Original Investigation

Prevalence of Vascular Complications Among Patients With Glucokinase Mutations and Prolonged, Mild Hyperglycemia

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IMPORTANCE Glycemic targets in diabetes have been developed to minimize complication risk. Patients with heterozygous, inactivating glucokinase (*GCK*) mutations have mild fasting hyperglycemia from birth, resulting in an elevated glycated hemoglobin (HbA_{1c}) level that mimics recommended levels for type 1 and type 2 diabetes.

OBJECTIVE To assess the association between chronic, mild hyperglycemia and complication prevalence and severity in patients with *GCK* mutations.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study in the United Kingdom between August 2008 and December 2010. Assessment of microvascular and macrovascular complications in participants 35 years or older was conducted in 99 *GCK* mutation carriers (median age, 48.6 years), 91 nondiabetic, familial, nonmutation carriers (control) (median age, 52.2 years), and 83 individuals with young-onset type 2 diabetes (YT2D), diagnosed at age 45 years or younger (median age, 54.7 years).

MAIN OUTCOMES AND MEASURES Prevalence and severity of nephropathy, retinopathy, peripheral neuropathy, peripheral vascular disease, and cardiovascular disease.

RESULTS Median HbA_{1c} was 6.9% in patients with the *GCK* mutation, 5.8% in controls, and 7.8% in patients with YT2D. Patients with *GCK* had a low prevalence of clinically significant microvascular complications (1% [95% CI, 0%-5%]) that was not significantly different from controls (2% [95% CI, 0.3%-8%], *P*=.52) and lower than in patients with YT2D (36% [95% CI, 25%-47%], *P*<.001). Thirty percent of patients with *GCK* had retinopathy (95% CI, 21%-41%) compared with 14% of controls (95% CI, 7%-23%, *P*=.007) and 63% of patients with YT2D (95% CI, 51%-73%, *P*<.001). Neither patients with *GCK* nor controls required laser therapy for retinopathy compared with 28% (95% CI, 18%-39%) of patients with YT2D (*P*<.001). Neither patients with *GCK* patients nor controls had proteinuria and microalbuminuria was rare (*GCK*, 1% [95% CI, 0.2%-6%]; controls, 2% [95% CI, 0.2%-8%]), whereas 10% (95% CI, 4%-19%) of YT2D patients had proteinuria (*P*<.001 vs *GCK*) and 21% (95% CI, 13%-32%) had microalbuminuria (*P*<.001). Neuropathy was rare in patients with *GCK* (2% [95% CI, 0.3%-8%]) and controls (95% CI, 0% [0%-4%]) but present in 29% (95% CI, 20%-50%) of YT2D patients (*P*<.001). Patients with *GCK* had a low prevalence of clinically significant macrovascular complications (4% [95% CI, 1%-10%]) that was not significantly different from controls (11% [95% CI, 5%-19%]; *P*=.09), and lower in prevalence than patients with YT2D (30% [95% CI, 21%-41%], *P*<.001).

CONCLUSIONS AND RELEVANCE Despite a median duration of 48.6 years of hyperglycemia, patients with a *GCK* mutation had low prevalence of microvascular and macrovascular complications. These findings may provide insights into the risks associated with isolated, mild hyperglycemia.

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In both type 1[1] and type 2 diabetes,[2] hyperglycemia is associated with microvascular complications over time. Intensive treatment to lower blood glucose levels reduces the development of microvascular complications.[3,4] In type 1 diabetes, lowering the blood glucose has been shown to have long-term beneficial effects on reducing macrovascular disease.[5] In type 2 diabetes, the follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) showed that lowering the level of hyperglycemia reduces the risk of macrovascular end points.[6] Additionally, associations have been seen between measures of glycemia and coronary heart disease throughout the nondiabetic range.[7]

Except for during pregnancy, a target glycated hemoglobin (HbA_{1c}) level lower than 7% has been recommended for people with diabetes,[8,9] yet longitudinal studies have few patients with sustained glycemia within this recommended target.[1,2] It is therefore of clinical importance to know the complication prevalence and severity in individuals with a long and sustained duration of glycemia at a level above that of the nondiabetic population but that mimics the current target range of 7%. Individuals with a heterozygous, inactivating mutation in the gene encoding the enzyme glucokinase have mild hyperglycemia that is present from birth. Their HbA_{1c} level is typically between 5.6% and 7.6%,[10,11] and their fasting plasma glucose level is between 99 mg/dL and 156 mg/dL (to convert to millimoles per liter, multiply by 0.0555).[11,12] These patients rarely require pharmacological treatment,[13] and their lipid and blood pressure levels are similar to that of the general population.[14,15] The hyperglycemia in patients with a glucokinase *GCK* mutation is therefore an isolated risk factor for complications.[14,15]

ACR *albumin to creatinine ratio*
GCK *glucokinase*
HbA_{1c} *glycated hemoglobin*
PVD *peripheral vascular disease*
YT2D *young-onset type 2 diabetes*

We assessed the prevalence and severity of microvascular and macrovascular complications in patients with *GCK* mutations to give further information about the relationship between current glycemic targets and diabetes-related complications. We also assessed these outcomes in nondiabetic, nonmutation carriers (control) and in patients with young-onset type 2 diabetes (YT2D).

Methods

Study Population

This study was approved by the Devon and Torbay research ethics committee and the National Health Service (NHS) Scotland Research Coordinating Centre, both located in the United Kingdom. Recruitment was undertaken between August 2008 and December 2010, and each patient provided written consent. Individuals known to have a *GCK* mutation through genetic testing in Exeter (the location of the UK testing center) were invited to participate. The majority of patients with a *GCK* mutation were from the southwest of England and Scotland, the 2 areas with the largest number of *GCK* cases in the United Kingdom. All family members aged 18 years or older were invited to participate. If genetic status was unknown in family members, diagnostic molecular genetic testing was performed to ascertain their mutation status, usually after the assessment of glycaemia and microvascular and macrovascular complications. To identify potential survival bias within families, we examined pedigrees of recruited patients with *GCK* and assessed the vital status of siblings and parents not recruited. We attempted to determine their mutation status and, when DNA of the deceased was not available, used the high penetrance of GCK maturity onset diabetes of the young (MODY) mutations and the autosomal dominant form of transmission to make obligate assignments of mutation carriage to the diabetic parent of a known mutation carrier when the other parent was known not to have diabetes. Deaths were balanced between mutation and nonmutation carrier siblings and parents (see supplementary data in the Supplement regarding family members who were not recruited). All patients were white as reported by the patients' referring clinicians.

Patients in the YT2D group were diagnosed before the age of 45 years, had not used insulin within a year of diagnosis, and were older than 35 years at the time of the study. These patients were recruited from an existing research cohort from southwest England, prioritized by proximity to Exeter. Patients unable to travel to Exeter were assessed at home or at a local hospital.

Assessment of Glycemia

The HbA_{1c} concentration was measured for all patients and analyzed in the biochemistry laboratory at the Royal Devon and Exeter NHS Foundation Trust (United Kingdom) on an automated glycohemoglobin analyzer (Tosoh G8 anion exchange HPLC, Tosoh Bioscience).

Assessment of Complications

Detailed methods of assessments are described in the Supplement. Data were collected by 1 of 2 researchers. The assessment of retinal photographs, biochemical measurements, and electrocardiographic assessment were blinded to assignment. However, researchers were not always blinded to participant group during clinical assessments (see the Supplement). Interrater and intrarater reliability analysis showed acceptable levels of measurement agreement (data in the Supplement regarding intrarater and interrater reliability for height and ankle-brachial pressure index). First void, midstream urine samples were analyzed to assess nephropathy. Persistent microalbuminuria was diagnosed when 2 albumin to creatinine ratios (ACRs) were between 22 µg/mg and 265 µg/mg for men and 31 µg/mg and 265 µg/mg for women.[16] (To convert albumin from micrograms per milligrams to milligrams per millimole, divide by 8.84.) Proteinuria was diagnosed when 2 ACRs were more than 265 µg/mg in either sex and reported as a protein to creatinine ratio. Retinopathy was assessed using bilateral digital images. Images were graded by 2 readers, who were blinded to each other's results, using the English Retinopathy Minimum Grading Classification[17] (eTable 1 in the Supplement). Peripheral neuropathy was assessed using vibration perception threshold. Cutaneous perception was assessed using a 10-g Semmes-Weinstein monofilament. To as-

sess peripheral vascular disease (PVD), intermittent claudication was defined by clinical diagnosis or by a positive San Diego Claudication Questionnaire[18] and the ankle-brachial pressure index was measured. To assess cardiovascular disease, patients completed the World Health Organization's Rose Chest Pain Questionnaire.[19] A resting 12-lead electrocardiogram was performed on those aged 40 years or older and assessed using Minnesota coding.[20] Patient-reported episodes of angina, myocardial infarction, and stroke were documented and confirmed by reviewing patients' medical records. When adjudication of an end point was required, this was provided by a senior clinician.

Statistical Analysis

The majority of data were not normally distributed so data are presented as median and interquartile range. For the linear association between HbA_{1c} and age, a bivariable linear regression model was used to determine the increase in HbA_{1c} per year of age, with HbA_{1c} as the dependent variable and age as the independent variable. Model assumptions of linearity between predictor and outcome, normality of residuals, and homoscedasticity were checked and met. Comparisons of complications between groups were assessed using Mann-Whitney U and Kruskal-Wallis tests for continuous variables, and χ^2 and Fisher exact tests for discrete variables.

All significance tests were 2-sided and a *P* value less than .05 was considered statistically significant. Analysis was carried out using SPSS Statistics, version 19.

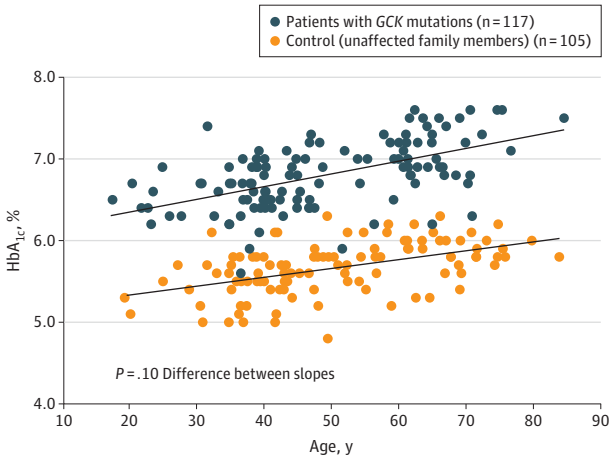
Results

We recruited 126 adults with a *GCK* mutation (mutation details in eTable 2 in the Supplement), 107 unaffected family members and spouses (control), and 83 patients with YT2D from across the United Kingdom. Nine patients with a *GCK* mutation were excluded due to their potential for coincidental type 1 or type 2 diabetes. We identified these individuals using a robust outlier detection method as described by Horn et al[21] to identify those higher than the range of normal (HbA_{1c} >7.6%). Two participants in the control group who met American Diabetes Association criteria for diabetes (HbA_{1c} >6.5%) were also removed from analysis.

The **Figure** shows that patients of all ages with a *GCK* mutation had mild hyperglycemia as measured by HbA_{1c} level. The median (interquartile range [IQR]) HbA_{1c} level was consistently higher in the 117 patients in the *GCK* group (6.8% [IQR, 6.5%-7.1%]) than in the 105 participants in the control group (5.7% [IQR, 5.5%-5.9%]; *P* < .001). Glycemic levels were higher in older patients in both groups, with a slope of 0.17% per year for the *GCK* group (95% CI, 0.12%-0.22%, *P* < .001) and a slope of 0.12% per year (95% CI, 0.08%-0.16%, *P* < .001) for the control group (*P* = .10 for the difference between slopes).

To examine those most likely to have developed complications, assessments were performed in a subgroup of patients aged 35 years or older (99 patients with *GCK*, 91 control patients from 44 families, and 83 patients with YT2D).

Figure. Scatterplot of glycated hemoglobin (HbA_{1c}) by Age in Patients With *GCK* (n=117) Compared With Control (n=105)



Linear regression lines show increasing glycated hemoglobin (HbA_{1c}) with age.

We compared enrolled patients with *GCK* with all UK patients with *GCK* using data from the Molecular Genetics Diagnostic Laboratory, Exeter. The 99 patients with *GCK* were similar in median age to the 360 UK patients known to have a *GCK* mutation (48.6 years [IQR, 40.1-62.7] for the subgroup patients vs 49 years [IQR, 42-61] for the UK patients; *P* = .90), but had a higher median body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) (26.1 [IQR, 22.3-29.3] for the subgroup patients vs 24.5 [IQR, 22.0-28.0] for the UK patients; *P* = .05) and were different in sex distribution (men, 20% for the subgroup patients vs 32% for the UK patients, *P* = .02). The 83 patients with YT2D were similar to the cohort of 397 patients with YT2D from which they were recruited (Diabetes Alliance for Research in England) in median age (54.7 years [IQR, 49.2-62.0] for the YT2D group vs 52 years [IQR, 46-63] for the recruiting cohort; *P* = .26), BMI (32.2 [IQR, 28.3-37.0] for the YT2D group vs 32.4 [IQR, 28.0-37.7] for the recruiting cohort; *P* = .98), and sex (men, 63% for the YT2D group vs 60% for the recruiting cohort, *P* = .62).

In the subgroup of patients aged 35 years or older, the level of hyperglycemia (HbA_{1c} and fasting plasma glucose) was higher in patients with a *GCK* mutation than in the controls but was milder than in patients with YT2D (**Table 1**). Duration of hyperglycemia was a median of 48 years in patients with a *GCK* mutation, a duration equal to current age, vs a median of 17 years among patients with YT2D (*P*<.001). Twenty-two percent of patients with a *GCK* mutation were taking glucose-lowering agents (0% insulin) compared with 90% of YT2D patients (60% insulin; *P*<.001; Table 1).

Microvascular Complications

Overall, the prevalence of clinically significant microvascular complications (more than a background of retinopathy or persistent microalbuminuria or proteinuria) was low in patients with a *GCK* mutation (1% [95% CI, 0%-5%]) and not significantly different from the control group (2% [95% CI, 0.3%-

Table 1. Characteristics of a Subgroup of Participants in the 3 Groups

Characteristics	Median (IQR)			*P* Value	
	GCK Group (n = 99)	Control Group (n = 91)[a]	YT2D Group (n = 83)	*GCK* vs Control Groups	*GCK* vs YT2D Groups
Men, No. (%)	20 (20)	41 (45)	52 (63)	<.001	<.001
Current age, y	48.6 (40.1-62.7)	52.2 (42.3-64.8)	54.7 (49.2-62.0)	.49	.06
BMI	26.1 (22.3-29.3)	28.0 (25.3-31.2)	32.2 (28.3-37.0)	.004	<.001
Age hyperglycemia or diabetes diagnosis, y	33 (24-44)	NA	40 (35-42)	NA	.001
Duration hyperglycemia, y	48 (40-62)	NA	17 (9-23)	NA	<.001
Fasting plasma glucose, mg/dL	117 (126-135)	94 (86-101)	144 (112-187)	<.001	<.001
HbA_{1c}, %	6.9 (6.5-7.1)	5.8 (5.5-5.9)	7.8 (7.2-8.7)	<.001	<.001
Glucose-lowering agents, No. (%)	22 (22)	NA	78 (90)	NA	<.001
Blood pressure, mm Hg				.65	.004
Systolic	125 (116-141)	128 (119-140)	135 (123-149)	.65	.004
Diastolic	78 (72-84)	79 (74-86)	79 (71-89)	.31	.38
Antihypertensive treatment, No. (%)	25 (25)	19 (19)	56 (68)	.48	<.001
Cholesterol, mg/dL					
Total	190 (165-210)	200 (175-230)	160 (140-180)	.03	<.001
HDL	62 (50-78)	56 (49-68)	42 (38-54)	.03	<.001
LDL	103 (83-126)	118 (94-153)	79 (64-97)	.07	<.001
Triglycerides, mg/dL	85 (69-108)	102 (71-135)	131 (99-193)	.01	<.001
Cholesterol: high-density lipoproteins	2.9 (2.4-3.6)	3.5 (2.8-4.2)	3.6 (2.9-4.5)	.002	.001
Lipid-lowering treatment, No. (%)	25 (24)	11 (12)	68 (82)	.02	<.001
eGFR, mL/min/1.73 m^2[b]	82 (68-92)	84 (73-93)	81 (62-100)	.20	.80
Smoking status, No. (%)					
Never	59 (60)	45 (49)	28 (34)	.16	.01
Ever	40 (40)	46 (51)	55 (66)		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimation of glomerular filtration rate; *GCK*, glucokinase; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NA, not applicable; YT2D, young-onset type 2 diabetes.

SI conversion factors: To convert HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; glucose to mmol/L, multiply by 0.555; triglycerides to mmol/L, multiply by 0.0113.

[a] First-degree relatives (n = 32), second-degree relatives (n = 9), spouses (n = 38), distant relative (n = 3), and nonblood relative (n = 9).

[b] Measured using the 4-variable modification of diet in renal disease equation eGFR.[16]

8%], *P* = .52). In contrast, 36% (95% CI, 25%-47%) of the YT2D group had evidence of clinically significant microvascular disease (*P* < .001 vs the *GCK* group; **Table 2**).

Persistent microalbuminuria was rare in the *GCK* group (1 of 97 patients; 1% [95% CI, 0.2%-6%]) and in the control group (2 of 89 patients; 2% [95% CI, 0.2%-8%]; Table 2). This rate was lower than that seen in the YT2D group, in which 17 of 80 patients (21% [95% CI, 13%-32%]) were identified (*P* < .001 vs the *GCK* group). No patients had persistent proteinuria in the *GCK* and control groups, whereas 8 of 80 patients (10% [95% CI, 4%-19%]) of the YT2D group had this condition (*P* < .001 vs the *GCK* group).

A higher prevalence of any level of retinopathy was seen in the *GCK* group compared with the control (27 of 90 patients (30%) in the *GCK* group [95% CI, 21%-41%] vs 12 of 87 patients (14%) in the control group [95% CI, 7%-23%], *P* = .007). However, this was exclusively due to background retinopathy, and 22 of 27 patients (81%) with background retinopathy had minimal disease with fewer than 5 microaneurysms. A larger percentage of those with YT2D had any retinopathy (52 of 83 patients in the YT2D group (63% [95% CI, 51%-73%], *P* < .001 vs the *GCK* group). Additionally, the degree of retinopathy in the YT2D group was more severe, with maculopathy in 17 of 83 patients (20% [95% CI, 12%-31%]) than in 0 of 90 patients in the *GCK* group (*P* < .001) and laser therapy in 23 of 83 patients in the YT2D group (28% [95% CI, 18%-39%]) than in 0 of 90 patients in the *GCK* group (*P* < .001).

Peripheral neuropathy was rare in patients with *GCK* mutations (2 of 93 patients; 2% [95% CI, 0.3%-8%]) and no cases were found in the control group (0% [95% CI, 0%-4%]). In contrast, 24 of 83 patients (29% [95% CI, 20%-50%]) of the YT2D group had peripheral neuropathy (*P* < .001 vs the *GCK* group).

Macrovascular Complications

The prevalence of clinically diagnosed macrovascular complications was low in the *GCK* group (4 of 97 patients, 4% [95% CI, 1%-10%) and the control group (10 of 91 patients, 11% [95% CI, 6%-20%]). This contrasts with the YT2D group, in which 30% (95% CI, 21%-41%) had clinically diagnosed macrovascular disease (*P* < .001) (Table 2).

There were no cases of intermittent claudication in the *GCK* group and the control group and 5 of 83 patients (6% [95% CI, 0%-13%]) in the YT2D group. The prevalence of PVD (ankle-brachial pressure index of <0.5 or ≥1.40, amputation, or intermittent claudication) was low in the *GCK* group (1%) and control group (3%). The prevalence was significantly higher in the YT2D group (13 of 83 patients; 16% [95% CI, 8%-25%]), *P* < .001 vs the *GCK* group).

The presence of ischemic heart disease was low in the *GCK* group (2 of 99 patients; 2% [95% CI, 0.2%-7%]) and the con-

Table 2. Prevalence and Severity of Complications in the 3 Groups

	No./Total (% [95% CI]) of Participants			*P* Value	
	GCK (n = 99)	Control (n = 91)	YT2D (n = 83)	*GCK* vs Control Groups	*GCK* vs YT2D Groups
Microvascular Complications					
Renal					
Persistent microalbuminuria	1/97 (1 [0.2-6])	2/89 (2 [0.2-8])	17/80 (21 [13-32])	.60	<.001
Proteinuria	0/97 (0 [0-4])	0/91 (0 [0-4])	8/80 (10 [4-19])	>.99	<.001
Retinal					
Any degree of retinopathy	27/90 (30 [21-41])	12/87 (14 [7-23])	52/83 (63 [51-73])	.007	<.001
Background retinopathy (all severities)	27/90 (30 [21-41])	12/87 (14 [7-23])	34/83 (41 [30-52])		
<5 Microaneurysms	22/27 (81 [62-94])	12/12 (100 [74-100])	13/34 (38 [22-56])	.02	.05
>5 Microaneurysms	5/27 (19 [6-38])	0/12 (0 [0-26])	21/34 (62 [44-78])		
Preproliferative retinopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	7/83 (8 [3-17])	>.99	.005
Proliferative retinopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	8/83 (10 [4-18])	>.99	.002
Maculopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	17/83 (20 [12-31])	>.99	<.001
Advanced eye disease	0/90 (0 [0-4])	0/87 (0 [0-4])	3/83 (4 [1-10])	>.99	.005
Laser therapy for retinopathy	0/90 (0 [0-4])	0/87 (0 [0-4])	23/83 (28 [18-39])	>.99	<.001
Peripheral neuropathy[a]	2/93 (2 [0.3-8])	0/89 (0 [0-4])	24/83 (29 [20-50])	.16	<.001
Clinically significant microvascular disease[b]	1/99 (1 [0-5])	2/91 (3 [0.2-8])	30/83 (36 [25-47])	.52	<.001
Macrovascular Complications					
Vascular					
Intermittent claudication[c]	0/97 (0 [0-4])	0/91 (0 [0-4])	5/83 (6 [0-13])	>.99	.14
Significantly reduced ABPI (ABPI<5.0)	0/97 (0 [0-3])	0/91 (0 [0-3])	0/83 (0 [0-4])	>.99	>.99
Significantly increased ABPI (ABPI≥1.40)	1/97 (1 [0.2-6])	3/91 (3 [0.7-9])	9/83 (11 [5-20])	.30	.006
Amputation	0/97 (0 [0-4])	0/91 (0 [0-4])	4/83 (5 [1-12])	.10	.04
Peripheral vascular disease[d]	1/93 (1 [0-5])	3/89 (3 [0-9])	13/83 (16 [8-25])	.30	<.001
Angina[e]	4/93 (4 [1-10])	10/89 (11 [5-19])	18/83 (22 [13-32])	.07	<.001
Myocardial infarction	2/89 (2 [0.2-7])	2/97 (2 [0.2-8])	5/83 (6 [2-14])	.99	.16
Ischemic heart disease[f]	2/99 (2 [0.2-7])	5/91 (5 [2-13])	13/83 (16 [10-29])	.32	.001
Minnesota coding: coronary disease probable[g]	9/69 (13 [6-23])	20/81 (25 [16-36])	19/75 (25 [16-37])	.07	.06
Cerebral vascular events					
Stroke	0/99 (0 [0-4])	0/91 (0 [0-4])	4/83 (5 [1-12])	>.99	.04
Clinically diagnosed macrovascular disease[h]	4/99 (4 [1-10])	10/91 (11 [5-19])	25/83 (30 [21-41])	.09	<.001

Abbreviations: ABPI, ankle-brachial pressure index; *GCK*, glucokinase; YT2D, young-onset type 2 diabetes.

[a] Vibration perception threshold greater than 25 V mean or monofilament at 3 or fewer sites.

[b] More than a background of retinopathy or persistent microalbuminuria or proteinuria.

[c] Clinically diagnosed or had a positive result from the San Diego Claudication Questionnaire.

[d] Clinically diagnosed, or had an ABPI of less than 0.5, an ABPI of at least 1.40, an amputation, or a positive result from the San Diego Claudication Questionnaire.

[e] Clinically diagnosed or had a positive result from the Rose Chest Pain Questionnaire.

[f] Myocardial infarction or angina.

[g] "Probable" is the most severe classification in the Minnesota coding, which is thought to indicate probable ischamic heart disease.

[h] Intermittent claudication, amputation, angina, myocardial infarction, or stroke.

trol group (5 of 91 patients; 5% [95% CI, 2%-13%]). The prevalence of ischemic heart disease was higher in YT2D patients (13 of 83 patients; 16% [95% CI, 10%-29%]), *P* = .001 vs *GCK* group). Minnesota coding identified probable coronary disease in 9 of 69 of patients (13%) in the *GCK* group and 20 of 81 patients (25%) in the control group, and in 19 of 75 patients (25%) in the YT2D group. No patients in either the *GCK* or control groups had experienced a stroke compared with 4 of 83 patients (5%) in the YT2D group.

Discussion

Patients with a *GCK* mutation have a low prevalence of clinically significant microvascular and macrovascular complications despite their lifelong hyperglycemia.[10,11] In these patients, an average of nearly 50 years of isolated hyperglycemia within current target ranges for diabetes control has a negligible association with complication development. This work

is, to our knowledge, the first systematic assessment of complication development in patients with a *GCK* mutation.

Previous studies have suggested that complications are rare in patients with *GCK* mutations,[10,14,15] but, unlike our study, these studies mainly used data from clinical notes,[10,15] reviewed a small number of patients,[10,14] did not include a control group,[10,15,22] or had a mean age younger than 37 years.[10,14,15] We have used clinically recognized and standardized techniques for each participant, with high levels of intraobserver and interobserver reproducibility and reliability. The prevalence and severity of complications in patients with *GCK* mutations was similar to that of the control group. The presence of complications in our control group was not surprising, for hyperglycemia-related complications have previously been reported in the general population.[23-27] In contrast to other studies, we have addressed the potential issues of selection bias and survival bias. The *GCK* group and YT2D group were generally representative of the large cohorts from which they were selected. There is no evidence to suggest that *GCK* patients were excluded from the study because of premature death.

Retinopathy (evidence of at least 1 microaneurysm) in people without diabetes occurs in 5% to 9% of the nondiabetic general population with an age range of 43 to 84 years.[25,28] The prevalence of background retinopathy in our control group was similar. We identified a higher prevalence rate for background retinopathy in our patients with a *GCK* mutation, but the vast majority of these patients had mild background retinopathy with fewer than 5 microaneurysms. None of our patients with a *GCK* mutation had sight-threatening retinal disease. Previous studies involving *GCK* mutation carriers found prevalence rates of proliferative retinopathy of 0% to 4%.[14,15,22] These studies used direct fundoscopy, whereas we used digital retinal imaging with primary, secondary, and, where required, arbitration grading and did not exclude concomitant type 1 or type 2 diabetes.

All other microvascular complications had comparably low prevalence rates in patients with a *GCK* mutation and in the control group. Microalbuminuria has been reported in 6.6% to 9.4% of the nondiabetic population[23,24] and in 0% to 6% of patients with a *GCK* mutation.[10,14,15,29] Rather than relying on urinalysis sticks as in previous *GCK* studies,[15,22] we excluded urinary tract infection and biochemically confirmed the diagnosis of microalbuminuria with 3 consecutive, early morning urine samples. Our prevalence rates were similar to those previously reported in patients with a *GCK* mutation but were lower than previously reported in the general population. We did not identify any patients with *GCK* with proteinuria. The prevalence of neuropathy was also low in the *GCK* and control groups in our study. Previous studies have reported a prevalence of 4% to 5% in patients with *GCK*.[10,14,15,29]

An increase in HbA_{1c} level of 1% results in a 10% to 20% increase in cardiovascular disease risk and predicts cardiovascular risk both in people with diabetes and in the general population.[30] Our data suggest that macrovascular complications are not increased in individuals with *GCK* mutations and are in keeping with earlier studies reporting a prevalence of cardiovascular disease between 0.7% to 12%.[10,14,15] Our finding of a low prevalence of cardiovascular disease in the *GCK* group, even with their slightly elevated HbA_{1c} levels, provides evidence that isolated hyperglycemia is rarely associated with macrovascular complications. Although treatment is not advocated for patients with a *GCK* mutation outside pregnancy, 22% of our *GCK* group were treated with glucose-lowering agents, which is consistent with previous studies.[13,22] Recent work has shown that pharmacological treatment does not alter HbA_{1c} levels in patients with a *GCK* mutation, so this is unlikely to confound our findings.[13]

We have shown that patients with *GCK* mutations, who have mild hyperglycemia from birth, have significantly lower diabetes-related complication prevalence and severity compared with individuals with a shorter duration of more severe hyperglycemia (patients with YT2D). Retinopathy, nephropathy, peripheral neuropathy, and angina were all significantly more common in the YT2D group. However, several considerations warrant mentioning prior to extrapolating findings in patients with *GCK* mutations to other subtypes of diabetes. Patients with *GCK* mutations have been shown to have a similar degree of insulin resistance and obesity as the general population,[14,15] whereas the patients in our YT2D cohort have been exposed to many metabolic risk factors for complication development. Obesity, hypertension, and dyslipidemia found in patients with type 2 diabetes may alter the effect of glycemia on the risk of complications. Patients with type 1 and type 2 diabetes have a more variable blood glucose profile than do patients with a *GCK* mutation; this variability may affect the complication prevalence and severity rates. Patients with *GCK* mutations are born with hyperglycemia so there may be early compensation for this, resulting in protection from vascular complications. It also means that patients with a *GCK* mutation are younger than patients diagnosed with diabetes later in life with the same duration of hyperglycemia. Age as well as duration is likely to be important in complication development. Despite these caveats, our ability to study individuals with isolated hyperglycemia has provided a useful natural experiment for understanding the development of complications.

Our study is limited by the relatively small number of patients known to have *GCK* mutations, which necessitates a cross-sectional study rather than a longitudinal study and limits its power. Although the prevalence of complications was low for both the *GCK* mutation and control groups, we are unable to prove equivalence with our sample size. We would need a control group more than 10 times larger to detect statistical significance between the groups at the prevalences we observed. However, with the exception of mild background retinopathy, the prevalence of all complications was very low in the patients with a *GCK* mutation, with similar CIs to the control participants and significantly lower than those seen in the YT2D group. Even if proved to be statistically different, it is unlikely that differences in the low prevalence rates seen would be of clinical significance. Our definition of the YT2D cohort's duration of hyperglycemia is not precise because individuals may have been unaware that they had type 2 diabetes and complications can occur in up to 50% of people before a medical

diagnosis for symptoms is sought.[31] Even with this likely underestimation of duration of hyperglycemia in the patients in the YT2D cohort, their duration should not be as long as the patients with a *GCK* mutation whose hyperglycemia is present from birth. Because the researchers who conducted clinical assessments of macrovascular disease were aware of the clinical category of many of the patients, not all clinical assessments were collected in a blinded fashion. Finally, there were more women recruited in our *GCK* group. This is unlikely to affect microvascular disease rates but could affect macrovascular disease rates. With so few cases in the *GCK* group, it is not possible to adjust for this difference statistically. However, the prevalence of coronary heart disease in the *GCK* mutation group for both men and women is similar to that reported in England for a similar age range (45-54 years)[32]: 5% for the *GCK* group vs 3.6% for England in men and 1.2% for the *GCK* group vs 1.3% for England in women. Although these results are similar to those of the general population, our CIs were wide and larger numbers would be required to investigate this further.

Conclusions

Patients with *GCK* mutations over a median of 48.6 years had a low prevalence of vascular complications. These findings provide insights into the risks associated with isolated mild hyperglycemia.

ARTICLE INFORMATION

Author Contributions: Dr Steele had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Steele, Hattersley.
Acquisition of data: Steele, Wensley, Colclough.
Analysis and interpretation of data: Steele, Shields, Ellard, Hattersley.
Drafting of the manuscript: Steele, Shields.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Steele, Shields.
Obtained funding: Steele, Hattersley.
Administrative, technical, or material support: Steele, Wensley, Colclough.
Study supervision: Shields, Ellard, Hattersley.

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