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ORIGINAL ARTICLE

Hypoglycemia in sulfonylurea-treated *KCNJ11*-neonatal diabetes: Mild-moderate symptomatic episodes occur infrequently but none involving unconsciousness or seizures

Monica S Lanning[1] | David Carmody[1] | Łukasz Szczerbiński[2] | Lisa R Letourneau[1] | Rochelle N Naylor[1] | Siri Atma W Greeley[1]

[1]Section of Adult and Pediatric Endocrinology, Diabetes, & Metabolism, Departments of Medicine and Pediatrics, The University of Chicago, Chicago, Illinois

[2]Medical University of Bialystok, Bialystok, Poland

Correspondence
Siri Atma Greeley, MD, PhD, Department of Pediatrics, The University of Chicago, 5841 S Maryland Avenue, MC 1027, IL 60637.
Email: sgreeley@peds.bsd.uchicago.edu

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Background: Neonatal diabetes mellitus (NDM) caused by mutations in *KCNJ11* can be successfully treated with high dose oral sulfonylureas; however, little data is available on the risk of hypoglycemia.

Objective: To determine the frequency, severity, and clinical significance of hypoglycemia in *KCNJ11*-related NDM.

Methods: Utilizing the University of Chicago Monogenic Diabetes Registry, parents completed an online questionnaire addressing hypoglycemia. Continuous glucose monitoring (CGM) data was available for 7 subjects.

Results: Thirty subjects with *KCNJ11*-related permanent NDM (166 patient-years on sulfonylurea) had median sulfonylurea dose of 0.39 mg/kg/day (0.24-0.88 IQR, interquartile range) with median HbA1c 5.7% (39 mmol/mol) (5.5-6.1 IQR, 37-43 mmol/mol). Hypoglycemia (<70 mg/dL) was reported monthly once or less frequently in 89.3% of individuals, but 3 (10.7%) reported once weekly or more. Of all hypoglycemic episodes reported, none involved seizures or unconsciousness and thus did not meet the current ISPAD definition of severe hypoglycemia. Seven individuals wore a CGM for a total of 912 hours with blood sugars falling below 70 mg/dL for 5.8% of the time recorded, similar to ranges reported for people without diabetes.

Conclusions: In our cohort of *KCNJ11*-related permanent NDM, hypoglycemia is infrequent and mild despite the high doses of sulfonylurea used and near-normal level of glycemic control. Long-term follow-up on larger numbers will be required to clarify the incidence and determinants of hypoglycemia in this unique population.

KEYWORDS

hypoglycemia, *KCNJ11*, monogenic diabetes, neonatal diabetes, sulfonylurea

1 | INTRODUCTION

Persistent hyperglycemia requiring treatment diagnosed within the first 6 months of life is referred to as neonatal diabetes mellitus (NDM). NDM is a rare condition with an estimated incidence of 1 in 90 000 to 160 000 live births.[1,2] NDM may be transient or permanent and is typically monogenic in etiology with over 20 genes implicated[3]. Mutations in *KCNJ11*, one of the genes encoding the ATP-sensitive potassium (K_{ATP}) channel, represent the most common cause of permanent NDM and are frequently associated with developmental delay and neurological features.[4,5]

The identification of *KCNJ11* mutations has dramatic clinical implications with the majority of patients being able to transition from insulin therapy to oral sulfonylurea (SU) treatment.[4] A number of reports have demonstrated measurable improvements in neurodevelopmental capabilities after transitioning to SU treatment in *KCNJ11*-related

diabetes[6–9] and some limited data suggests earlier introduction of SUs is advantageous.[10] However, there is limited data on hypoglycemia in NDM subjects treated with SU medications. We sought to determine the frequency, severity, and clinical significance of hypoglycemia in subjects with *KCNJ11*-related diabetes in order to evaluate the risks and benefits of adjusting SU treatment in this group.

2 | RESEARCH DESIGN AND METHODS

All subjects were consented for participation through protocols approved by the Institutional Review Board at the University of Chicago. Subjects with *KCNJ11*-related NDM were consented for participation through the University of Chicago Monogenic Diabetes Registry (http://monogenicdiabetes.uchicago.edu/our-research/registration) through which longitudinal information regarding the diagnosis and treatment of diabetes, other medical problems or complications, family history, and genetic testing results are collected through surveys and medical records.[11] Key data gathered through self- or parent/care-giver report includes age, weight, HbA1c, continuous glucose monitor records, and medication information. To assess hypoglycemia in patients with *KCNJ11*-related permanent NDM treated with SUs, the study team developed a questionnaire through an iterative process. After defining the research question and sub-questions, constructs were defined to guide question development. Selected questions mapped onto the research sub-questions. The questionnaire was pretested with colleagues with expertise/experience in monogenic diabetes, as well as with individuals with personal experience with diabetes management. This tool queried frequency and severity of hypoglycemia since starting SU treatment, frequency of home glucometer measurements, self-defined hypoglycemia threshold, symptoms associated with hypoglycemia, and other medication side effects (Figure S1, Supporting information). Caregivers were asked about the frequency of hypoglycemia that they deemed 'mild to moderate' (defined in our survey as "conscious and mostly able to help themselves") and episodes of hypoglycemia that they deemed "severe" (defined in our survey as "partially or fully unconscious, having a seizure, or otherwise unable to assist with their own care" following published guidelines from ISPAD (2009) and ADA (2005)).[12,13] All episodes of hypoglycemia that were deemed "severe" by caregivers were reviewed in detail by our research team according to current ISPAD guidelines (2014) that define "severe" as involving seizures or loss of consciousness.[14] This questionnaire was delivered online using REDCap and was sent in conjunction with another study on behavior and sleep characteristics of this population.[15]

Inclusion criteria for our study were those patients in the University of Chicago Monogenic Diabetes Registry identified to have a mutation in *KCNJ11* as the cause of their diabetes who are currently taking SU therapy and whose caregivers responded to follow-up contact for this study. Data are displayed as median (interquartile range, IQR) unless otherwise specified. All data collected were self-reported by the subject or caregiver.

3 | RESULTS

Of the 459 individuals with an established monogenic etiology for diabetes within the University of Chicago Monogenic Diabetes Registry at the time of this study, we distributed surveys to the 72 who had a *KCNJ11* mutation and received responses from 30 subjects, all with permanent NDM (28 probands and 2 affected family members; Table 1). The non-responders consisted of 31 subjects with permanent neonatal diabetes (24 probands and 7 affected family members) and 11 with transient neonatal diabetes. It is notable that all of the responders had a permanent neonatal diabetes phenotype, while none of those with transient diabetes responded. Among probands with permanent neonatal diabetes, there was a response rate of 54%, and proband responders (n = 28) and non-responders (n = 24) were similar by all characteristics, including household income and age at assessment, as reported previously.[15] The majority of responses were from parents or guardian caregivers who completed the questionnaire on behalf of subjects, who were mostly children (mean age: 10.2 years, median: 8 years [5.25-12.75 IQR]). The specific *KCNJ11* variants included R201H (n = 10), R201C (n = 5), V59 M (n = 7) and other less common variants (one each of G53D, H46L, I182T, Q52L, and V59A, and two with H186D).[4] The median age at diagnosis was 0.15 years (0.09-0.29 IQR), the median age at SU initiation was 1.2 years (0.3-5.8 IQR), and the median HbA1c at the time of survey collection was 5.7% (39 mmol/mol) (5.5%-6.1% IQR; Table 1). Two subjects had outlier HbA1c values of 8.6% (70 mmol/mol; variant R201H, SU dose 0.11 mg/kg/day) and 12.1% (109 mmol/mol; variant R201C, SU dose 1.42 mg/kg/day). Removing these two HbA1c outliers, the median HbA1c remained 5.7% (39 mmol/mol), but the IQR shifted down to 5.5% to 5.8% (37-40 mmol/mol). The median SU dose, in the form of glyburide pills, was 0.39 mg/kg/day (0.24-0.88 IQR). After removing the SU doses of the two subjects with HbA1c outliers, the median and IQR SU dose were essentially unchanged (median: 0.39 mg/kg/day, 0.25-0.79 IQR).

Episodes of hypoglycemia deemed "mild to moderate" (survey definition: "conscious and mostly able to help themselves") were reported once a month or less frequently in 89.3% (n = 28) of individuals. There was wide variation in the frequency of blood glucose monitoring, ranging from 3 times daily to less than once weekly, with median HbA1c values of 5.7% (39 mmol/mol) (5.5%-6.1% IQR) (37–43 mmol/mol). When examining specific mutations, V59M mutations with a median glyburide dose of 0.79 mg/kg/day (0.46-0.91 IQR) reported the least hypoglycemia with 4 out of 7 respondents (57%) reporting mild to moderate hypoglycemia several times a year. R201H and R201C mutations, despite having lower median doses of SU (0.29 and 0.45 mg/kg/day, respectively) reported mild to moderate hypoglycemia more often, with the most common response being once a month (56%). The three subjects (10.7%) who reported hypoglycemia as "once a week" or "more than once a week" had SU doses of 2.354, 0.405 and 0.386 mg/kg/day (Table 2).

Six respondents (n = 28; 21.4%) reported at least one episode of hypoglycemia they deemed "severe" since starting SU treatment (survey definition: "partially or fully unconscious, having a seizure, or

TABLE 1 Summary of cohort

	n (%) or median (IQR)
Total subjects	30
Male	14 (46.7%)
Age at assessment (y)	8 (5.25-12.75)
Age at neonatal diabetes mellitus (NDM) diagnosis (y)	0.15 (0.09-0.29)
Age at sulfonylurea (SU) initiation (y)	1.2 (0.3-5.8)
HbA1c	5.7 (5.5%-6.1%) (DCCT); 39 (37-43 mmol/mol) (IFCC)
Dose of sulfonylurea	0.39 (0.24-0.88 mg/kg/day)
Hypoglycemia once a month or less frequently[a]	25/28 (89.3%)
Severe hypoglycemic episodes[a,b] (based on 2014 ISPAD guidelines)	0/6 (0%)
Lowest reported BG	45 (35-55 mg/dL); 2.5 (1.9-3.1 mmol/L)
Frequency of BG testing[c]	
Less than once a week	7 (23.3%)
Once a week	5 (16.7%)
Once a day	3 (10%)
Twice a day	5 (16.7%)
Three or more times a day	9 (30%)
Self-definition of hypoglycemia[a]	
Less than 80 mg/dL	2 (6.7%)
Less than 70 mg/dL	13 (43.3%)
Less than 60 mg/dL	7 (23.3%)
Less than 50 mg/dL	6 (20%)

[a] Two participants did not respond to this question.

[b] See the text for further description of these episodes. Six caregivers responded "yes" to survey question asking if their subject had ever had a severe hypoglycemic episode with severe defined as: "partially or fully unconscious, having a seizure, or otherwise unable to assist with their own care" (based on 2009 ISPAD guidelines). Each reported event was reviewed in detail. None involved loss of consciousness or seizure (current 2014 ISPAD severe hypoglycemia guideline). One individual reported hospitalization due to hypoglycemia.

[c] One participant did not respond to this question.

otherwise unable to assist with their own care"). However, upon expert review, none of these events were clinically severe based on the 2014 ISPAD definition of severe hypoglycemia in children (seizure or loss of consciousness). Further information on these 6 episodes, as well as SU doses and HbA1c comparisons for these subjects, can be found in Table S1.

When respondents were asked what they considered to be a "low blood sugar," the median response was a blood glucose level below 60 mg/dL (3.3 mmol/L) (57.5-70 mg/dL IQR, 3.2-3.9 mmol/L).

TABLE 2 Frequency of mild to moderate hypoglycemia by mutation

	R201C	R201H	V59M	Other[a]
More than once a week (*n*)	0	1[b]	0	1[c]
Once a week (*n*)	0	0	1[d]	0
Once a month (*n*)	3	6	0	3
Several times a year (*n*)	2	2	4	2
Once a year (*n*)	0	1	0	0
Never (*n*)	0	0	1	1

[a] Others include one subject each with a G53D, H46L, I182T, Q52L, and V59A mutation, and two with H186D mutations.

[b] Sulfonylurea (SU) dose reported as 0.405 mg/kg/day and reported checking blood sugar approximately once per week.

[c] This individual (with V59A) reported a sulfonylurea dose of 2.354 mg/kg/day and reported checking blood sugar 3 or more times per day.

[d] Sulfonylurea dose reported as 0.386 mg/kg/day and reported checking blood sugar approximately once per week.

The median lowest blood glucose level reported since SU initiation was 45 mg/dL (2.5 mmol/L) (35-55 mg/dL IQR, 1.9-3.1 mmol/L). Four respondents (13.8%, *n* = 29) reported no instances of hypoglycemia. When asked to describe their most recent hypoglycemic episode, 12 respondents (40%, *n* = 30) associated the episode with a missed or smaller than normal meal. Five respondents (16.7%, *n* = 30) associated the episode with increased physical activity.

A wide range of both neuroglycopenic and adrenergic symptoms of hypoglycemia were reported among subjects. Most reported both types of symptoms (*n* = 25) with the most common being irritability (*n* = 16), shakiness (*n* = 16), fatigue (*n* = 15), mood swings (*n* = 13), hunger (*n* = 13), and lack of coordination (*n* = 10).

To augment the survey data, continuous glucose monitoring (CGM) data was requested from all participants and their healthcare providers, and was available for 7 individuals (total of 912.4 hours; see eg, Figure S2). For the data collected, glucose remained within the target range of 70 to 140 mg/dL (3.9-7.8 mmol/L) for 72.6% of the time; 20.6% of the time was above 140 mg/dL and 5.8% of the time was below 70 mg/dL.

4 | DISCUSSION

SU use has transformed the lives of NDM subjects with mutations associated with the K_{ATP} channel.[4,16] In other forms of diabetes,

insulin and SU use have been associated with frequent and severe hypoglycemia.[17,18]There have been observed benefits of SU use in those with *KCNJ11*-related NDM not related to glycemic control, including neurological and psychomotor improvements.[4,19] High doses of SU are required in subjects with *KCNJ11*-related NDM, particularly if treatment is commenced at an older age, and there are anecdotal reports that higher doses are associated with improved neurological outcomes.[20,21]

No one in our cohort had any hypoglycemic episodes consistent with the current ISPAD definition of severe hypoglycemia in children—seizures or full unconsciousness due to hypoglycemia. Reported rates of severe hypoglycemia in pediatric and adolescent subjects with type 1 diabetes taking insulin vary from 8 to 30 events per 100 patient-years.[12] In a recent meta-analysis of patients with type 2 diabetes taking SUs, the incidence of severe hypoglycemia was reported at 0.8% (studies analyzed ranged from 0 to 0.1 episodes of severe hypoglycemia per patient per year), equivalent to 0 to 10 events per 100 patient-years.[22] While we cannot rule out the possibility that some episodes of severe hypoglycemia may have been undetected or unreported within our cohort, given that the responders were similar to the non-responders, we believe this cohort is representative of this rare population of patients and represents a relatively large amount of data (166 patient-years of follow-up).

Because many of the questions asked in our survey were based on symptomatic definitions of hypoglycemia instead of number-based cutoffs, it is challenging to assess how frequently asymptomatic blood glucose values <70 mg/dL may have occurred. Continuous glucose monitors can give valuable insight in this area. From 7 respondents, the average time <70 mg/dL was 5.8%. This is comparable to what has been reported in children and adults with type 1 diabetes, with 1 study reporting a median time <70 mg/dL of 2.2% and another reporting an average of 91 min/day (6% of time) <70 mg/dL.[23,24] It is important to note that both of these studies were randomized controlled trials, so may have attracted more motivated or more closely controlled patients. Interestingly, there are also studies of CGM use in various non-diabetes populations, including 32 adult subjects with normal glycemic tolerance that spent 3.2% $\pm$ 3% of the time with CGM <70 mg/dL, with a range of 0% to 12%,[25] while another study of 74 healthy controls showed some age-dependence in spending 0.6% to 2.9% of the time with CGM <70 mg/dL (the youngest group was 8-15 years of age and was similar to the overall average at 1.8% of the time).[26]

Our data suggests that mild to moderate hypoglycemia occurs in those with *KCNJ11*-related diabetes, but within our cohort, was not severe according to current ISPAD definitions. Because the participants were not checking their glucose levels very frequently (40% of subjects checked their blood glucose once a week or less often), there is uncertainty about how often mild to moderate hypoglycemia is occurring in this group of subjects; future study will be required to clarify the true frequency. Of note, the frequency of mild to moderate hypoglycemia is rarely and inconsistently reported in the type 1 diabetes literature since it occurs so frequently.[14]

Importantly, the apparent infrequency of true severe hypoglycemia may help to reassure healthcare providers prescribing high doses of SU to this unique group of patients. When transitioning to SU therapy, patients should be encouraged to participate in prospective studies of these rare forms of diabetes in order to help to address the remaining uncertainties regarding possible hypoglycemia, optimal dosing of SU, and the potential neurodevelopmental and behavioral benefits of SU use. Those with K_{ATP} channel mutations should be made aware that mild to moderate hypoglycemia may occur and they should thus be equipped to monitor blood glucose levels. However, it remains unclear what frequency of monitoring is appropriate or whether blood sugars should only be monitored when patients have symptoms suggestive of possible hypoglycemia.

Two subjects had HbA1c values that were significantly higher than the rest of the cohort. The subject with HbA1c of 12.1% received a genetic diagnosis later in life (age 16), which has been associated with a requirement for higher SU doses and greater difficulty in achieving glycemic control.[20] Indeed, this participant has had difficulty in achieving optimal glycemic control despite previously having a SU dose as high as 2.7 mg/kg/day, and thus has been continued on other medications such as insulin, metformin, and sitagliptin. However, because his HbA1c has been as low as 7.9% previously, it is possible that medication adherence may partly explain the very high HbA1c of 12.1% he had at the time of this study. Data was limited on the subject with HbA1c of 8.6%, but again, because he previously had an HbA1c as low as 5.8%, medication adherence challenges likely played a role in his less optimal glycemic control during this study.

4.1 | Limitations

This study began prior to 2014, and thus, now outdated definition of severe hypoglycemia was used on survey materials. By reviewing all episodes using the current 2014 ISPAD guidelines, we were able to clarify that none of these episodes were clinically severe. Although these episodes did not involve seizures or unconsciousness, the fact that they involved hypoglycemia and were concerning to caregivers supports the need for additional research on the determinants of hypoglycemia in this study population, whether or not it is severe. Their survey used in this study has not been validated previously, although it was created through a multistep process, as described in Section 2. Most information collected in this study was based on caregiver report, and thus may be more susceptible to recall bias than data derived from blood glucose monitoring devices or medical records.

4.2 | Summary

Of all reported episodes of hypoglycemia, none were severe according to the current ISPAD definition. There was a wide range of SU doses and hypoglycemia frequency reported, indicating higher doses do not correlate with hypoglycemia in this cohort. Further study will be necessary to clarify what the optimal target HbA1c value should be in this population. We also demonstrate the wide variability in the frequency of glucometer testing and self-defined hypoglycemia in those with *KCNJ11*-related NDM. It is most useful to focus on the data from blood glucose readings and CGM, and to continue to

inquire about hypoglycemia with these patients and caregivers. More research is needed in order to better estimate hypoglycemic frequency in this population, determine the causes of these hypoglycemic episodes, and determine whether it is the SU dose or outside factors that play a larger role. These studies might include investigations into insulin secretion or counter-regulatory responses in patients with K_{ATP} channel mutations.

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Conflict of interest

The authors declare no potential conflict of interests.

ORCID

Siri Atma W Greeley http://orcid.org/0000-0002-0741-3567

REFERENCES

1. Iafusco D, Massa O, Pasquino B, et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. *Acta Diabetol*. 2012;49(5):405–408.
2. Wiedemann B, Schober E, Waldhoer T, et al. Incidence of neonatal diabetes in Austria-calculation based on the Austrian Diabetes Register. *Pediatr Diabetes*. 2010;11(1):18–23.
3. Greeley SAW, Naylor RN, Philipson LH, Bell GI. Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. *Curr Diab Rep*. 2011;11(6):519–532.
4. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 2006;355(5):467–477.
5. Busiah K, Drunat S, Vaivre-Douret L, et al. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2013;1(3):199–207.
6. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: Extending the age of KCNJ11 mutation testing in neonatal DM. *Pediatr Diabetes*. 2010;11(3):203–207.
7. Mlynarski W, Tarasov AI, Gach A, et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. *Nat Clin Pract Neurol*. 2007;3(11):640–645.
8. Slingerland AS, Nuboer R, Hadders-Algra M, Hattersley AT, Bruining GJ. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the *KCNJ11* gene. *Diabetologia*. 2006;49(11):2559–2563.
9. Hashimoto Y, Dateki S, Hirose M, et al. Molecular and clinical features of KATP-channel neonatal diabetes mellitus in Japan. *Pediatr Diabetes*. 2017;18(7):532–539.
10. Shah RP, Spruyt K, Kragie BC, Greeley SAW, Msall ME. Visuomotor performance in KCNJ11-related neonatal diabetes is impaired in children with DEND-associated mutations and may be improved by early treatment with sulfonylureas. *Diabetes Care*. 2012;35(10):2086–2088.
11. Greeley SAW, Naylor RN, Cook LS, Tucker SE, Lipton RB, Philipson LH. Creation of the web-based University of Chicago Monogenic Diabetes Registry: using technology to facilitate longitudinal study of rare subtypes of diabetes. *J Diabetes Sci Technol*. 2011;5(4):879–886.
12. Clarke W, Jones T, Rewers A, Dunger D, Klingensmith GJ. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2009;10(2):134–145.
13. American Diabetes Association. Defining and reporting hypoglycemia in diabetes. *Diabetes Care*. 2005;28(5):1245–1249.
14. Ly TT, Maahs DM, Rewers A, Dunger D, Oduwole A, Jones TW. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(S20):180–192. https://doi.org/10.1111/pedi.12174.
15. Landmeier KA, Lanning M, Carmody D, Greeley SAW, Msall ME. ADHD, learning difficulties and sleep disturbances associated with KCNJ11-related neonatal diabetes. *Pediatr Diabetes*. 2017;18(7):518–523.
16. Babenko AP, Polak M, Cavé H, et al. Activating mutations in the *ABCC8* gene in neonatal diabetes mellitus. *N Engl J Med*. 2006;355(5):456–466.
17. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. *Diabetes Care*. 2014;37(1):9–16.
18. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577–1589.
19. Beltrand J, Elie C, Busiah K, et al. Sulfonylurea therapy benefits neurological and psychomotor functions in patients with neonatal diabetes owing to potassium channel mutations. *Diabetes Care*. 2015;38(11):2033–2041.
20. Thurber BW, Carmody D, Tadie EC, et al. Age at the time of sulfonylurea initiation influences treatment outcomes in KCNJ11-related neonatal diabetes. *Diabetologia*. 2015;58(7):1430–1435.
21. Shimomura K, Hörster F, De Wet H, et al. A novel mutation causing DEND syndrome: a treatable channelopathy of pancreas and brain. *Neurology*. 2007;69(13):1342–1349.
22. Schopman JE, Simon ACR, Hoefnagel SJM, Hoekstra JBL, Scholten RJPM, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2014;30(1):11–22.
23. Beck RW, Hirsch IB, Laffel L, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care*. 2009;32(8):1378–1383.
24. Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. *Diabetes Care*. 2011;35(2):204–10.
25. Mazze RS, Strock E, Wesley D, et al. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. *Diabetes Technol Ther*. 2008;10(3):149–159.
26. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. *Diabetes Care*. 2010;33(6):1297–1299.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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