Hypoglycemia in People with Type 2 Diabetes and CKD

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Abstract

Background and objectives Among people with diabetes mellitus, CKD may promote hypoglycemia through altered clearance of glucose-lowering medications, decreased kidney gluconeogenesis, and blunted counter-regulatory response. We conducted a prospective observational study of hypoglycemia among 105 individuals with type 2 diabetes treated with insulin or a sulfonylurea using continuous glucose monitors.

Design, setting, participants & measurements We enrolled 81 participants with CKD, defined as eGFR<60 ml/min per 1.73 m^2, and 24 control participants with eGFR≥60 ml/min per 1.73 m^2 frequency-matched on age, duration of diabetes, hemoglobin A1c, and glucose-lowering medications. Each participant wore a continuous glucose monitor for two 6-day periods. We examined rates of sustained level 1 hypoglycemia (<70 mg/dl) and level 2 hypoglycemia (<54 mg/dl) among participants with CKD. We then tested differences compared with control participants as well as a second control population (n=73) using Poisson and linear regression, adjusting for age, sex, and race.

Results Over 890 total days of continuous glucose monitoring, participants with CKD were observed to have 255 episodes of level 1 hypoglycemia, of which 68 episodes reached level 2 hypoglycemia. Median rate of hypoglycemic episodes was 5.3 (interquartile range, 0.0–11.7) per 30 days and mean time spent in hypoglycemia was 28 (SD 37) minutes per day. Hemoglobin A1c and the glucose management indicator were the main clinical correlates of time in hypoglycemia (adjusted differences 6 [95% confidence interval, 2 to 10] and 13 [95% confidence interval, 7 to 20] fewer minutes per day per 1% higher hemoglobin A1c or glucose management indicator, respectively). Compared with control populations, participants with CKD were not observed to have significant differences in time in hypoglycemia (adjusted differences 4 [95% confidence interval, −12 to 20] and −12 [95% confidence interval, −29 to 5] minutes per day).

Conclusions Among people with type 2 diabetes and moderate to severe CKD, hypoglycemia was common, particularly with tighter glycemic control, but not significantly different from groups with similar clinical characteristics and preserved eGFR.

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Introduction

Hypoglycemia is an important cause of morbidity and mortality for people with diabetes mellitus. It causes symptoms related to the counter-regulatory response, including sympathetic activation, and leads to incapacitation that requires assistance from others or causes accidents (1). Severe hypoglycemia is associated with increased risks of cardiovascular events and mortality (2–4), and asymptomatic hypoglycemia has been associated with systemic inflammation and oxidative stress (5–7). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, participants with type 2 diabetes assigned to an intensive glycemic target experienced higher rates of severe hypoglycemia and a higher mortality rate than those assigned to a conventional glycemic target; although not proven, many have speculated that hypoglycemia mediated this increased mortality (3,8). In addition, fear of hypoglycemia can adversely affect patient wellbeing and self-care, and hypoglycemia can limit the implementation of intensive glycemic control, which is the cornerstone of preventing diabetes complications (1).

CKD may increase the risk of hypoglycemia. With reduced GFR, kidney gluconeogenesis and clearance of insulin and other glucose-lowering medications are reduced, and the counter-regulatory response to hypoglycemia may be blunted (9–11). In the ACCORD trial, severe hypoglycemia requiring assistance was more common in participants with a lower eGFR or higher urine albumin excretion (12), and the excess mortality observed when targeting intensive glycemic control was most pronounced among participants with CKD at baseline (13). CKD has also been associated with severe hypoglycemia in other studies (4,14), but the full burden of hypoglycemia among people with type 2 diabetes and CKD, including asymptomatic episodes, is not well defined.

We conducted a prospective study to examine the incidence and severity of hypoglycemia among people with type 2 diabetes and moderate to severe CKD. The study featured use of continuous glucose monitoring (CGM) for up to 12 days per participant to detect all episodes of hypoglycemia, including those that were not clinically apparent, and quantify glycemic variability, which correlates with risk of hypoglycemia (15). We aimed to describe the occurrence of hypoglycemia in this population and hypothesized that hypoglycemia was more frequent in the target population than control populations with type 2 diabetes and normal eGFR.

Materials and Methods

Study Design

The Continuous Glucose Monitoring to Assess Glycemia in CKD (CANDY) study was a prospective, observational, cohort study designed to examine hypoglycemia and glycemic variability and to evaluate the performance of biomarkers of mean glycemia among people with type 2 diabetes and moderate to severe CKD (Supplemental Figure 1). Participants were enrolled between August 7, 2015 and July 12, 2017. Each participant wore a blinded CGM device for two nonconsecutive 6-day periods separated by approximately 2 weeks (to ensure that glycemia was not influenced by transient environmental factors). Clinical data were collected at the initial study visit, and blood and spot urine samples were collected at the end of each CGM period. Follow-up was concluded at the end of the second CGM period. The study was approved by Institutional Review Boards of the University of Washington and the Puget Sound Veterans Affairs Health Care System, and each participant granted written informed consent. Deidentified data will be shared in accordance with policies for human trial participants when mutually agreeable to requestors and investigators.

Study Population

Participants were recruited from three health care systems in Seattle, Washington: the University of Washington and associated clinics, Harborview Medical Center, and the Puget Sound Veterans Affairs Health Care System. Patients with a clinical diagnosis of type 2 diabetes treated with sulfonylurea or insulin (agents known to cause hypoglycemia) were eligible. Exclusion criteria included age <18 years, history of kidney transplant, dialysis treatment, pregnancy, current use of clinical CGM, current therapy for cancer or with erythropoietin, and inability to speak English.

We first recruited participants with moderate to severe CKD (eGFR of 6 to <60 ml/min per 1.73 m^2). We then recruited CANDY control participants (with eGFR≥60 ml/min per 1.73 m^2) from the same source population, frequency-matching on the distributions of age, duration of diabetes, hemoglobin A1c, and glucose-lowering medication use of participants with CKD. Of the 149 consented, 105 completed the study. Nine participants were found to meet exclusion criteria after consent was obtained, 13 declined to participate, and 17 were lost to follow-up. One participant completed the study, but the data from the CGM was insufficient for analysis.

Participants in the INITIATION trial (Australian New Zealand Clinical Trials Registry identifier: ACTRN12610000797077) with eGFR≥60 ml/min per 1.73 m^2 were included as additional controls to provide an additional comparator group that used identical CGM devices. The INITIATION study was a clinical trial of people with type 2 diabetes who initiated insulin therapy for unsatisfactory glycemic control in Victoria, Australia (16,17). Participants were randomly assigned to self-monitored blood glucose or blinded CGM to guide insulin titration. We used CGM data from the end of the INITIATION trial (24 weeks after insulin initiation), when most participants were taking insulin (as in the CANDY trial).

CGM

The Medtronic iPro2 Professional blinded CGM and Enlite sensor (Medtronic, Northridge, CA) were used to monitor glycemia. With this equipment, blood glucose concentrations are calculated from interstitial glucose levels and recorded every 5 minutes, with a detection range of 40–400 mg/dl. Trained research coordinators placed each CGM device and provided each participant with instructions regarding CGM maintenance and care. Each participant was also provided with a Freestyle Lite glucose meter (Abbott, Alameda, CA) to check self-monitored fingerstick capillary blood glucose at least twice a day to calibrate the CGM.

Study physicians evaluated each CGM report by hand for quality control, excluding periods of time with evidence of CGM malfunction or marked (>30%) dyssynchrony between CGM and fingerstick glucose values. Participants were blinded to all CGM data until they completed the study, at which time CGM reports were provided to them and their clinical provider. In 18 instances, a pattern of recurrent severe hypoglycemia was identified after a participant's first CGM period, and results of that period were disclosed to the participant and provider midway through the study to promote safety.

Outcomes

Thresholds used to define level 1 (<70 mg/dl) and level 2 hypoglycemia (<54 mg/dl) were taken from an international consensus on use of CGM (15). A discrete hypoglycemia episode was declared only when three consecutive measurements met the diagnostic threshold, and participants were not considered at risk for a recurrent episode until three consecutive normal values ≥70 mg/dl were observed; alternative definitions were explored in sensitivity analyses. Each hypoglycemia episode was confirmed by a study physician through hand review of CGM data and participant logs. Other glycemia metrics evaluated included time in range (70–180 mg/dl), time in hypoglycemia (<70 mg/dl), time above range (>180 mg/dl), coefficient of variation (SD divided by mean of all CGM glucose concentrations, a preferred metric of glycemic variability), SD and interquartile range of all CGM glucose concentrations (alternative variability metrics), and the glucose management indicator (GMI) (a measure of mean blood glucose calculated from all CGM glucose concentrations) (15,18).

Clinical Data

Race, ethnicity, education, general health, smoking, and past medical history were defined by self-report. Medications were inventoried with assistance from electronic health

records. Many participants used multiple glucose-lowering medications; all participants studied were required by design to use insulin, a sulfonylurea, or both. Insulin usage was categorized by type of insulin, frequency of dosing, and duration of effect: long- or intermediate-acting only, mixed insulin (a combination of intermediate- and short-acting insulin), basal bolus (use of a long- or intermediate-acting plus a separate short-acting insulin), or no insulin. The mean of two eGFR measurements was calculated from creatinine (measured at two separate study visits) traceable to isotope dilution mass spectrometry (IDMS) using the CKD Epidemiology Collaboration equation (19). Hemoglobin A1c was measured by HPLC at the University of Missouri, conforming to National Glycohemoglobin Standardization Program (NGSP) standards, from whole blood collected at the end of each CGM period; the mean of the two values was used for analyses. During CGM, participants were asked to keep a log of medication use, physical activity, and meals, although logging was not strictly enforced and most logs appeared incomplete.

Statistical Analyses

Incidence rates were calculated as number of events divided by total valid observation time at risk, scaled to episodes per 30 days. For times in, below, and above range, each glucose concentration was presumed to count for 5 minutes. We graphically quantified the burden of hypoglycemia as the number of minutes during which hypoglycemia occurred by time of day across participants. We compared most hypoglycemia outcomes between CKD and control groups *via* the two-sample *t* test, assuming nonequal variance; differences in hypoglycemia rates between CKD and controls were compared *via* Poisson regression. Correlates of time below range were examined using linear regression with robust Huber–White SEM, adjusting for age, sex, and race. Differences in time below range and coefficient of variation between groups were additionally adjusted for mean CGM blood glucose. All analyses were performed using the R statistical computing environment version 3.4.0. A two-tailed P value <0.05 was taken as evidence of statistical significance in all analyses.

Results

Participant Characteristics

The 81 analyzed participants with CKD had a mean (SD) age of 69 (10) years, diabetes duration of 20 (11) years, body mass index of 33.8 (5.7) kg/m^2, eGFR of 38 (14) ml/min per 1.73 m^2, and hemoglobin A1c of 7.7% (1.4%) (Table 1); 74% were white, 51% had a college education, 89% used insulin (mainly basal bolus regimens), 21% used sulfonylureas, and 36% used other glucose-lowering medications (mainly biguanides and GLP1 receptor agonists). In comparison, CANDY control participants had overlapping but slightly lower distributions of age and duration of diabetes and a similar distribution of glucose-lowering medication use (by design). Control subjects from the INITIATION trial were younger (mean age 59 [SD 10] years), with a shorter duration of diabetes (mean 10 [SD 6] years) and more use of long-without short-acting insulin (by INITIATION design), biguanides, and dipeptidyl peptidase-4 inhibitors.

Hypoglycemia in CKD

Over 890 total days of CGM, participants with CKD were observed to have 255 episodes of hypoglycemia, including 68 episodes of level 2 hypoglycemia (Table 2). None of the 255 episodes were reported by participants to require assistance from others—the definition used to define severe hypoglycemia in many large studies. A representative participant report of 6 days of CGM monitoring with three episodes of hypoglycemia is shown in Figure 1.

Hypoglycemia was most frequent from 1 to 8 AM (Figure 2). Mean duration of hypoglycemic episodes was 100 (SD 56) minutes, and mean nadir glucose was 58 (SD 4) mg/dl. Median rate of hypoglycemic episodes was 5.3 (interquartile range, 0.0–11.7) per 30 days, and mean time spent in hypoglycemia was 28 (SD 37) minutes per day. When the number of consecutive measurements required to define an episode ranged from 1 to 6, median rate of hypoglycemic episodes varied from 4.8 to 7.3 per 30 days (Supplemental Table 1). In additional sensitivity analyses, hypoglycemia incidence rates and time in hypoglycemia were similar to or lower than observed in primary analyses when 17 participants using acetaminophen or paracetamol were excluded or when the second observation period was excluded for 18 participants who were informed of CGM results after the first observation period (for safety concerns) (Supplemental Tables 2 and 3).

Hemoglobin A1c and GMI were the main clinical correlates of time in hypoglycemia. Each 1% higher hemoglobin A1c was associated with 6 minutes less hypoglycemia per day, and each 1% higher GMI was associated with 13 minutes less hypoglycemia per day (Figure 3, Table 3). The correlation of GMI with time in hypoglycemia ($r=-0.39$; $P<0.001$) was numerically stronger than that of hemoglobin A1c with time in hypoglycemia ($r=-0.25$; $P=0.01$). Older age, insulin dosage, and usage of insulin were nominally associated with lower coefficient of variation (Supplemental Table 4).

Comparisons by CKD Status

Hypoglycemia occurred most commonly during the night for participants with and without CKD, although CANDY participants with CKD appeared qualitatively to have a stronger predominance of nighttime hypoglycemia and less evening or postprandial hypoglycemia than controls (Figure 2). Within the CANDY study, hypoglycemia rates and other glycemia metrics were generally similar for participants with and without CKD (Table 2), and there was no clear relationship between eGFR and time in hypoglycemia (Figure 3). For INITIATION control participants, mean blood glucose concentration was lower, unadjusted hypoglycemia rate and time in hypoglycemia were higher, and time in hyperglycemia was lower than for CANDY participants with CKD (Table 2). Adjusting for mean CGM glucose, participants with CKD were not observed to have significant differences in time in hypoglycemia: 4 (95% confidence interval [95% CI], −12 to 20) minutes per day compared with CANDY controls, and −12 (95% CI, −29 to 5) minutes per day compared with INITIATION controls. Similarly, adjusting for mean CGM glucose, participants with CKD were not observed to have significant differences in glucose coefficient of variation: 1.5% (95% CI, −1.6% to 4.6%) compared with CANDY controls, and −1.1% (95% CI, −3.3% to 1.1%) mg/dl compared with INITIATION controls.

Table 1. Characteristics of participants in two studies using continuous glucose monitoring to assess hypoglycemia and glycemic variability

Characteristic	CANDY Study		INITIATION Study
	CKD, *n*=81	Control Participants, *n*=24	Control Participants, *n*=73
Demographics			
Age (years)	69 (10)	64 (10)	59 (10)
Men	52 (64)	15 (62)	43 (59)
Race/ethnicity			
White	60 (74)	20 (83)	NA
Black	12 (15)	2 (8)	NA
Other	9 (11)	2 (8)	NA
Hispanic ethnicity	8 (10)	3 (12)	NA
Highest level of education			
High school	22 (27)	7 (29)	NA
Trade school	17 (21)	7 (29)	NA
College	23 (28)	7 (29)	NA
Graduate school	19 (23)	3 (12)	NA
Health history			
General health			
Excellent/very good	14 (17)	8 (33)	NA
Good	26 (32)	8 (33)	NA
Fair or poor	41 (51)	8 (33)	NA
Current smoking	2 (2)	3 (12)	NA
History of myocardial infarction	13 (16)	1 (4)	NA
History of heart failure	18 (22)	1 (4)	NA
History of stroke	12 (15)	1 (4)	2 (3)
Duration of diabetes	20 (11)	16 (8)	10 (6)
Medication use			
Insulin[a]	72 (89)	21 (88)	73 (100)
Long- or intermediate-acting only	22 (27)	4 (17)	73 (100)
Mixed insulin	4 (5)	0 (0)	1 (1)
Basal bolus	46 (57)	17 (71)	0 (0)
No insulin	9 (11)	3 (12)	0 (0)
Insulin dose, units/kg per d	0.56 (0.43)	0.65 (0.49)	
Insulin secretagogues	18 (22)	5 (21)	50 (68)
Sulfonylureas	17 (21)	5 (21)	50 (68)
Meglitinides	1 (1)	0 (0)	0 (0)
Other glucose-lowering agents[b]	29 (36)	18 (75)	65 (89)
DPP-4 inhibitors	3 (4)	0 (0)	17 (23)
GLP-1 agonists	11 (14)	5 (21)	1 (1)
Biguanides	18 (22)	14 (58)	63 (86)
SGLT-2 inhibitors	1 (1)	5 (21)	0 (0)
TZDs	0 (0)	0 (0)	6 (8)
α Glucosidase inhibitor	0 (0)	0 (0)	2 (3)
Antihypertensive medications	77 (95)	21 (88)	50 (68)
ACEi/ARBs	60 (74)	21 (88)	50 (68)
β Blockers	38 (47)	5 (21)	10 (14)
Lipid-lowering medications	75 (93)	20 (83)	47 (64)
Statins	75 (93)	20 (83)	47 (64)
Acetaminophen	13 (16)	2 (8)	2 (3)
Physical characteristics			
Body mass index, kg/m^2	33.8 (5.7)	32.4 (6.2)	33.5 (6.2)
Systolic BP, mm Hg	132 (21)	136 (17)	NA
Diastolic BP, mm Hg	72 (13)	78 (12)	NA
Laboratory values			
eGFR, ml/min per 1.73 m^2	38 (14)	83 (11)	77 (8)
Urine ACR, mg/g	132 (8)	26 (7)	NA
Hemoglobin A1c, %	7.8 (1.4)	7.6 (1.1)	7.4 (0.9)

Entries are mean (SD) for continuous variables or *n* (%) for categorical variables, except geometric mean (SD) for urine ACR. Missing data in CANDY: history of stroke (*n*=2), duration of diabetes (*n*=4), urine ACR (*n*=3), hemoglobin A1c (*n*=1). Missing data in INITIATION: eGFR (*n*=7), hemoglobin A1c (*n*=1). CANDY, Continuous Glucose Monitoring to Assess Glycemia in Chronic Kidney Disease; NA, not available; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter 2; TZD, thiazolidinedione; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; ACR, albumin-to-creatinine ratio.

[a]Insulin usage was categorized by type of insulin, frequency of dosing and duration of effect: long- or intermediate-acting only, mixed insulin (a combination of intermediate- and short-acting insulin), basal bolus (use of a long- or intermediate-acting plus a separate short-acting insulin), or no insulin.

[b]Many participants used multiple glucose-lowering medications; all were required by design to use insulin, a sulfonylurea, or both.

Table 2. Glycemia metrics assessed using continuous glucose monitoring

Metric	CANDY Study			INITIATION Study	
	CKD, *n*=81	Controls, *n*=24	*P* Value[a]	End of Study, *n*=73	*P* Value[b]
Observation time					
Total time, d	890	276		1456	
Average time per participant, d	11 (2.3)	12 (2.5)		6. (0.8)	
Mean blood glucose, mg/dl	170 (40.0)	158 (30.4)		154 (30.4)	
Glucose management indicator, %	7.4 (1.0)	7.1 (0.7)		7.0 (0.7)	
Level 1 hypoglycemia, <70 mg/dl					
No. of events	255	80		220	
No. (%) of participants with at least one event	56 (69)	16 (67)		51 (70)	
Duration of episode, min	100 (56)	116 (86)	0.51	104 (76)	0.76
Nadir glucose, mg/dl	58 (4)	55 (7)	0.16	59 (6)	0.13
Rate, episodes per 30 d	5.3 (0.0–11.7)	5.9 (0.0–10.9)	0.97	10.1 (0.0–18.5)	0.01
Level 2 hypoglycemia, <54 mg/dl					
No. of events	68	25		78	
No. (%) of participants with at least one event	34 (42)	11 (46)		27 (37)	
Time in range					
Time in hypoglycemia, min <70 mg/dl per d	28 (37)	29 (36)	0.93	49 (71)	0.02
10 PM–10 AM	23 (32)	22 (29)		39 (63)	
10 AM–10 PM	5 (11)	7 (13)		10 (21)	
Time <54 mg/dl	6 (12)	9 (15)		13 (29)	
Time in range, min 70–180 mg/dl per d	886 (325)	998 (312)	0.14	985 (268)	0.03
Time above range, min >180 mg/dl per d	526 (337)	414 (316)	0.14	406 (275)	0.01
Glycemic variability					
SD of glucose readings, mean (SD)	52 (14)	46 (15)	0.11	49 (14)	0.22
IQR of glucose readings, mean (SD)	72 (23)	63 (24)	0.15	69 (24)	0.56
CV% of glucose readings, mean (SD)	31 (6)	29 (7)	0.36	32 (8)	0.27

Data are displayed as *n* (%), mean (SD), or median (IQR). CANDY, Continuous Glucose Monitoring to Assess Glycemia in Chronic Kidney Disease; IQR, interquartile range; CV, coefficient of variation.
[a]*P* value compares CANDY participants with CKD with CANDY controls.
[b]*P* value compares CANDY participants with CKD with INITATION study controls.

Discussion

Hypoglycemia detected by CGM was quite common in this clinic-based study of people with long-standing type 2 diabetes and moderate to severe CKD. Hypoglycemia episodes were often long (mean 100 minutes [SD 56]), blood glucose often reached low concentrations (mean 58 [SD 4] mg/dl, 27% of episodes <54 mg/dl), and early morning was the highest-risk time of day, presumably during sleep, which is consistent with prior studies of type 1 and type 2 diabetes without CKD. Hemoglobin A1c and the

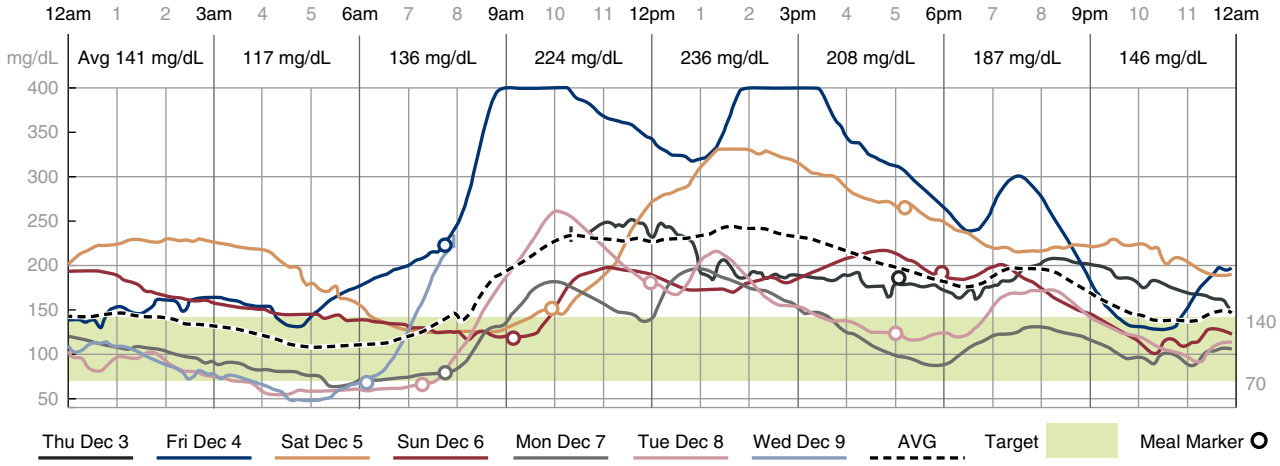

Figure 1. | Representative visual report of hypoglycemia glycemia observed for a study participant over 6 days of CGM. Each line represents blood glucose concentration tracked for 1 day, from midnight to midnight. The manufacturer-suggested target range of 70–150 mg/dl is shown as a tan band. Over 6 days, this participant experienced three episodes of level 1 hypoglycemia (<70 mg/dl), including one episode of level 2 hypoglycemia (<54 mg/dl), all starting between 3 and 6 AM. AVG, average.

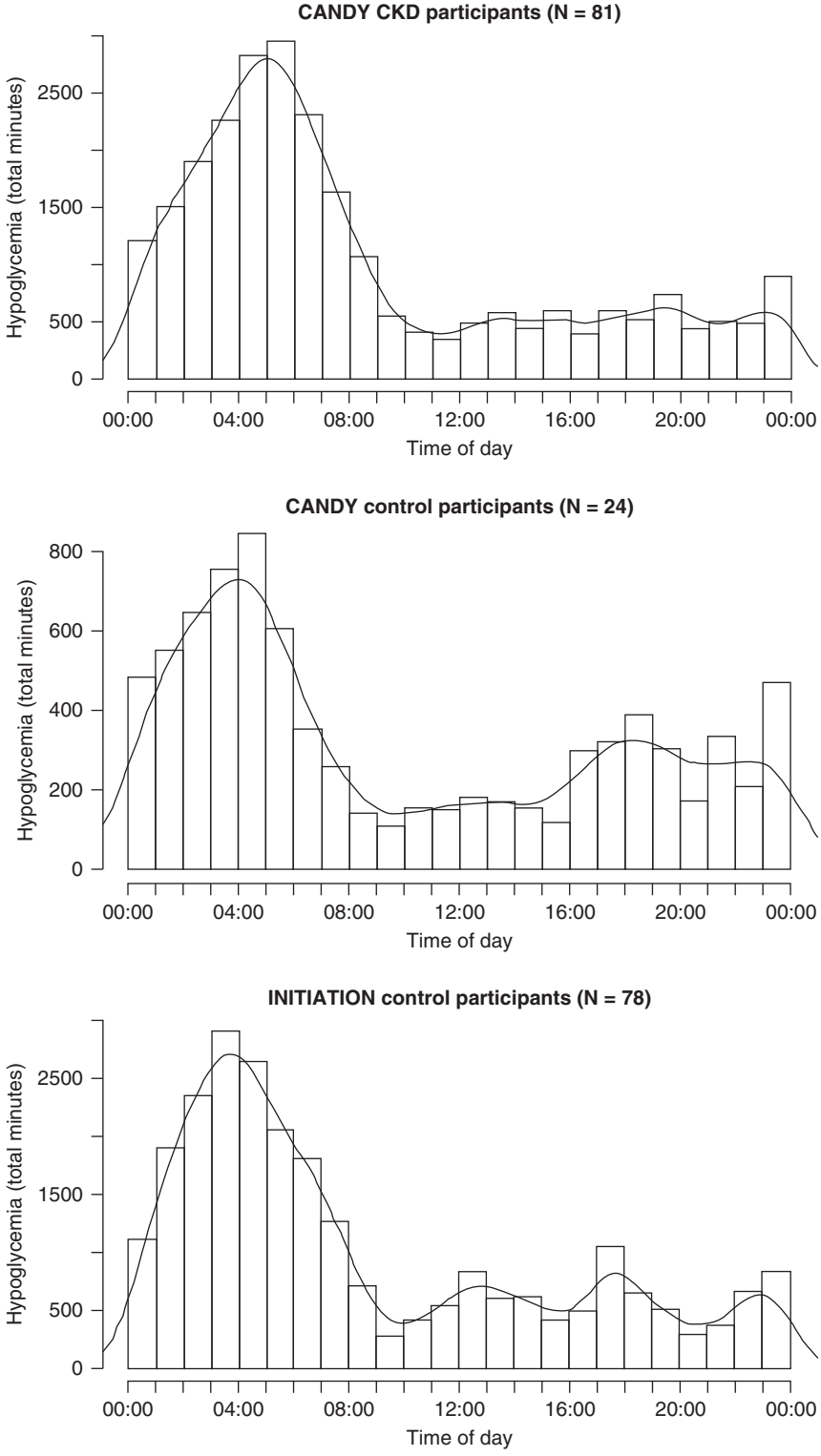

Figure 2. | **Time spent in hypoglycemia (<70 mg/dl) according to time of day.** Hypoglycemia was most frequent from 1 to 8 AM.

GMI were inversely correlated with time in hypoglycemia, confirming in this population that hypoglycemia is a trade-off for the benefits of intensive glycemic control. Counter to our hypothesis, metrics of hypoglycemia and glycemic variability were not significantly worse comparing participants with CKD to two control populations.

Most published studies examining hypoglycemia in CKD have evaluated severe episodes requiring assistance from others, now termed level 3 hypoglycemia (14,15). None of the observed episodes in our study required assistance from others, suggesting that hypoglycemia rates that come to the attention of health care providers reported

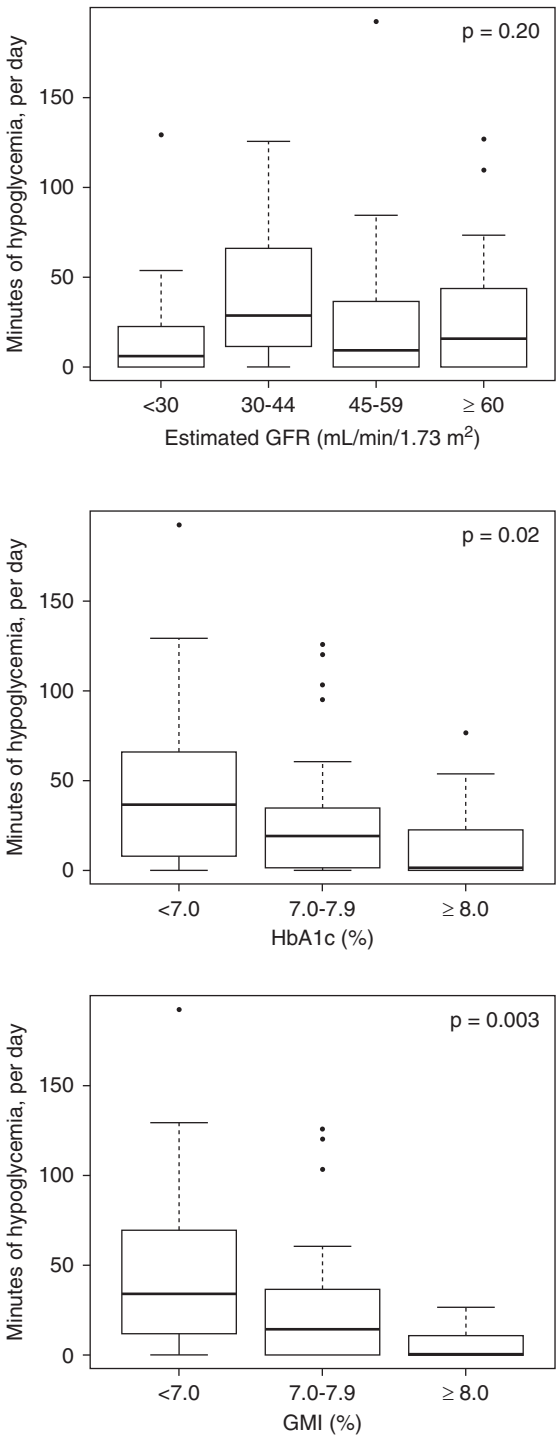

Figure 3. | Time spent in hypoglycemia was not related to eGFR and inversely related to hemoglobin A1c and GMI. (A) Time spent in hypoglycemia according to eGFR among all 106 study participants. (B) Time spent in hypoglycemia according to hemoglobin A1c (HbA1c) among 81 study participants with eGFR<60 ml/min per 1.73 m^2. (C) Time spent in hypoglycemia according to the GMI among 81 participants with eGFR<60 ml/min per 1.73 m^2.

in many studies markedly underestimate total episodes of self-reported hypoglycemia. For example, ACCORD participants with serum creatinine >1.3 mg/dl (but still low enough to be eligible for ACCORD) who were assigned to intensive glycemic control experienced 0.05 episodes of level 3 hypoglycemia per year, on average, whereas we observed 5.3 episodes of level 1 hypoglycemia per month (12). We are unaware of other studies that have comprehensively evaluated hypoglycemia and glycemic variability in moderate to severe CKD using CGM, and our data are therefore important to define and describe the extent of this problem. Other studies have suggested high rates of hypoglycemia among patients treated with dialysis, although direct comparisons are difficult because of differences in study populations and technology (20–27).

We observed no correlation of eGFR with hypoglycemia among CANDY participants with CKD. It is possible that CKD *per se* does not actually increase the risk of hypoglycemia, or that CKD increases the likelihood that hypoglycemia events become clinically apparent (explaining increased severe hypoglycemia requiring assistance in other studies) without altering the underlying rate of level 1 hypoglycemia. However, other aspects of study design and population may also have influenced this result. In CANDY, control participants were matched to participants with CKD on duration of diabetes and use of glucose-lowering medications; if long-standing diabetes (with resulting reduced residual β cell function) and differential use of glucose-lowering medications are important causes of hypoglycemia in CKD, this design would have reduced expected differences. In addition, the CANDY control population was small and perhaps not representative of uncomplicated type 2 diabetes in general. Although the INITIATION trial was also a relevant control population, particularly because of similarities in CGM technology, there are important differences that may confound our comparison, including new use of insulin and better overall glycemic control.

Lower hemoglobin A1c and GMI were the only clinical risk factors we identified for hypoglycemia among participants with CKD. Although mean blood glucose (reflected by hemoglobin A1c) and glycemic variability are only moderately correlated (15), our results confirm that better overall glycemic control generally comes with a trade-off of increased hypoglycemia risk. These results support recommendations of the American Diabetes Association to individualize target hemoglobin A1c for patients with type 2 diabetes, taking into account hypoglycemia risk and considering higher targets for patients with comorbidities such as CKD (28,29). These results also suggest that mean glycemia measured by CGM and expressed using the new metric of GMI may reflect risk of hypoglycemia more accurately than hemoglobin A1c (18), perhaps because of limitations to the accuracy or precision of hemoglobin A1c among people with diabetes and CKD.

The main strength of our study was the use of a state-of-the-art CGM system to comprehensively ascertain hypoglycemia and glycemic variability in CKD for periods of time sufficient to characterize usual glycemic patterns (mean 11 [SD 2.3] days per participant). In addition, the sample size with CKD was reasonably large, the population included a range of moderate to severe CKD, and hemoglobin A1c was measured using gold standard methods. Other limitations included the observational design, which precludes conclusions regarding causality of associations, lack

Table 3. Associations of clinical characteristics with time spent in hypoglycemia among 81 CANDY study participants with type 2 diabetes and CKD

Characteristic	*N*	Mean (SD), min/d	Difference (95% CI), min/d	Adjusted Difference (95% CI), min/d
Age, yr				
<60	12	15 (19)	0 (Ref.)	0 (Ref.)
60–69	28	29 (38)	14 (−3 to 32)	9 (−6 to 24)
70–79	34	33 (43)	18 (1 to 36)	14 (−2 to 31)
≥80	7	19 (16)	4 (−11 to 19)	−3 (−20 to 13)
eGFR, ml/min per 1.73 m^2				
45–59	28	25 (41)	0 (Ref.)	0 (Ref.)
30–44	30	39 (36)	14 (−6 to 33)	9 (−10 to 29)
<30	23	18 (30)	−7 (−26 to 12)	−11 (−26 to 5)
Hemoglobin A1c category				
<7.0%	25	41 (46)	0 (Ref.)	0 (Ref.)
7.0%–7.9%	27	31 (38)	−10 (−32 to 13)	−11 (−31 to 9)
≥8.0%	28	13 (19)	−27 (−47 to −9)	−25 (−42 to −7)
Hemoglobin A1c, per 1% increment			−8 (−13 to −3)	−6 (−10 to −2)
Glucose management indicator				
<7.0%	28	44 (44)	0 (Ref.)	0 (Ref.)
7.0%–7.9%	39	24 (32)	−20 (−39 to −1)	−15 (−34 to 4)
≥8.0%	14	6 (9)	−38 (−55 to −22)	−29 (−45 to −12)
GMI, per 1% increment			−16 (−23 to −9)	−13 (−20 to −7)
Insulin dose, units/kg per d				
No insulin	9	7 (12)	0 (Ref.)	0 (Ref.)
0.01–0.5	38	33 (44)	26 (10 to 42)	14 (−1 to 29)
0.51–1.0	23	27 (29)	19 (5 to 33)	9 (−5 to 24)
>1.0	11	29 (36)	22 (0.4 to 44)	12 (−13 to 36)
Insulin dosage, per 0.44 unit/kg per d increment			3 (−7 to 13)	2 (−9 to 13)
Duration of diabetes, yr				
<10	8	20 (28)	0 (Ref.)	0 (Ref.)
10–19	30	19 (28)	−1 (−21 to 20)	−4 (−23 to 17)
≥20	40	38 (43)	18 (−4 to 40)	21 (−1 to 43)
Body mass index				
<30	21	27 (28)	0 (Ref.)	0 (Ref.)
30–34	33	31 (42)	4 (−14 to 23)	9 (−8 to 27)
35–39	18	17 (30)	−10 (−27 to 8)	−7 (−24 to 11)
≥40	9	39 (48)	12 (−20 to 44)	9 (−14 to 31)
Medications				
Insulin				
None	9	7 (12)	0 (Ref.)	0 (Ref.)
Any	72	30 (38)	31 (2 to 61)	16 (−13 to 45)
Insulin secretagogues				
No	63	28 (33)	0 (Ref.)	0 (Ref.)
Yes	18	27 (49)	11 (−21 to 44)	4 (−28 to 35)
Other glucose-lowering agents				
No	52	26 (34)	0 (Ref.)	0 (Ref.)
Yes	29	31 (43)	4 (−12 to 19)	10 (−5 to 26)

Adjusted differences are adjusted for age, sex, and race. CANDY, Continuous Glucose Monitoring to Assess Glycemia in Chronic Kidney Disease; 95% CI, 95% confidence interval; Ref., reference; GMI, glucose management indicator.

of high-quality data on patient-reported outcomes, and lack of data linking glycemic patterns to clinical outcomes. Intervention studies are required to more rigorously evaluate the comparative effects of glucose-lowering medications (including newer basal insulins such as degludec and U-300 glargine) and real-time, unblinded CGM on glycemia in CKD. Unfortunately, self-reported data on symptoms and other patient-reported effects of these episodes were not uniformly well ascertained. Further investigation is needed to determine how the broad range of hypoglycemic events affects how patients with CKD feel and function, and also to determine whether these episodes elicit a harmful pathophysiologic response or increase the risk of adverse clinical outcomes, such as cardiovascular events.

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.11650918/-/DCSupplemental.

Title Page

Supplemental Table 1. Hypoglycemia incidence using alternative definitions of hypoglycemia.

Supplemental Table 2. Sensitivity analysis assessing glycemia outcomes among CANDY and INITIATION participants who did not report use of acetaminophen or paracetamol.

Supplemental Table 3. Sensitivity analysis assessing glycemia outcomes in CANDY, excluding the second observation period for 18 CANDY participants (15 with CKD, three controls) who were informed of their results from the first observation for safety.

Supplemental Table 4. Associations of clinical characteristics with blood glucose coefficient of variation among 81 CANDY study participants with type 2 diabetes and CKD.

Supplemental Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of CANDY study.

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