Evaluation of Serum 1,5 Anhydroglucitol Levels as a Clinical Test to Differentiate Subtypes of Diabetes

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OBJECTIVE — Assignment of the correct molecular diagnosis in diabetes is necessary for informed decisions regarding treatment and prognosis. Better clinical markers would facilitate discrimination and prioritization for genetic testing between diabetes subtypes. Serum 1,5 anhydroglucitol (1,5AG) levels were reported to differentiate maturity-onset diabetes of the young due to *HNF1A* mutations (HNF1A-MODY) from type 2 diabetes, but this requires further validation. We evaluated serum 1,5AG in a range of diabetes subtypes as an adjunct for defining diabetes etiology.

RESEARCH DESIGN AND METHODS — 1,5AG was measured in U.K. subjects with: HNF1A-MODY (n = 23), MODY due to glucokinase mutations (GCK-MODY, n = 23), type 1 diabetes (n = 29), latent autoimmune diabetes in adults (LADA, n = 42), and type 2 diabetes (n = 206). Receiver operating characteristic curve analysis was performed to assess discriminative accuracy of 1,5AG for diabetes etiology.

RESULTS — Mean (SD range) 1,5AG levels were: GCK-MODY 13.06 μg/ml (5.74–29.74), HNF1A-MODY 4.23 μg/ml (2.12–8.44), type 1 diabetes 3.09 μg/ml (1.45–6.57), LADA 3.46 μg/ml (1.42–8.45), and type 2 diabetes 5.43 (2.12–13.23). Levels in GCK-MODY were higher than in other groups ($P < 10^{-4}$ vs. each group). HNF1A-MODY subjects showed no difference in unadjusted 1,5AG levels from type 2 diabetes, type 1 diabetes, and LADA. Adjusting for A1C revealed a difference between HNF1A-MODY and type 2 diabetes (P = 0.001). The discriminative accuracy of unadjusted 1,5AG levels was 0.79 for GCK-MODY versus type 2 diabetes and 0.86 for GCK-MODY versus HNF1A-MODY but was only 0.60 for HNF1A-MODY versus type 2 diabetes.

CONCLUSIONS — In our dataset, serum 1,5AG performed well in discriminating GCK-MODY from other diabetes subtypes, particularly HNF1A-MODY. Measurement of 1,5AG levels could inform decisions regarding MODY diagnostic testing.

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An estimated 2% of diabetes in Europe is caused by monogenic disorders of the β-cell (maturity-onset diabetes of the young [MODY]) (1). The two most common types of MODY in clinical practice are caused by mutations in the genes encoding hepatocyte nuclear factor 1-α (*HNF1A*) and glucokinase (*GCK*) (1). Making the correct molecular diagnosis allows individualization of treatment, for example the use of low-dose sulfonylurea as a first line in MODY due to *HNF1A* mutations (HNF1A-MODY) (2). It also conveys important information about prognosis and guides investigation of family members. Despite these clear advantages, individuals with MODY are frequently misdiagnosed as having either type 1 or type 2 diabetes or do not have confirmatory molecular testing performed even when MODY is suspected.

Although HNF1A-MODY and MODY due to GCK mutations (GCK-MODY) have distinct phenotypes (1,3), differentiating these from each other and from common forms of diabetes can be challenging in clinical practice. Molecular genetic testing, if positive, is definitive but is currently too expensive for indiscriminate use. Therefore, there is a need for novel biochemical screening tools to identify and direct efficient genetic analysis in those for whom a probable monogenic diagnosis of diabetes exists. Ideally such a test would be highly specific for a MODY subtype and would allow differentiation between type 1 and type 2 diabetes.

A recent report suggests that measurement of serum 1,5 anhydroglucitol (1,5AG) may represent such a test, at least to discriminate HNF1A-MODY from type 2 diabetes (4). 1,5AG is a metabolically inactive monosaccharide that reaches steady state between ingestion and urinary excretion with near complete renal reabsorption at a specific fructose-mannose active transporter (5,6). Due to structural similarity, glucose competitively inhibits this reabsorption, such that in times of significant glycosuria, 1,5AG is excreted in the urine and consequently serum levels fall (7). Thus, poor glycemic control is associated with low serum 1,5AG levels (8). A low renal threshold for glucose also results in a serum 1,5AG level lower than expected (9). As *HNF1A* mutations are characterized by low renal glucose threshold (10) due to decreased expression of the high-affinity low-capacity glucose co-transporter 2 (*SGLT2*) (11), it was hypothesized that 1,5AG levels could be a biomarker for HNF1A-MODY. An initial report of serum 1,5AG levels in Polish subjects (4) found that mean 1,5AG levels were 50% lower in patients with HNF1A-MODY

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compared with those with type 2 diabetes matched for glycemic control.

We sought to evaluate this hypothesis in a larger independent sample set with a wider range of diabetes subtypes and to assess the performance of serum 1,5AG levels as an adjunctive test in identifying subtypes of diabetes.

RESEARCH DESIGN AND METHODS

Subjects were collected in Oxford, U.K. The MODY samples comprise subjects with a confirmed mutation in either *HNF1A* (n = 23 from 12 families) or *GCK* (n = 23 from 10 families). Median family size was 2.5 members (range 1–6), and half the families comprised only one individual. Nineteen of the HNF1A-MODY subjects had diabetes, one had IGT, and three were normoglycemic. Oral glucose tolerance test (OGTT) data from the time of sampling were available for all nondiabetic subjects.

The remaining subjects were from the Young Diabetes in Oxford (YDX) study, comprising subjects diagnosed with diabetes ≤45 years of age recruited from either primary (n = 82) or secondary (n = 198) care. Within the group are cases of classical type 1 diabetes (n = 29), latent autoimmune diabetes in adults (LADA, n = 42), and type 2 diabetes (n = 209). Type 1 diabetes was defined as permanent insulin treatment since diagnosis with additional evidence of severe β-cell dysfunction (C-peptide undetectable or homeostasis model assessment of β-cell function [HOMA %B] <10%), positive GAD antibodies (>14 World Health Organization [WHO] units/ml), or both. LADA was defined as diabetes with positive GAD antibodies but no requirement for insulin treatment within 3 months of diagnosis. Those not requiring permanent insulin treatment at diagnosis with negative antibodies were classified as having type 2 diabetes. Subjects in the type 2 diabetic group did not meet current clinical criteria for MODY diagnostic testing (12) or had been tested and were negative for mutations in *HNF1A*/*HNF4A* (n = 9) or *GCK* (n = 4). Briefly, clinical criteria for HNF1A-MODY testing was young onset (<25 years) of familial non–insulin dependent diabetes and for *GCK* testing was young onset of mild fasting hyperglycemia (5.5–8 mmol/l).

Two of the LADA subjects and 31 of the type 2 subjects were of non-European ethnicity (14 Asian, 11 Black, 1 Chinese, and 7 mixed or other).

Clinical details, anthropometry, and fasting blood samples were collected for all subjects (Table 1). The study was approved by the Oxfordshire Local Research Ethics Committee, and all subjects gave informed consent.

1,5AG was measured using an enzymatic colorimetric assay (GlycoMark, GlycoMark, NY) (13). Intra-assay coefficient of variance (CV) was 0.46%, and inter-assay CV ranged from 1.74 to 2.37%. GADA was measured by a radioimmunoassay using 35S-labeled full-length GAD65, and results were expressed in WHO units per milliliter derived from a standard curve calibrated from international reference material (National Institute for Biological Standards and Control code 97/550). Samples were considered positive if they had levels above 14 WHO units/ml (97.5th percentile of healthy school children) (14).

Values for age of diagnosis, duration of diabetes, BMI, creatinine, A1C, fasting plasma glucose (FPG) and 1,5AG level were not normally distributed and were $\log_{10}$ transformed. Geometric mean and SD range were calculated. ANOVA was calculated across the groups. For 1,5AG levels, pairwise comparisons (using T test with Bonferroni correction for multiple testing) were also calculated between the different diabetes subtypes. We then examined the effect of correcting 1,5AG levels for A1C, and, in the type 2 diabetes and MODY subgroups, for the effects of treatment modality. As 1,5AG levels can be lowered in chronic renal failure (15), subjects with serum creatinine >150 μmol/l were excluded from the analysis (one subject with LADA and nine with type 2 diabetes).

Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminative accuracy of 1,5AG with regard to diabetes etiology. The performance of 1,5AG level as a diagnostic discriminator was compared with A1C and FPG. All statistical analysis was performed in SPSS version 16, and $P < 0.05$ was assumed to be significant.

RESULTS

Table 1 shows the characteristics of the subjects and the results of the biochemical investigations. Geometric mean (SD range) 1,5AG levels were: GCK-MODY 13.06 μg/ml (5.74–29.74), HNF1A-MODY 4.23 μg/ml (2.12–8.44), type 1 diabetes 3.09 μg/ml (1.45–6.57), LADA 3.46 μg/ml (1.42–8.45), and type 2 diabetes 5.43 μg/ml (2.12–13.23).

Upon first examination of the unadjusted data, we found no difference in mean 1,5AG levels between subjects with HNF1A-MODY and type 2 diabetes ($P > 0.05$). There was also no difference in 1,5AG levels between HNF1A-MODY and either of the autoimmune groups ($P > 0.05$). As previously reported (16), we found 1,5AG levels were higher in those with type 2 diabetes compared with those in the autoimmune groups (type 2 vs. type 1 diabetes, $P = 0.011$, type 2 diabetes vs. LADA, $P = 0.015$). After controlling for A1C, adjusted 1,5AG level was lower in HNF1A-MODY than in type 2 diabetic subjects ($P = 0.001$). Adjusting for A1C did not alter the relationships between 1,5AG levels in the other diabetic subgroups. Reanalysis adjusting for shared family membership in the MODY cases and excluding the non-European individuals had no effect on these findings (data not shown). Duration of diabetes also did not have a significant effect on 1,5AG levels, but in the type 2 diabetic subjects we observed a progressively lower 1,5AG level (and higher A1C) with escalating treatment requirement. This was not seen in the MODY subgroups. The three panels in Fig. 1 show scatter plots of unadjusted 1,5AG levels plotted against A1C. These illustrate the considerable overlap between HNF1A-MODY and common forms of diabetes at all values of A1C. This suggests that, in our dataset at least, 1,5AG levels will not be a very useful clinical indicator of HNF1A-MODY. We investigated this question further by constructing ROC curves. For HNF1A-MODY and type 2 diabetes, the area under the curve (AUC) was 0.60 (Fig. 2*B*), confirming that in our set of subjects unadjusted 1,5AG levels are poorly discriminative between HNF1A-MODY and type 2 diabetes. We then repeated the ROC curve analysis using 1,5AG levels adjusted for A1C. This improved the AUC to 0.75.

Our most striking finding was that subjects with GCK-MODY had a higher 1,5AG level than any of the other groups ($P \leq 0.0003$ for all pairwise comparisons, both uncorrected and corrected for A1C). Figure 1 illustrates that the GCK-MODY cases show good separation from other kinds of diabetes. ROC curve analysis to examine the discriminative accuracy of 1,5AG level for GCK-MODY (from type 2 diabetes) gave an AUC of 0.79 in our subjects (Fig. 2*A*). Similarly for GCK-MODY versus HNF1A diabetic subjects, the AUC was 0.86 (Fig. 2*C*). Both of these estimates

Table 1—*Characteristics of the subjects studied*

	Type 1 diabetes	LADA	Type 2 diabetes	Diabetic HNF1A-MODY	GCK-MODY	Nondiabetic *HNF1A* mutation carriers	*P* (ANOVA)
n	29	42	209	19	24	4	
% Male	55	69	61	38	46	25	0.09
Diagnosis age (years)	16.7 (7.2−38.5)	32.9 (25−43.3)	36.2 (29.1−45.1)	21.5 (13.5−29.1)	21.5 (11.6−40.0)	30.0* (19.3−46.6)	<0.001
Diabetes duration (years)	17.8 (9.4−33.6)	10.3 (3.2−33.2)	11.7 (4.5−30.3)	15.1 (6.1−37.2)	12.3 (6.5−23.5)	NA	0.003
BMI (kg/m^2)	26.9 (23.1−31.4)	27.2 (22.4−33)	33 (26.9−40.4)	25.2 (21.1−30.3)	27.7 (22−34.8)	22.8 (20.2−25.8)	0.26
Serum creatinine (μmol/l)	94 (83−106)	92 (76−110)	96 (73−125)	84 (75−95)	87 (75−101)	82 (78−86)	0.07
A1C (%)	7.9 (7.1−8.8)	7.9 (6.9−9.1)	7.8 (6.5−9.3)	7.2 (6.2−8.3)	6.8 (5.6−8.3)	5.2 (4.9−5.6)	<0.001
Fasting glucose (mmol/l)	9.5 (5.3−17.0)	8.4 (5.6−12.7)	8.2 (5.7−11.9)	8.3 (5.9−11.5)	7.7 (5.8−10.3)	5.3 (4.3−6.4)	0.08
1,5AG (μg/ml)	3.09 (1.45−6.57)	3.46 (1.42−8.45)	5.43 (2.12−13.23)	4.23 (2.12−8.44)	13.06 (5.74−29.74)	18.03 (10.48−31.0)	<0.001
Adjusted 1,5AG	4.09 ± 1.73	4.99 ± 2.38	7.58 ± 3.28	5.25 ± 2.50	15.84 ± 3.53	19.83 ± 0.70	<0.001

Data are geometric means (SD range) and means ± SD adjusted for A1C. *P* value refers to ANOVA across the diabetic groups. Manufacturer's quoted reference range for 1,5AG: 10.7–32.0 μg/ml for male patients and 6.8–29.3 μg/ml for female patients. *Age at sampling.

were improved by adjusting for A1C to values of 0.94 and 0.96, respectively.

We calculated threshold values of 1,5AG designed to reflect maximum sensitivity and specificity in our dataset; for GCK-MODY versus type 2 diabetes, a 1,5AG >11 μg/ml gave a sensitivity and specificity of 75% for identifying the GCK-MODY cases, while 70% of the type 2 diabetes cases fall below this cut off. For GCK-MODY versus HNF1A-MODY, 1,5AG >7.5 μg/ml gave sensitivity of 86% and specificity of 84% for identifying GCK-MODY, while 89% of HNF1A-MODY diabetic subjects had 1,5AG levels below this.

In clinical practice, A1C <8% and FPG 5.5–8.5 mmol/l are often used as biochemical discriminators to identify those individuals with apparent monogenic diabetes most likely to have GCK-MODY (12). In our dataset, these criteria did not perform as well as 1,5AG. Although they gave similar sensitivity to the above for identifying GCK-MODY cases, specificities were much lower at 42, 58, and 66% for A1C, FPG, and the combined criteria, respectively.

We examined how serum 1,5AG could perform as a preselection for cases for *GCK* diagnostic sequencing. This was done by estimating the proportion of positive tests for GCK-MODY that would be identified by setting different prevalences of GCK-MODY in the baseline sample set using the threshold levels described above. When the type 2 diabetes and GCK-MODY groups from this study are combined, 25% of cases in this combined group with a 1,5AG value >11 μg/ml have a *GCK* mutation. This would be a similar rate of positive test pick-up to that achieved using standard clinical criteria by the U.K. diagnostic testing center (17). However, the prevalence of GCK-MODY in this combined group is 10%, which is somewhat higher than we would expect, even in a group referred for genetic investigation. Recalculating based on a more realistic prevalence of GCK-MODY representing 5% of the diabetes cases would halve the positive test rate to 12.5%, which would probably still be an acceptable pick-up rate given the changes in management and prognosis that result from rediagnosing type 1 or type 2 diabetes as a *GCK* mutation. This is also comparable with many other diagnostic genetic tests in the U.K. Other models that add fasting glucose and A1C thresholds to the calculation do not improve these rates in our dataset.

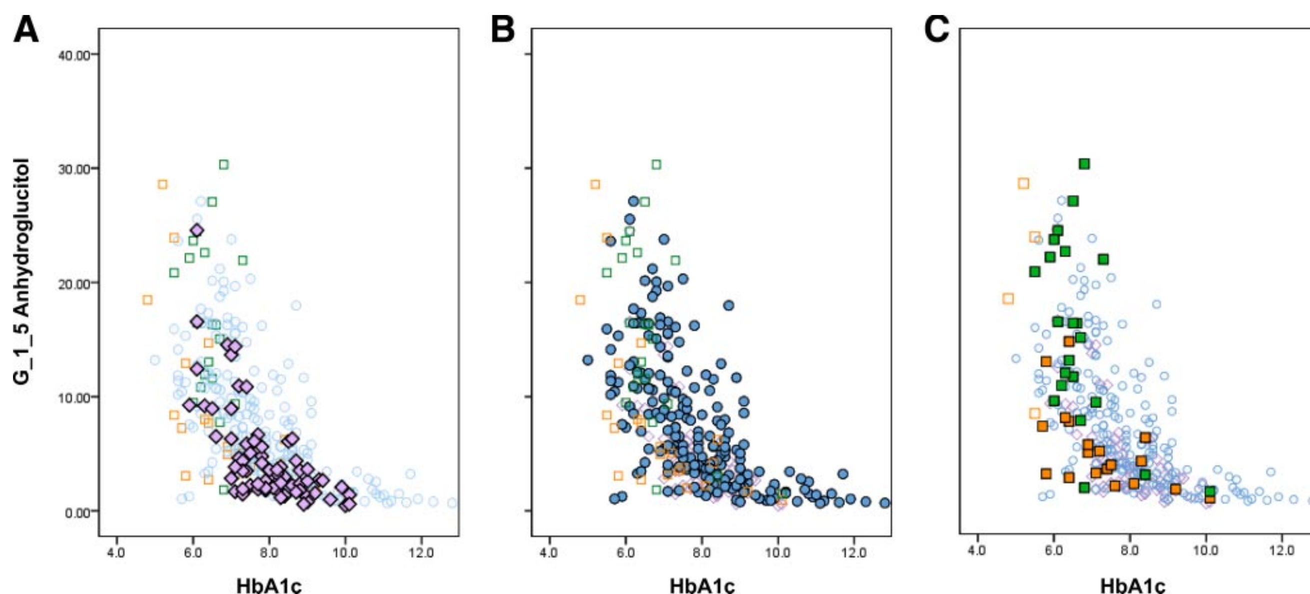

Figure 1—*Scatter plots of serum 1,5AG levels (μg/ml) versus A1C (%) for the different subtypes of diabetes. For clarity the data points are plotted on three panels with a filled symbol to emphasize a different diabetic subtype in each panel: lilac diamonds, subjects with autoimmune diabetes (type 1 + LADA combined); blue circles, type 2 diabetes; orange squares, HNF1A-MODY; and green squares, GCK-MODY.* A: *Distribution of autoimmune diabetes.* B: *Type 2 diabetes.* C: *Both MODY subtypes. Three subjects with A1C >12.5% are not shown for increased clarity of the figure but were included in the analysis.*

CONCLUSIONS— Identifying monogenic forms of diabetes and assigning the subtypes correctly currently depends on recognizing a clinical phenotype and arranging confirmatory molecular testing. Additional biochemical tests that aid prioritization of cases for genetic testing would have great clinical utility.

1,5AG is an attractive candidate marker for HNF1A-MODY because it utilizes the known characteristic of low renal threshold for glucose seen in *HNF1A* mutations. We confirm the previous finding (4) that 1,5AG levels are lower in HNF1A-MODY than type 2 diabetes, but this difference is only apparent after adjustment for A1C. This is necessary because the lower A1C in our HNF1A-MODY group (7.2 vs. 7.8%, $P = 0.04$) has the effect of diminishing the difference in unadjusted 1,5AG levels (the previous study was well matched at baseline for A1C). Adjusting for A1C increased the discriminative accuracy of 1,5AG to identify HNF1A-MODY from type 2 diabetes with the AUC of the ROC curve rising from 0.60 to 0.75. This is still of rather limited clinical utility (AUC of ≥0.8 representing a useful test) and would require further validation to design a suitable model that includes A1C. Ideally this validation would include more HNF1A-MODY cases with higher A1C, as we have limited data on A1C >9%. A further limitation for a role of 1,5AG in a diagnostic strategy to detect HNF1A-MODY is that we found no difference in 1,5AG levels between HNF1A-MODY and either form of autoimmune diabetes.

The most striking finding in our study was the higher 1,5AG levels in subjects with GCK-MODY compared with all other groups. This is likely to be explained by the known modest postchallenge glucose increment seen in those with *GCK* mutations (18). Postprandial glucose levels rarely rise high enough to cause glycosuria, resulting in levels of

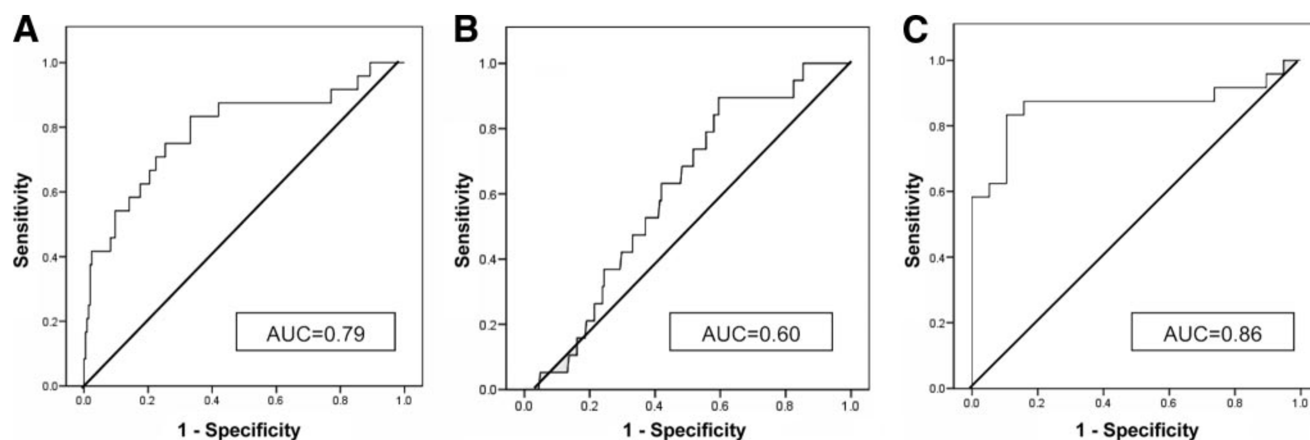

Figure 2—*ROC curves illustrating discriminative capacity of unadjusted 1,5AG to distinguish between diabetes subgroups.* A: *GCK-MODY and type 2 diabetes.* B: *HNF1A-MODY and type 2 diabetes.* C: *GCK-MODY and HNF1A-MODY.*

1,5AG that are mainly within the normal range. Our ROC curve analyses result in promising estimates for the ability of 1,5AG to discriminate GCK-MODY from both type 2 diabetes and HNF1A-MODY.

Though 1,5AG levels are likely to be influenced by recent dietary intake, we made no attempt to adjust for this. The ROC curve results are reassuring that this test will perform well in routine clinical practice where prior dietary information is not likely to be available.

There are some limitations to extrapolating this finding to a general type 2 diabetes clinic population: The subjects in this study were selected for age of diagnosis ≤45 years, where the pretest probability of possessing a *GCK* mutation is likely to be higher than in an unselected group of patients with type 2 diabetes (*GCK* mutations in fasting hyperglycemia fall from a prevalence of 40% in children [19] to ~1% in adults diagnosed over 50 years of age [20]). In the <45 years of age range the likely prevalence of *GCK* mutations is difficult to estimate but probably in the range of 3–5%.

We found that duration of diabetes did not have a significant effect on 1,5AG level; however, the type 2 diabetic patients on diet treatment had a higher 1,5AG than those on oral hyperglycemic agents or insulin. This suggests that postprandial glucose excursion is not normalized by treatment of diabetes. Therefore, we would predict that 1,5AG levels might be less useful in discriminating GCK-MODY from those with type 2 diabetes who are well-controlled on diet treatment.

There was very little overlap between the 1,5AG levels in our GCK-MODY and HNF1A-MODY groups. This discriminative performance benefits from the fact that two major characteristics of these subtypes of MODY (low renal threshold and low postchallenge increment) have opposite effects on 1,5AG levels and suggests 1,5AG analysis might have the most potential as a discriminative test between these two MODY subtypes. Currently patients suspected of having MODY are frequently selected for *GCK* rather than *HNF1A* mutation testing on the basis of the characteristic pattern seen on OGTTs: In GCK-MODY a mild fasting hyperglycemia with a modest 2-h increment (90th centile <4.6 mmol/l) is observed (12), while in HNF1A-MODY FPG may be normal but with a high 2-h postchallenge level (mean >5 mmol/l) (18).

Although an OGTT is quoted as the gold standard investigation (12), it is time consuming, difficult to interpret in those on treatment, and has large day-to-day variability (21). A 1,5AG measurement would in theory be a useful, more cost-effective, and practical alternative to an OGTT, as it reflects postprandial glucose excursion from a single nonfasting blood sample. OGTT data were not available on our GCK-MODY cases, so we were not able to directly assess the correlation with 2-h glucose. However, a relationship between 1,5AG levels and OGTT has been examined previously; in subjects with IGT 1,5AG levels were strongly correlated ($r = -0.8$) with 2-h glucose levels, and this was greater than the correlation seen with FPG and the correlation between A1C and either fasting or 2-h values (22). Similarly, 1,5AG levels showed good correlation with postprandial continuous glucose monitoring system readings (23) and 2-h postprandial capillary measurements (24). This supports the use of 1,5AG as a surrogate for postchallenge glucose and merits further validation in GCK-MODY.

In conclusion, we suggest future research should focus on the role of the 1,5AG level as a tool to differentiate MODY subtypes in those already suspected of having a monogenic form of diabetes.

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