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Association of Both Short-term and Long-term Glycemic Variability With the Development of Microalbuminuria in the ACCORD Trial

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Both long- and short-term glycemic variability have been associated with incident diabetes complications. We evaluated their relative and potential additive effects on incident renal complications in the Action to Control Cardiovascular Risk in Diabetes trial. A marker of short-term glycemic variability, 1,5-anhydroglucitol (1,5-AG), was measured in 4,000 random 12-month postrandomization plasma samples (when hemoglobin A_{1c} [HbA_{1c}] was stable). Visit-to-visit fasting plasma glucose coefficient of variation (CV-FPG) was determined from 4 months postrandomization until the end point of microalbuminuria or macroalbuminuria. Using Cox proportional hazards models, high CV-FPG and low 1,5-AG were independently associated with microalbuminuria after adjusting for clinical risk factors. However, only the CV-FPG association remained after additional adjustment for average HbA_{1c}. Only CV-FPG was a significant risk factor for macroalbuminuria. This post hoc analysis indicates that long-term rather than short-term glycemic variability better predicts the risk of renal disease in type 2 diabetes.

ARTICLE HIGHLIGHTS

- The relative and potential additive effects of long- and short-term glycemic variability on the development of diabetic complications are unknown.
- We aimed to assess the individual and combined relationships of long-term visit-to-visit glycemic variability, measured as the coefficient of variation of fasting plasma glucose, and short-term glucose fluctuation, estimated by the biomarker 1,5-anhydroglucitol, with the development of proteinuria.
- Both estimates of glycemic variability were independently associated with microalbuminuria, but only long-term glycemic variability remained significant after adjusting for average hemoglobin A_{1c}.
- Our findings suggest that longer-term visit-to-visit glucose variability improves renal disease prediction in type 2 diabetes.

Chronic elevations in blood glucose have long been recognized as a main driver of renal disease in patients with both type 1 and type 2 diabetes (T2D). Recent reports from intensive glucose-lowering studies in T2D have shown that long-term glycemic variability may contribute to the risk of microvascular events beyond the overall level of glycemic control (1,2).

Measurement of 1,5-anhydroglucitol (1,5-AG) has been proposed as a valid estimate of short-term glucose variability (3,4). Because glucosuria interferes with 1,5-AG renal reabsorption, lower plasma 1,5-AG may reflect hyperglycemic episodes over recent weeks. A single plasma 1,5-AG level of <6 μg/mL was associated with cardiovascular risk in populations with and without diabetes (5,6) and with microvascular events in patients with diabetes (7).

Long-term glycemic variability assessment requires collecting glucose or hemoglobin A_{1c} (HbA_{1c}) values and calculating various variability metrics over multiple visits. Assessing

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short-term glycemic variability estimated by a single 1,5-AG measurement may be simpler and easier to interpret and provide similar clinical relevance. Combining short-term with long-term estimates of glycemic variation may improve the prediction of outcomes.

In the current study, we assessed the individual and combined relationships of 1,5-AG and visit-to-visit glucose variability with the development of renal complications in T2D.

RESEARCH DESIGN AND METHODS

Plasma samples and data were from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. ACCORD was a two-by-two factorial, randomized, parallel trial of an intensive (HbA_{1c} <6.0% [42.1 mmol/mol]) versus standard (HbA_{1c} 7.0–7.9% [53–62.8 mmol/mol]) glucose-lowering regimen, including distinct blood pressure and lipid intervention arms (8,9). Within 4 months, the median HbA_{1c} level had fallen from 8.1% (65 mmol/mol) at baseline to 6.5% (47.5 mmol/mol) in the intensive and to 7.5% (58.5 mmol/mol) in the standard group and remained stable thereafter. Fasting plasma glucose (FPG) concentrations were measured every 4 months for a maximum of 84 months. Serum creatinine levels were measured every 4 months for the first year, followed by annual and study closeout measurements (8). Urine albumin and creatinine levels were measured annually and at study closeout. For this analysis, we randomly selected 4,000 participants (equally distributed across two glycemic treatment arms). We measured their 1,5-AG levels at 12 months postrandomization to avoid the substantial glycemic variability resulting from the initiation of glucose-lowering protocols in both treatment groups, to have time to capture a sufficient number of subsequent renal events, and to evaluate the association after a glucose-lowering intervention. Participants with missing outcomes, outcomes before the 12-month collection, and fewer than two glucose measures after the 4-month time point were excluded from the analysis.

Primary and Secondary Outcomes

Primary outcomes were the times (starting at 12-month time point) to the development of *1)* microalbuminuria (ratio of urine albumin to creatinine ≥30 mg/g) and *2)* macroalbuminuria (ratio of urine albumin to creatinine ≥300 mg/g) (8). The ACCORD study determined both primary outcomes. A secondary composite outcome included the time to the first of at least two consecutive values of estimated glomerular filtration rate <45 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation (10) or renal failure (initiation of dialysis, end-stage renal disease, renal transplantation, or serum creatinine >291.72 μmol/L in the absence of an acute reversible cause) classified by ACCORD investigators. Patients randomly assigned to active lipid-lowering treatment were excluded from this analysis because of the impact of fenofibrate on plasma creatinine (and thus estimated glomerular filtration rate) levels (11).

Glucose Variability

A single 12-month serum sample was used to measure 1,5-AG concentrations. We measured them in duplicate (intra-assay coefficient of variation [CV] 1.6%) and in eight batches (interassay CV 3.2%) using an enzymatic assay (Diazyme Laboratories, Poway, CA). Long-term visit-to-visit glucose variability was quantified by the CV of FPG (CV-FPG) using FPG measured longitudinally from 4 months postrandomization, when the initial separation between glucose treatment arms occurred (and FPG levels remained stable thereafter) (1,2).

Statistical Analysis

Differences between participants who did and did not develop an event were assessed by the Wilcoxon test for continuous variables and the χ^2 or Fisher exact test, as appropriate, for categorical variables. Cox proportional hazards models were used to test the association of study outcomes with CV-FPG and 1,5-AG. CV-FPG was included as a continuous and time-dependent covariate (12). Based on a previous report (6) and confirmed here by penalized linear splines models, a 1,5-AG level of ≤6 μg/mL was categorized as low. The proportionality of all model predictors was confirmed by goodness-of-fit tests using Schoenfeld residuals (13). CV-FPG was scaled and log transformed. Analyses were sequentially adjusted for variables (models 1–4; see table legend for details). Models 3 and 4 included CV-FPG and 1,5-AG in the same model to test for their independent effects. Models including 1,5-AG were adjusted for a 1,5-AG assay batch effect.

If CV-FPG or 1,5-AG was significant in model 4, we tested for differential risks between the glucose treatment arms for microalbuminuria and the secondary composite outcome (macroalbuminuria events were too infrequent). Interaction *P* values were calculated between CV-FPG or 1,5-AG and the treatment arms in models 1 and 4. To evaluate the additive risk of the two glycemic variability measures, we compared the risk of developing microalbuminuria and the secondary composite outcome in those with high CV-FPG (defined by the median) and low 1,5-AG versus those with low CV-FPG and high 1,5-AG.

All statistical analyses were performed using R (version 4.2.2; https://www.r-project.org). A two-sided *P* value <0.05 was considered statistically significant.

Data and Resource Availability

The ACCORD database is available upon request from the NHLBI Specimen and Data Repository (https://biolincc.nhlbi.nih.gov/studies/accord/). The data supporting the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Participants

Among 3,998 participants (two participants with missing identification codes were excluded from analysis), median (interquartile range) values of 1,5-AG for the intensive and

Table 1—Baseline characteristics by primary and secondary composite outcomes

	Microalbuminuria*			Macroalbuminuria†			Secondary composite‡		
Characteristic	No (n = 2,097)	Yes (n = 534)	P	No (n = 3,400)	Yes (n = 189)	P	No (n = 2,776)	Yes (n = 318)	P
Age, years§	61.93 (5.95)	63.46 (6.67)	<0.01	62.35 (6.26)	63.58 (6.52)	0.01	62.31 (6.25)	65.27 (6.56)	<0.01
Intensive glycemic treatment, %	1,069 (51.0)	260 (48.7)	0.37	1,722 (50.6)	80 (42.3)	0.03	1,404 (50.6)	157 (49.4)	0.73
Intensive BP treatment, %	579 (27.6)	136 (25.5)	0.35	944 (27.8)	52 (27.5)	1	940 (33.9)	148 (46.5)	<0.01
Female sex	1,061 (50.6)	288 (53.9)	0.18	1,698 (49.9)	86 (45.5)	0.27	1,409 (50.8)	206 (64.8)	<0.01
Race			0.72			0.16			0.2
Black	355 (16.9)	91 (17.0)		588 (17.3)	41 (21.7)		575 (20.7)	55 (17.3)	
Hispanic	122 (5.8)	33 (6.2)		215 (6.3)	16 (8.5)		174 (6.3)	28 (8.8)	
White	1,317 (62.8)	343 (64.2)		2,132 (62.7)	113 (59.8)		1,669 (60.1)	196 (61.6)	
Other	303 (14.4)	67 (12.5)		465 (13.7)	19 (10.1)		358 (12.9)	39 (12.3)	
Diabetes duration, years§	10.07 (7.21)	10.8 (7.20)	0.04	10.56 (7.42)	12.78 (7.65)	<0.01	10.59 (7.37)	13.78 (8.65)	<0.01
CVD history	538 (25.7)	188 (35.2)	<0.01	978 (28.8)	75 (39.7)	<0.01	814 (29.3)	104 (32.7)	0.24
History of heart failure	66 (3.1)	26 (4.9)	0.07	123 (3.6)	17 (9.0)	<0.01	109 (3.9)	22 (6.9)	0.02
History of eye disease	543 (25.9)	176 (33.0)	<0.01	1,017 (29.9)	83 (43.9)	<0.01	843 (30.4)	143 (45.0)	<0.01
Smoker	878 (46.7)	228 (48.4)	0.55	1,450 (48.1)	80 (51.9)	0.39	1,180 (48.4)	124 (42.5)	0.07
Insulin use	1,429 (68.3)	327 (61.6)	<0.01	2,235 (66.0)	99 (52.9)	<0.01	1,805 (65.3)	163 (51.6)	<0.01
Fibrate use	1,948 (93.6)	494 (92.9)	0.62	3,165 (93.6)	171 (91.4)	0.32	2,579 (93.4)	287 (90.8)	0.11
ARB use	1,733 (82.9)	442 (83.1)	0.96	2,784 (82.0)	146 (78.1)	0.21	2,259 (81.5)	248 (78.5)	0.23
ACE inhibitor use	1,089 (52.1)	239 (44.9)	<0.01	1,679 (49.5)	75 (40.1)	0.02	1,354 (48.8)	135 (42.7)	0.05
BMI, kg/m^2§	32.05 (5.37)	32.29 (5.20)	0.36	32.26 (5.38)	32.18 (5.60)	0.84	32.30 (5.40)	32.64 (5.62)	0.3
Diastolic BP, mmHg§	75.7 (10.20)	73.86 (10.55)	<0.01	75.62 (10.45)	72.58 (9.72)	<0.01	76.07 (10.40)	73.70 (10.75)	<0.01
Systolic BP, mmHg§	134.82 (15.43)	135.74 (16.06)	0.23	136.34 (16.18)	139.9 (17.71)	<0.01	137.75 (16.09)	141.57 (17.36)	<0.01
HDL cholesterol, mg/dL§	44.06 (12.11)	43.18 (11.99)	0.13	43.56 (12.18)	41.46 (11.25)	0.02	44.77 (12.66)	43.87 (12.86)	0.23
LDL cholesterol, mg/dL§	107.89 (34.67)	107.46 (32.97)	0.8	107.19 (34.97)	107.85 (35.91)	0.8	108.99 (35.51)	111.05 (39.56)	0.34
Total cholesterol, mg/dL§	186.68 (40.82)	187.95 (41.77)	0.52	187.44 (42.85)	189.5 (42.70)	0.52	190.43 (43.02)	197.10 (50.28)	0.01
Triglycerides, mg/dL§	179.67 (130.16)	192.13 (156.89)	0.06	191.07 (166.19)	206.82 (121.67)	0.2	192.53 (185.70)	215.33 (171.22)	0.04
HbA_{1c}, %§	8.19 (0.97)	8.35 (1.10)	<0.01	8.27 (1.03)	8.45 (1.15)	0.02	8.30 (1.06)	8.40 (1.12)	0.14
Fasting glucose, mg/dL§	171.74 (50.22)	175.47 (54.89)	0.13	175.43 (54.17)	175.62 (61.35)	0.96	176.40 (56.78)	174.14 (60.31)	0.5
eGFR, mL/min/1.73 m^2§	86.18 (16.28)	80.84 (19.16)	<0.01	85.13 (17.20)	77.68 (20.26)	<0.01	86.33 (16.45)	64.06 (19.36)	<0.01

Data are given as n (%) unless otherwise indicated. ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate from Chronic Kidney Disease Epidemiology Collaboration equation. *Development of ratio of urine albumin to creatinine ≥30 mg/g after year-1 examination. †Development of ratio of urine albumin to creatinine ≥300 mg/g after year-1 examination. ‡Two consecutive values of eGFR < 45 mL/min/1.73 m^2, renal failure or end-stage renal disease (dialysis), or serum creatine >3.3 mg/dL after year-1 examination in patients who were not randomly assigned to receive fenofibrate treatment. §Mean (SD).

standard treatment arms were 11.6 (7.6–16.4) and 7.4 (4.0–12.1) μg/mL, respectively. Microalbuminuria developed in 534 of 2,631 (median follow-up 60 months), macroalbuminuria in 189 of 3,589 (median follow-up 63 months), and the secondary composite outcome in 248 of 3,094 (median follow-up 61 months) qualifying participants. Baseline characteristics stratified by the events are listed in Table 1. Multiple risk factors for renal disease were present for each outcome.

Glucose Variability and Risk of Renal Outcomes

Individually, both CV-FPG and low 1,5-AG were associated with microalbuminuria in model 1 and remained significantly associated after adjusting for other risks factors (model 2; CV-FPG hazard ratio 1.16 [95% CI 1.07, 1.26]; $P < 0.001$; low 1,5-AG 1.29 [1.06, 1.56]; $P = 0.011$) (Table 2). Including both CV-FPG and low 1,5-AG in the model (model 3) yielded similar hazard ratios and CIs, indicating an independent association of CV-FPG and low 1,5-AG with the development of microalbuminuria. After additionally adjusting for average HbA_{1c} (model 4), the association of low 1,5-AG with microalbuminuria was attenuated. CV-FPG, but not 1,5-AG, was significantly associated with macroalbuminuria in models 1 to 3 and remained so in model 4 (1.22 [1.03, 1.44]; $P = 0.022$). For the secondary composite outcome, CV-FPG, but not low 1,5-AG, was a significant risk factor after adjusting for age (model 1), but not after further adjusting for other covariates.

Stratified analyses were performed for CV-FPG, because only CV-FPG remained significant in model 4 (Table 3). The association between CV-FPG and microalbuminuria was significant in the standard glucose control group after full adjustment (model 4; interaction $P = 0.139$). Again, CV-FPG showed a stronger association with the secondary composite outcome in the standard glucose control group than in the intensive glucose control group (interaction $P < 0.001$). Participants within both high CV-FPG and low 1,5-AG categories did not show a significantly greater risk of developing microalbuminuria or the secondary composite outcome than those with other combinations of these variability metrics (results not shown).

DISCUSSION

In this study, both CV-FPG and low 1,5-AG were independently associated with the development of microalbuminuria after adjusting for multiple risk factors. However, only the association of CV-FPG remained after adjusting for average glycemic control. Higher CV-FPG, but not low 1,5-AG, was a significant risk factor for macroalbuminuria. Higher CV-FPG was more harmful in those receiving less intensive glucose control, consistent with our previous findings (1,2). Combining both high CV-FPG and low 1,5-AG did not increase the risk of either primary or secondary outcomes. These results confirm the potential value of estimates of glycemic variability for determining the risk of renal complications. However, it does not seem that a single measure of 1,5-AG is sufficient to capture this risk, and determination of longer-term glucose variation is still needed. The trend of CV-FPG being associated with greater risk in participants

Table 2—HRs for CV-FPG and 1,5-AG estimated by Cox proportional hazards model

	Model 1*		Model 2†		Model 3‡		Model 4§	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Microalbuminuria (534 events in 2,631 participants)‖								
Log(CV)-FPG	1.20 (1.11, 1.30)	**<0.001**	1.16 (1.07, 1.26)	**<0.001**	1.15 (1.06, 1.25)	**0.001**	1.13 (1.04, 1.23)	**0.004**
1,5-AG <6 μg/mL	1.30 (1.08, 1.57)	**0.006**	1.29 (1.06, 1.56)	**0.011**	1.25 (1.03, 1.52)	**0.025**	1.07 (0.87, 1.31)	0.546
Macroalbuminuria (189 events in 3,589 participants)¶								
Log(CV)-FPG	1.44 (1.23, 1.68)	**<0.001**	1.28 (1.09, 1.52)	**0.003**	1.29 (1.09, 1.53)	**0.003**	1.22 (1.03, 1.44)	**0.022**
1,5-AG <6 μg/mL	1.31 (0.95, 1.79)	0.095	1.08 (0.77, 1.53)	0.659	1.02 (0.72, 1.44)	0.928	0.82 (0.57, 1.18)	0.279
Secondary composite (318 events in 3,094 participants)#								
Log(CV)-FPG	1.21 (1.09, 1.34)	**<0.001**	1.05 (0.95, 1.17)	0.324	1.05 (0.95, 1.16)	0.352	1.06 (0.95, 1.17)	0.311
1,5-AG <6 μg/mL	0.93 (0.70, 1.23)	0.593	1.12 (0.83, 1.49)	0.465	1.10 (0.82, 1.47)	0.525	1.25 (0.89, 1.74)	0.197

P values <0.05 (bold font) are considered statically significant. HR, hazard ratio. *Age adjusted. †Model 1 plus multivariate. Adjusted for significantly different baseline factors for each outcome. For microalbuminuria: diabetes duration, cardiovascular disease (CVD) history, history of eye disease, use of insulin and ACE inhibitors, diastolic blood pressure (BP), HbA_{1c}, and estimated glomerular filtration rate (eGFR). For macroalbuminuria: glycemic treatment arm, diabetes duration, CVD history, history of heart failure, history of eye disease, use of insulin and ACE inhibitors, diastolic BP, systolic BP, HDL cholesterol, HbA_{1c}, and eGFR. For secondary composite outcome: BP treatment arm, sex, diabetes duration, history of heart failure, history of eye disease, use of insulin and ACE inhibitors, diastolic BP, systolic BP, total cholesterol, triglycerides, and baseline eGFR. ‡Adjusted as in model 2 and included both 1,5-AG and CV-FPG. §Adjusted as in model 3 and included cumulative mean of HbA_{1c} as a reflection of average glycemic control. ‖Development of ratio of urine albumin to creatinine ≥30 mg/g after year-1 examination. ¶Development of ratio of urine albumin to creatinine ≥300 mg/g after year-1 examination. #Two consecutive values of eGFR <45 mL/min/1.73 m^2, renal failure or end-stage renal disease (dialysis), or serum creatine >3.3 mg/dL after year-1 examination in patients who did not receive fenofibrate treatment.

Table 3—Stratified analysis between glucose variability and glycemic treatment group for microalbuminuria and secondary composite outcome

	Model 1*			Model 4†		
	HR (95% CI)	*P*	Interaction *P*	HR (95% CI)	*P*	Interaction *P*
Microalbuminuria‡						
Standard glycemic treatment group (274 events in 1,302 participants)	**1.29 (1.15, 1.45)**	**<0.001**	**0.093**	**1.18 (1.05, 1.33)**	**0.007**	0.139
Intensive glycemic treatment group (260 events in 1329 participants)	1.13 (1.02, 1.25)	**0.022**	—	1.05 (0.94, 1.17)	0.398	—
Secondary composite§						
Standard glycemic treatment group (161 events in 1,533 participants)	**1.41 (1.21, 1.63)**	**<0.001**	**0.004**	**1.30 (1.11, 1.51)**	**<0.001**	**<0.001**
Intensive glycemic treatment group (157 events in 1,561 participants)	1.04 (0.91, 1.20)	0.542	—	0.88 (0.77, 1.02)	0.087	—

P values <0.05 (bold font) are considered statistically significant. Differential risks of low 1,5-AG and CV-FPG were assessed by incorporating an interaction between each glucose variability and glycemic treatment group for each outcome. HR, hazard ratio. *Age adjusted. †Adjusted as in model 3 (i.e., adjusted for age plus significantly different baseline factors for each outcome and included both 1,5-AG and CV-FPG as detailed in the legend of Table 2) and included cumulative mean of HbA_{1c} as a reflection of average glycemic control. ‡Development of ratio of urine albumin to creatinine ≥30 mg/g after year-1 examination. §Two consecutive values of estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, renal failure or end-stage renal disease (dialysis), or serum creatine >3.3 mg/dL after year-1 examination in patients who did not receive fenofibrate treatment.

with less strict diabetes control suggests that the combination of both higher HbA_{1c} and glycemic variability may be more closely linked with the development of complications.

The limitations of our study include *1*) the potentially lower accuracy and statistical power of a single 1,5-AG measurement at 12 months versus repeated 1,5-AG measurements or continuous glucose monitoring for recording short-term glycemic variability and *2*) the post hoc nature of our analysis.

In summary, although long-term glycemic variability and short-term glycemic variability measured by 1,5-AG demonstrated the potential to predict renal complications in individuals with T2D, longer-term visit-to-visit glucose variability seems to provide superior prediction of renal disease compared with 1,5-AG.

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