reduced and glycemia is not altered).

Diet alteration is likely to have little impact on the glycemic status of people with GCK-MODY, as there is a small increment on oral glucose tolerance test (54) and preserved glucose homeostasis.

The lack of effectiveness of glucose-lowering therapy and the lack of complications seen in GCK-MODY mean treatment is not recommended (outside pregnancy). If a person on treatment is diagnosed with GCK-MODY, their treatment should be stopped unless there is good evidence of concurrent type 1 or type 2 diabetes (25).

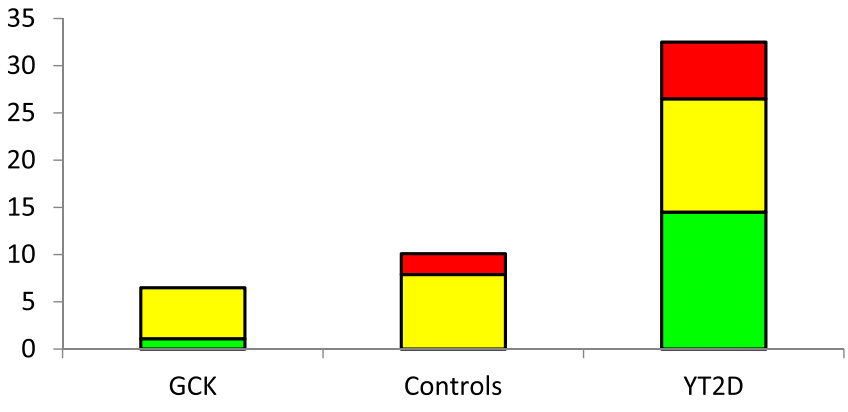

Figure 1—Prevalence of clinically significant microvascular (green) and clinically significant macrovascular (yellow) disease alone and combined microvascular and macrovascular disease combined (red) in patients with GCK-MODY (GCK), control subjects, and patients with young-onset type 2 diabetes (YT2D). Clinically significant microvascular disease, defined as greater than background retinopathy or persistent microalbuminuria or proteinuria; clinically significant macrovascular disease, defined as intermittent claudication, amputation, angina, myocardial infarction, or stroke.

GCK and Pregnancy

It is important to identify GCK-MODY in a pregnant woman diagnosed with gestational diabetes mellitus, as they require different management. The key difference is that fetal growth and, hence, the risk of complications predominantly depend on whether the fetus inherits the mutation rather than the degree of maternal glycemia (75–77).

Recognizing When Patients Presenting With Gestational Diabetes Mellitus Are Likely to Have a GCK Gene Mutation

Women with GCK-MODY will meet the International Association of the Diabetes and Pregnancy Study Groups/World Health Organization criteria for gestational diabetes mellitus because of their fasting hyperglycemia and are often first identified in pregnancy. Women with GCK-MODY will have a lower BMI,

younger age, and higher fasting glucose than those with non–GCK-MODY gestational diabetes mellitus (23). A pragmatic approach to identifying those with GCK-MODY in pregnancy is to genetically test all women with a BMI <25 kg/m^2 and a fasting blood glucose ≥5.5 mmol/L. This has a sensitivity of 68% and on average 2.7 patients will be needed to be tested to identify one case of GCK-MODY (23).

Inheritance of the GCK Gene Mutation Is the Main Determinant of Fetal Growth

The Pedersen hypothesis (78) states that in diabetic pregnancies, maternal high glucose crosses the placenta and results in fetal hyperglycemia. The high fetal glucose level results in increased stimulation of fetal insulin secretion. Fetal insulin acts as a growth hormone in utero, particularly during the third trimester, so there is an increased risk of macrosomia. The risk of macrosomia is linearly associated with the level of maternal glycemia in pregnancy (79).

In GCK-MODY pregnancy, whether the fetus senses the mild maternal hyperglycemia is determined by fetal genotype. Hence, the birth weight of offspring of women with GCK-MODY depends on whether the mutation is inherited or not (75–77,80). Half of the offspring will inherit the GCK-MODY mutation and so will have the same increased glucose set point as the mother, and, hence, fetal insulin secretion and birth weight will be normal. If the fetus does not inherit the mutation, it will sense the maternal glucose as high and have increased fetal insulin secretion. This results in increased corrected birth weight centile (Fig. 2) and a mean birth weight 700 g higher in babies that do not inherit a *GCK* gene mutation (77). Fifty-five percent of babies that do not inherit a maternal *GCK* gene mutation are greater than the 90th centile compared with 9% who do inherit the maternal *GCK* gene mutation ($P < 0.001$) (77).

Babies with a *GCK* gene mutation born to a mother without a mutation (a paternally inherited or de novo mutation) have a reduced birth weight of ~400 g as a result of reduced fetal insulin secretion causing reduced insulin-mediated growth (75–77). This will result in an approximate trebling in offspring classified as small for gestational age (<10th centile).

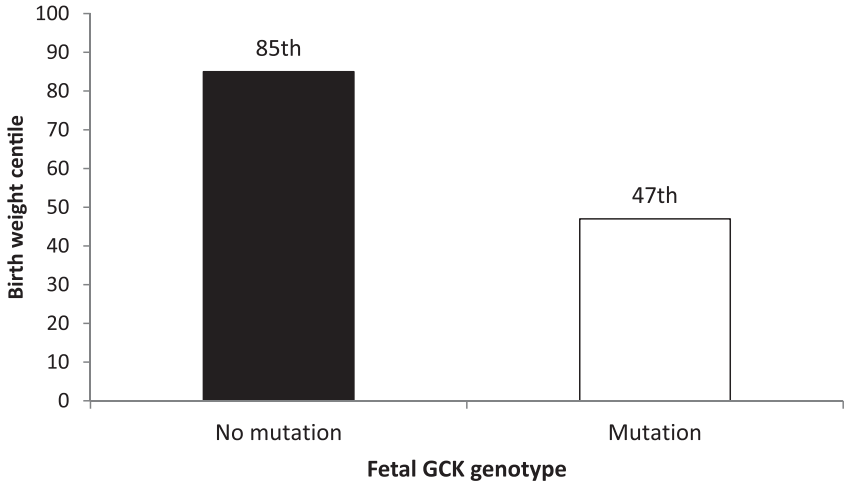

Figure 2—Mean birth weight centile in offspring of pregnant women with a *GCK* mutation (77). Baby unaffected, ■; baby affected, □.

Long-term Consequences for Offspring of Pregnant Women With GCK-MODY

The congenital anomaly risk in GCK-MODY pregnancies has not been reported and may be hard to accurately estimate given the small number of cases. Despite the impact on fetal growth, there is no evidence that the exposure to maternal hyperglycemia in pregnancies of GCK-MODY mothers has long-term consequences. In large studies, BMI, insulin secretion, insulin sensitivity, blood pressure, and lipid profile did not differ in the offspring exposed or not exposed to maternal hyperglycemia (76,81).

Clinical Management During Pregnancy

Offspring of women with GCK-MODY are at increased risk of macrosomia and the consequent obstetric complications only if the fetus has not inherited the maternal mutation (Fig. 2). Hence, treatment of the maternal hyperglycemia is only appropriate when the fetus has not inherited the mutation (82). We usually do not know fetal genotype during pregnancy, and the miscarriage risks of invasive fetal genotyping (chorionic villus sampling or amniocentesis) are not warranted unless done for another reason (83). This has led to a pragmatic solution: the management of these women in pregnancy based on fetal growth scans (Fig. 3).

Women with GCK-MODY should not be treated preconceptually with insulin, and treatment during the pregnancy should be based on clinical observation of the fetus (77). Several trials (84–86) have successfully used a fetal abdominal circumference <75th centile to identify those diabetes pregnancies that are safe to treat with diet treatment alone, as they are at low risk of adverse outcomes (including macrosomia). These data have been extrapolated to GCK-MODY pregnancies. Current advice is for fortnightly scans from 26 weeks' gestation. If the fetal abdominal circumference is rising disproportionally above the 75th centile, then, to prevent the risks associated with macrosomia, insulin treatment should be started and labor should be induced at 38 weeks (77,82).

Use of Insulin During GCK-MODY Pregnancy

Insulin treatment is only recommended for pregnant women with GCK-MODY if the fetus shows excessive growth (a surrogate for the fetus not inheriting the *GCK* gene mutation). If the fetus has inherited the mutation, reduced fetal growth can be seen with aggressive insulin treatment aiming for maternal euglycemia, whereas in this situation normal growth is expected with no treatment (Fig. 2) (77,82).

The intention behind using insulin treatment in pregnancy is to reduce fetal growth, but this was not seen in a retrospective study of 82 offspring of affected mothers (77). This probably reflects the difficulty in reducing the regulated hyperglycemia associated with GCK mutation. The defect in glucose sensing means that any exogenous insulin treatment will be counteracted by reduction in endogenous insulin secretion unless the dose of insulin exceeds a replacement dose (i.e., >0.5–1 unit/kg/day) (82). In addition,

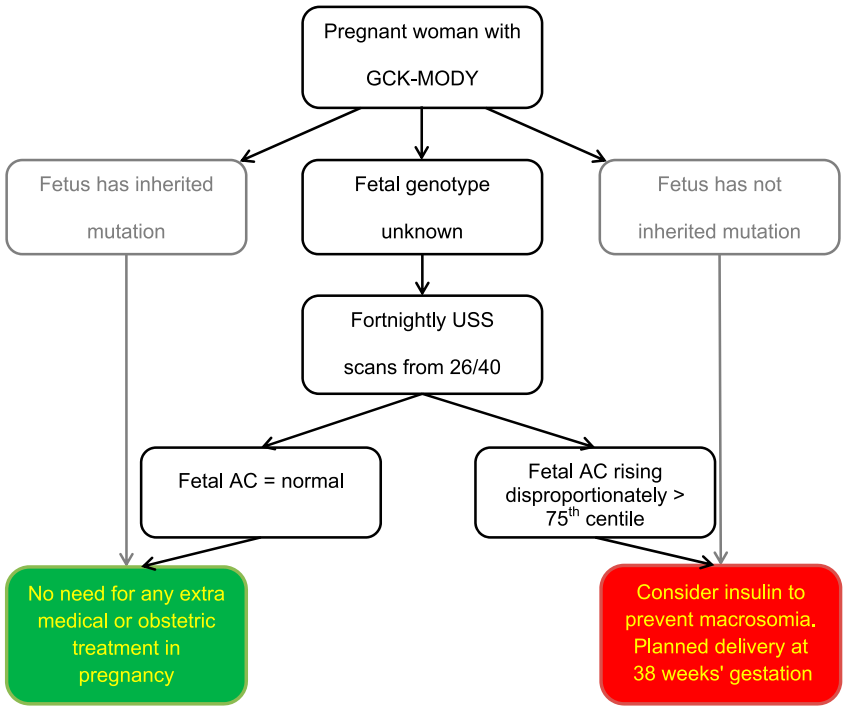

Figure 3—Flow diagram for the management of GCK-MODY pregnancy. AC, abdominal circumference; USS, ultrasound scan.

counterregulation maintains the higher glucose concentration in GCK-MODY (56). Anecdotal reports about pregnant women with GCK-MODY describe the women having symptoms of hypoglycemia when their glucose values are lowered to the usual pregnancy target range (M.H.S., unpublished observations).

Given the difficulty in lowering maternal glycemia, in pregnancy when there is increased fetal growth, it is important to consider induction at 38 weeks.

There is no published information on the effect of metformin in GCK-MODY pregnancy, which would be of interest given its safety in pregnancy, although data on its use outside pregnancy suggest that it is not effective in lowering glucose in GCK-MODY. (See above.) We would not recommend a sulfonylurea given its lack of efficacy outside pregnancy (see above) and recent evidence that glibenclamide crosses the placenta (87,88) and result in increased fetal growth and macrosomia (89).

Practical Management of People With GCK-MODY

GCK-MODY Is Best Not Considered a Subtype of Diabetes

People with GCK-MODY have lifelong mild stable fasting hyperglycemia. They do not respond to or require treatment (outside pregnancy) and are not at risk for the complications associated with diabetes. A major question given the implications is whether they are best considered a subgroup of nondiabetic hyperglycemia rather than a subtype of diabetes. A proportion (38–48%) of people with GCK-MODY will meet fasting or 2-h glucose criteria for diabetes (16,27,54), and approximately two-thirds will meet HbA_{1c} diagnostic criteria for diabetes (16). The key point is that they do not have the severe long-term consequences of a diagnosis of type 1 or type 2 diabetes or other monogenic forms of diabetes, and, hence, the label "diabetes" is misleading. It is clearly not appropriate that people with GCK-MODY should have the usual diabetes weighting for insurance (something accepted by all insurance firms we have approached on the behalf of patients [A.T.H., unpublished observations]). Similarly, they can successfully work in professions that usually have restrictions placed on people with diabetes (A.T.H., unpublished observations).

Family Screening When an Individual Is Diagnosed With GCK-MODY

When an individual is diagnosed with GCK-MODY, all family members who already have a diagnosis of diabetes should have molecular genetic testing for GCK-MODY. A patient who was thought to have type 1 or type 2 diabetes that is subsequently correctly diagnosed as GCK-MODY is likely to be able to stop treatment and reduce follow-up. Testing for a known mutation is much cheaper than analyzing the whole gene (£100 vs. £350) and is inexpensive compared with the lifetime costs of an incorrect diagnosis; genetic testing of family members with a diagnosis of diabetes is therefore recommended.

For family members without a diagnosis of diabetes, it can be argued that genetic screening is unnecessary. This should be broached on a case-by-case basis highlighting the pros, knowing the diagnosis and recognition that no treatment is required, versus the cons, a potential label of "diabetes." If family screening is considered, a fasting blood glucose should be the first step, as in the majority of cases a fasting glucose $<$5.4 mmol/L will rule out a diagnosis of GCK-MODY (54).

If family screening is not taken up, family members should be made aware of the diagnosis of GCK-MODY within other family members so that if they are ever diagnosed with hyperglycemia or diabetes, they can highlight a *GCK* gene mutation as being the likely cause and molecular genetic testing can be organized at this point. Women planning pregnancy should have their fasting glucose tested and, if raised, a genetic *GCK* test should be performed (if not done previously), as the diagnosis of GCK-MODY will alter how their pregnancy is managed.

Follow-up and Testing for People With GCK-MODY

Individuals with GCK-MODY do not need follow-up. Indeed, the follow-up of children in clinics that predominantly deal with type 1 diabetes may be detrimental (90). Additionally, with the absence of any case studies reporting sight-threatening retinopathy, the long-term study by Steele et al. (19) and the fact that 1 in 1,000 of the population is estimated to have GCK-MODY and yet remains undiagnosed and unscreened suggest that retinal screening is not appropriate in individuals with GCK-MODY. Retinal screening should only be undertaken if the individual develops concurrent type 1 or type 2 diabetes.

Individuals with GCK-MODY are at the same risk of developing type 1 and type

2 diabetes as the general population. If they develop these more common types of diabetes, they will be at risk for complications and are likely to require additional follow-up and treatment (40,90). However, achieving glycemia less than the levels found in untreated GCK-MODY is extremely difficult in patients with type 1 or type 2 diabetes who also have a GCK mutation [M.H.S. and A.T.H., unpublished observations]. We suggest that concurrent type 1 or type 2 diabetes should only be considered when the HbA_{1c} clearly and repeatedly exceeds 7.6% (the 95% confidence limits in GCK-MODY) (16).

CONCLUSIONS

Heterozygous inactivating mutations result in GCK-MODY. Those with GCK-MODY have a mild fasting hyperglycemia (5.4–8.3 mmol/L) that does not require treatment (outside pregnancy), does not need or respond to hypoglycemic treatment, and does not result in the severe complications of diabetes. The fetal growth in pregnancy is dependent on whether the fetus inherits the mother's mutation; fetal growth should be measured as a surrogate for fetal genotype and the use of insulin treatment based on this. In individuals with GCK-MODY outside pregnancy, and in line with the general population, ensuring a healthy diet and lifestyle is generally the only intervention necessary.

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