Journal of Diabetes Science and Technology
2015, Vol. 9(5) 999–1005

DOI: 10.1177/1932296815581052
dst.sagepub.com
SAGE

# Hypoglycemia in Type 2 Diabetes - More Common Than You Think: A Continuous Glucose Monitoring Study

**Richa Redhu Gehlaut, MD[1], Godwin Y. Dogbey, PhD[2], Frank L. Schwartz, MD, FACE[3], Cynthia R. Marling, PhD[4], and Jay H. Shubrook, DO, FACOFP, FAAFP, BC-ADM[5]**

## Abstract

**Background:** Hypoglycemia is often the limiting factor for intensive glucose control in diabetes management, however its actual prevalence in type 2 diabetes (T2DM) is not well documented.

**Methodology:** A total of 108 patients with T2DM wore a continuous glucose monitoring system (CGMS) for 5 days. Rates and patterns of hypoglycemia and glycemic variability (GV) were calculated. Patient and medication factors were correlated with rates, timing, and severity of hypoglycemia.

**Results:** Of the patients, 49.1% had at least 1 hypoglycemic episode (mean 1.74 episodes/patient/ 5 days of CGMS) and 75% of those patients experienced at least 1 asymptomatic hypoglycemic episode. There was no significant difference in the frequency of daytime versus nocturnal hypoglycemia. Hypoglycemia was more frequent in individuals on insulin (alone or in combination) ($P = .02$) and those on oral hypoglycemic agents ($P < .001$) compared to noninsulin secretagogues. CGMS analysis resulted in treatment modifications in 64% of the patients. T2DM patients on insulin exhibited higher glycemic variability (GV) scores (2.3 ± 0.6) as compared to those on oral medications (1.8 ± 0.7, $P = .017$).

**Conclusions:** CGMS can provide rich data that show glucose excursions in diabetes patients throughout the day. Consequently, unwarranted onset of hypo- and hyperglycemic events can be detected, intervened, and prevented by using CGMS. Hypoglycemia was frequently unrecognized by the patients in this study (75%), which increases their potential risk of significant adverse events. Incorporation of CGMS into the routine management of T2DM would increase the detection and self-awareness of hypoglycemia resulting in safer and potentially better overall control.

**Keywords**
continuous glucose monitoring system, glycemic variability, hypoglycemia, hypoglycemia unawareness, self-glucose monitoring, type 2 diabetes

Hypoglycemia is often one of the major limiting factors in intensive glycemic control for both type 1 diabetes (T1DM) and type 2 diabetes (T2DM).[1] Although hypoglycemia is well recognized in the management of T1DM, less is known about the true prevalence of hypoglycemia in patients with T2DM.[2] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[3,4] noted a significant increase in cardiovascular events in intensively treated T2DM patients associated with hypoglycemia. Thus, preventing hypoglycemia has become a major focus of T2DM management, especially in older and/or at-risk T2DM populations and treatment target recommendations have been relaxed.[5,6]

Individuals with T2DM who experience significant hypoglycemia have more health care visits (0.054 per patient-year)[7] and higher annual all-cause and diabetes-related health care

[1]Ohio University Heritage College of Osteopathic Medicine/O'Bleness Memorial Hospital, Diabetes Institute, Ohio University, Athens, OH, USA
[2]Heritage College of Osteopathic Medicine/CORE Research Office, Ohio University, Athens OH, USA
[3]Diabetes Institute, Ohio University, Athens, OH, USA
[4]School of Electrical Engineering and Computer Science, Russ College of Engineering and Technology and the Diabetes Institute, Ohio University, Athens, OH, USA
[5]Touro University California, College of Osteopathic Medicine, Vallejo, CA, USA

**Corresponding Author:**
Richa Redhu Gehlaut, MD, Ohio University Heritage College of Osteopathic Medicine/O'Bleness Memorial Hospital, Diabetes Institute at Ohio University, Western Reserve Hospital, Ste 315, 5655 Hudson Dr, Hudson, OH 44236, USA.
Email: rgehlaut@westernreservehospital.org

costs than patients without hypoglycemia (adjusted Δ = +$5024 and +$3747, respectively; both $P < .0001$). People with T2DM and hypoglycemia also report lower health-related quality of life scores[8] and a greater burden of depression.[9] Finally, hypoglycemia or the fear of hypoglycemia is a major reason for diabetes medications being discontinued by patients with T2DM, which contributes to poorer glycemic control in affected patients.[7]

Rates of hypoglycemia have been variably reported in T2DM. A retrospective study in Medicare beneficiaries 65 years or older from 1999 to 2011 showed that the admission rates for hypoglycemia increased by 11.7% (from 94 to 105 admissions per 100 000 person-years), while admission rates for hyperglycemia declined by 38.6% (from 114 to 70 admissions per 100 000 person-years).[10] In a 4-year retrospective study of nearly 20 000 Tennessee Medicaid patients, "serious hypoglycemia," defined as a hospitalization, emergency department admission, or death associated with hypoglycemia and a concurrent blood glucose of < 50 mg/dL (2.8 mmol/L), was reported at a crude rate of 1.23 per 100 person-years (95% confidence interval [CI], 1.08-1.38) in those taking sulfonylureas and 2.76 (95% CI, 2.47-3.06) in those on insulin.[11]

In the United Kingdom Prospective Diabetes Study (UKPDS) of patients with T2DM, a higher frequency of hypoglycemia was associated with intensive treatment compared to conventional treatment with either sulfonylureas or insulin.[12] The Veterans Affairs Cooperative Study on T2DM (VA SCDM), which compared a once-daily insulin injection regimen (standard) with an intensive insulin regimen (stepped), also revealed a higher incidence of hypoglycemia in the stepped group (0.03 vs 0.01 episodes per patient per year).[13]

With the development of continuous glucose monitoring systems (CGMS), there was an unexpected detection of very high rates of hypoglycemia in patients with T1DM[14-16] and T2DM.[17] McNally et al[18] used 72-hour CGMS tracings in patients with T2DM to investigate the frequency of hypoglycemia in patients treated with premixed, biphasic insulin and noted a very high prevalence of hypoglycemia (82% had at least 1 hypoglycemic event). Nocturnal hypoglycemia was double the daytime episodes, the majority of which were unrecognized. These studies suggested that the frequency of hypoglycemia in T2DM is much higher than previously appreciated clinically and indicated the need for further investigation.

Glycemic variability (GV) is defined as the fluctuation in blood glucose levels, or the swings between hyperglycemia and hypoglycemia. Abnormal excursions of blood glucose levels outside the normal physiologic range are indicative of excessive GV in patients with diabetes[19] and are associated with poor glycemic control.[20] It is now believed that excessive GV may contribute to long term complications through induction of oxidative stress[21] rather than tissue glycation, which is associated with chronic hyperglycemia. Since GV also measures changes of glucose levels in both the hyperglycemic and hypoglycemic ranges, the tissue damage from hypoglycemia is postulated to be mediated via increased catecholamine production and/or their effects on blood vessel and endothelial function as well as induction of proinflammatory and prothrombotic pathways.[22,23] Increased GV has also been shown to be a predictor of hypoglycemia[24] and increased risk of cardiac death in critically ill patients with T2DM.[25,26] Hypoglycemia-induced increases in blood pressure and heart rate, triggering of blood vessel constriction or acute thrombosis are probable explanations of these adverse events.[27,28] However, most studies on GV have been conducted in critical care settings and findings may not extend to T2DM patients in the outpatient setting.

While GV is not routinely assessed in clinical practice, there is increasing awareness that it is a significant component of overall glycemic control.[29] Service et al first proposed a method of measuring GV: the mean amplitude of glycemic excursion (MAGE) in 1970.[19] Since then, numerous GV metrics have been proposed without an agreed-on successor to MAGE.[30,31] The authors developed the consensus perceived glycemic variability (CPGV) metric, using machine learning methods on continuous glucose monitor (CGM) data acquired from T1DM patients, which automatically calculates a GV score from 24-hour CGM tracings.[32,33]

This is the largest study in the outpatient setting involving consecutive patients with T2DM on multiple diabetes medications to prospectively determine the frequency, timing, and severity of hypoglycemia using CGMS and to use CPGV to assess the rates of GV as it relates to hypoglycemia.

## Methods

This was a prospective, nonblinded trial of adult patients with T2DM for at least 6 months. The study was approved by the Ohio University Institutional Review Board. Participants were a convenience sample recruited from a midwestern academic diabetes/endocrine center. Exclusions included children (<18 years), pregnant patients, and patients who had the following: on insulin pump, bleeding disorders, on blood thinners (excluding aspirin), and cognitive dysfunction. Participants were on any of the following diabetes medications currently available except for sodium-glucose cotransporter 2 (SGLT2) inhibitors and dopamine agonists: oral medications (biguanides, sulfonylureas, meglitinides, thiazolidinediones [TZDs] and dipeptidyl-peptidase-4 [DPP-4] inhibitors), glucagon-like peptide-1 (GLP-1) receptor agonists, various insulin preparations, or any combination of the above medications. Types of medications used in the study are shown in Table 1.

The patients were subdivided into groups such as hypoglycemic agents versus nonhypoglycemic agents, insulin versus noninsulin, and none to one to two or more hypoglycemic agents. Hypoglycemia rates and GV were determined from 5 day CGMS tracings and were compared between different treatment modalities. Hypoglycemia was classified as mild (<70 mg/dl), severe (<50 mg/dl), symptomatic, or asymptomatic. A new hypoglycemic event was logged when the interval between 2

**Table 1.** Types of Medications Used in the Study.

| Medication | n |
|---|---|
| Insulin[a] | |
| Basal with/without analog insulin | 64 |
| Premixed insulin | 6 |
| Humulin N and R | 3 |
| U-500 | 2 |
| Insulin secretagogues[b] | |
| Sulfonylureas | 25 |
| Glinides | 2 |
| Noninsulin secretagogues[c] | |
| DPP-4 inhibitors | 31 |
| GLP-1 receptor agonists | 22 |
| Biguanides | 61 |
| Actos | 9 |
| Combination treatment | |
| With insulin included | 55 |
| No insulin included | 11 |
| With insulin + insulin secretagogues | 15 |

[a]19 patients were on insulin only, with no other diabetes medication. The rest were on combination treatment.
[b]All but 1 patient were on combination treatment.
[c]19 patients were on noninsulin secretagogues only. The rest were on combination treatment.

**Table 2.** Hypoglycemia-Related Definitions.

| | |
|---|---|
| Hypoglycemic event | Any glucose level below 70 mg/dl (3.9 mmol/L) as determined by self-glucose monitoring or CGM. |
| Mild hypoglycemia | Any glucose reading less than 70 mg/dl (3.9 mmol/L) but greater than 50 mg/dl (2.8 mmol/L). |
| Severe hypoglycemia | Any glucose reading less than 50 mg/dl (2.8 mmol/L) regardless of symptoms and whether they needed assistance from others. |
| 2 separate hypoglycemic events | Logged when the interval between 2 events was equal to or greater than 30 minutes. Daytime was classified as from 6:00 AM until 9:00 PM and nighttime from 9:00 PM until 6:00 AM. |
| Asymptomatic hypoglycemia | Interpreted as glucose level below 70 mg/dl (3.9 mmol/L) that was not documented as an event by the patient in their diary. |
| Pseudo-hypoglycemia | An event with the typical symptoms of hypoglycemia, but with a measured plasma glucose concentration over 70 mg/dL(3.9 mmol/L). This is common in patients with long-standing poor glycemic control when their plasma glucose concentration starts trending toward the normal range. |
| Hypoglycemia unawareness | Documented glucose of less than 70 mg/dl (3.9 mmol/L) and no reported symptoms. |

events was equal to or greater than 30 minutes. The time of day that the hypoglycemia occurred was also determined for each class of medication and/or combination.

At the initial baseline visit the research nurses confirmed that the participant was appropriate for the project, reviewed and completed the consent documents, and gave information regarding the Food and Drug Administration (FDA)-approved iPro™ Professional (Medtronic, Northridge, CA), CGMS which did not provide real-time glucose data to the patient. A glucose value is recorded every 5 minutes, giving a total of 288 readings a day. All participants received education on how to identify and treat mild and severe hypoglycemia. Participants in the study wore the device for 5 days and then returned to the clinical research center for downloading of the data into a research computer. Participants were also instructed to keep daily 4 point self-glucose monitoring (SGM) logs-recording their glucose before each meal and bedtime and record the self-perceived hypoglycemic episodes. All the patients used the same brand of glucose meter during the monitoring period. All CGM data downloaded in this study was then evaluated by one of the clinician investigators at the diabetes center and patients received a call back regarding their results as well as changes in treatment based on interpretation of the CGM data if indicated. Results on the CGMS download were reported in the range of 40-400mg/dl.

The CPGV metric was determined by extracting the iPro data download from the research computer and then processed in the SmartHealth Lab™ using proprietary software developed at Ohio University. The CPGV metric rates 24-hour CGM tracings on a continuous scale from 1 (low) to 4 (extremely high), which is based on consensus physician ratings as incorporated into a machine learning algorithm.[33] See Table 2 for hypoglycemia-related definitions

## Data Analysis

Where appropriate, the data were transformed into categorical variables using the threshold definitions that define the different severities of hypoglycemia. Summary data in the form of frequencies were generated for all categorical variables. For continuous variables, measures of central tendency and dispersion were generated. Relationships between categorical variables were explored using the chi-square test of association or differences in proportions as appropriate. The paired $t$ test was used for gauging differences in day and night hypoglycemic episodes. Analysis of variance (ANOVA) was used for differences in groups with respect to continuous outcome variables such as CPGV. Statistical significance was set at $p \leq .05$.

## Results

### *Hypoglycemia Rates in T2DM*

A total of 108 patients with T2DM were recruited. The patient characteristics are listed in Table 3.

Of the total patients in this study, 81% were on medications classified as being capable of causing hypoglycemia (insulin and insulin secretagogues as sulfonylureas and meglitidines), while 19% were on medications not usually

**Table 3.** Demographic Characteristics of Patients in the Sample.

| Gender | n[a] (%) |
|---|---|
| Female | 65 (61.3) |
| Male | 41 (38.7) |
| Age | |
| <65 | 65 (61.3) |
| ≥65 | 41 (38.7) |
| Insulin | |
| Yes | 74 (69.8) |
| No | 32 (30.2) |
| Duration of diabetes | |
| <10 | 44 (42.7) |
| ≥10 | 59 (57.3) |
| A1C (%) | |
| ≤7 | 35 (33) |
| >7 | 71 (67) |
| Associated history of depression | |
| Yes | 43 (41) |
| No | 62 (59) |

[a]The total sample size, n, was 108, but because of missing data the total varied from category to category.

associated with causing hypoglycemia (biguanides, DPP-4 inhibitors, GLP-1 receptor agonists, TZDs). About 36% were on at least 1 hypoglycemic agent and 45% were on more than 1. Only 30% were not on insulin during this study.

The incidence of hypoglycemia detected by CGMS, both mild and severe, was 49.1% (53 of 108 patients), which extrapolated out to 1.74 ± SD 2.54 episodes per patient per 5 days of CGM. Significantly, of these 108 patients studied, CGMS detected severe hypoglycemia (<50 mg/dl) in 10.2% (11 out of 108) and mild hypoglycemia in 25% of the patients (27 out of 108).

In all the 53 patients who had hypoglycemic events, severity of hypoglycemia was distributed as follows: 21% (11 out of 53) severe hypoglycemia, 51% (27 out of 53) mild, and 28.3% (15 out of 53) a combination of both mild and severe hypoglycemic events. The total number of patients demonstrating mild hypoglycemia (27) was more frequent than severe events (11) ($P$ = .009) and those with severe events also had frequent mild events (15) (see Table 4).

## *Daytime Versus Nighttime Hypoglycemia*

There was no statistically significant difference ($P$ = .9476) in the mean number of episodes of daytime hypoglycemia (1.78 per person) as compared to night time lows (1.81 per person) as shown in Table 5.

## *Impact of Diabetes Medications on Prevalence of Hypoglycemia in T2DM*

There was a statistically significant higher number of patients with hypoglycemia (35 out of 53; 66%) on insulin (alone or in combination with any other diabetes medication) as compared to those on noninsulin medications (18 out of 53 patients; $P$ = .02), see Table 6. Similarly, there was a significant difference in the proportion of patients with hypoglycemia who were on hypoglycemic agents (43 of 53) compared to those taking medications which normally do not cause hypoglycemia (10 out of 53; $P$ < .001) (see Table 6).

Out of the 53 patients who had hypoglycemic episodes, 10 (18.9%) were on none of the medications that typically cause lows, 20 (37.7%) were on one agent that can cause lows, and 23 (43.4%) were on multiple agents that could cause lows (sulfonylurea, glinide, insulin). There was no statistically significant difference in the proportion of patients with hypoglycemia between those on one and those on more than one hypoglycemic agent ($P$ = .073) (see Table 6).

**Table 4.** Hypoglycemic Severity and Hypoglycemia Awareness in Patients With Hypoglycemic Episodes.

| | n (%) | *P* value |
|---|---|---|
| Hypoglycemic severity | | |
| Mild | 27 (50.9) | .009[a] |
| Severe | 11 (20.7) | |
| Both | 15 (28.3) | |
| Hypoglycemia awareness | | |
| Yes | 13 (24.5) | <.001 |
| No | 40 (75.4) | |

[a]Comparison was between mild and severe hypoglycemia. There were more episodes of mild than severe hypoglycemia.

**Table 5.** Number of Hypoglycemic Events or Episodes Experienced by Hypoglycemia Patient During Day and Night.

| | n (number of patients with hypoglycemia) | Minimum number of episodes | Maximum number of episodes | Mean | SD |
|---|---|---|---|---|---|
| Day | 14 | 1 | 4 | 1.78 | 1.217 |
| Night | 11 | 1 | 3 | 1.81 | 0.981 |
| Day and night | 28 | 2 | 11 | 5.10 | 2.572 |

## *Hypoglycemia Awareness in T2DM*

Of the 53 participants who demonstrated hypoglycemia by CGMS, only 13 (24.5%) self-reported signs/symptoms with all hypoglycemic episodes. The majority (75%) of patients were not aware of their hypoglycemia at all times when detected by CGMS ($P$ < .001) (see Table 4).

## *Pseudo-hypoglycemia*

Interestingly, 21% of participants self-reported symptoms of hypoglycemia when neither their SGM nor CGM documented hypoglycemia to corroborate their symptoms. A statistically significant association was found between glycosylated hemoglobin (A1C) level and pseudo-hypoglycemia, as individuals with A1C ≤7% were about 4 times as

**Table 6.** Distribution of Patients With Hypoglycemia by Treatment Groups.

| | n (%) | *P*-value |
|---|---|---|
| Insulin | | |
| Insulin | 35 (66) | .02 |
| Noninsulin | 18 (34) | |
| Hypoglycemia-causing agents | | |
| Yes | 43 (81.1) | <.001 |
| No | 10 (18.9) | |
| Number of hypoglycemic agents | | |
| Only 1 | 20 (37.7) | .073 |
| 2 or more | 23 (43.4) | |
| None | 10 (18.9) | |

likely to have pseudo-hypoglycemia compared to those whose A1C was > 7%, ($P = .007$, unadjusted odds ratio = 3.8, 95% CI = 1.393 to 10.363).

### *Glycemic Variability*

Mean CPGV scores for T2DM patients on insulin were statistically significantly higher (2.3 ± 0.6) compared to those on oral medications (1.8 ± 0.7, $P = .017$), with the mean CPGV for entire population being (2.1 ±0.6).

### *Treatment Modified*

Treatment was modified in 64.4% of the group based on sensor results. Most common modifications were reducing the dose or frequency of the drug, changing the timing of administration of the hypoglycemic agent, and completely discontinuing the medication, and only in a few cases modifying the target pre- or postprandial blood glucose values.

### *Secondary Variables*

Duration of diabetes did not predict hypoglycemic episodes ($P = .733$) or hypoglycemia awareness ($P = .892$). There was also no statistically significant association between occurrence of hypoglycemic episodes and an A1C < 7.0% ($P = .077$). Although data are not shown, Beck's inventory scores for depression revealed that there was also no statistically significant association between the occurrence of hypoglycemic episodes and depression ($P = .332$) in this T2DM population. Furthermore, no statistically significant association was found between occurrence of hypoglycemic episodes and age ($P = .398$) or gender ($P = .242$).

## Discussion

About half of all of T2DM participants screened in this study experienced at least one episode of hypoglycemia during 5 days of CGMS with 21% of those experiencing a severe hypoglycemic episode(<50 mg/dl). Thus, this study confirms earlier studies which demonstrate that CGMS detects a high frequency of previously unrecognized hypoglycemia in individuals with T2DM on oral hypoglycemic agents, insulin, or their combination.[17,18] The vast majority of our patients (81%) were on both insulin and/or an oral hypoglycemic agent, which contributed to the high rate of hypoglycemia.

This study did show that even in people who are on medications not known to cause hypoglycemia, it does occur. In this study 18.9% of participants with hypoglycemic episodes were not on any insulin secretagogues or insulin. Two of those participants had glucose readings below 50 mg/dl—1 was on a GLP-1receptor agonist and 1 was on a GLP-1 receptor agonist plus metformin. This is an important reminder that hypoglycemia can occur for many reasons. We did not collect data on participants' daily activities or alcohol consumption, so we were unable to determine if these factors played a role in these events.

Hypoglycemia unawareness was also a significant problem detected in this population as 75% of the individuals had at least one hypoglycemic episode detected by CGMS that was not sensed or documented by the patient. Importantly of the 53 people who had hypoglycemia—14 of them were on beta-blockers at the time, and of those 14 participants, 11 had hypoglycemic unawareness. This reemphasizes the warnings we should give to people who are taking beta blockers and the blunting of the physiologic response to hypoglycemia.

There was also a subpopulation of patients (21%) who reported symptoms of hypoglycemia at a time when they were not low either by SGM or CGMS (pseudo-hypoglycemia). It is interesting in our cohort that lower A1C levels < 7% were not associated with a higher frequency of overt hypoglycemia, yet pseudo-hypoglycemia was documented more frequently in those patients with lower A1Cs. Given the high frequency of pseudo-hypoglycemia in some of these patients suggests increased symptom awareness, fear, or even anticipation of hypoglycemia. Pseudo-hypoglycemia is a common symptom in T2DM patients with anxiety and diabetes distress;[34] this may be an explanation for the above observation.

Incorrect identification of this condition can lead to reduced medication adherence and defensive eating practices that may undermine treatment plans. This is an important safety issue for patients with true hypoglycemia to avoid accidents and macrovascular events. Thus both awareness of hypoglycemia and correct identification of individual symptoms of hypoglycemia needs to be stressed more in every patient with T2DM who is on any medication or combination of medications which can cause hypoglycemia.

Previous studies have reported that the incidence of hypoglycemia in patients with T2DM increases progressively with use of oral hypoglycemic agents (sulfonylureas and meglitidines) and insulin and with escalating doses of insulin increasing that frequency.[2,35] For participants with hypoglycemia in this study, there was a statistically significant difference in the frequency of hypoglycemia for those on insulin (alone or in combination) versus the noninsulin group and also for those on hypoglycemic agents. However, there was

no relationship between the number of diabetes medications and frequency of hypoglycemia.

Weber et al,[17] in a small study, dramatically reduced the prevalence of hypoglycemia in their T2DM patients with a subsequent 3-day CGMS. Two-thirds of participants in this study had a change in treatment as a result of information gained from CGM. This resulted in reduction of dose of insulin or oral medications or removal of an agent.

Using the GV metric developed by the authors, much higher CPGV values were observed in T2DM patients on insulin compared to those on oral medications. Given that T2DM is a progressive disease with increasing insulin deficiency and increased reliance on exogenous insulin,[14] it makes sense that there would be higher rates of both hypoglycemia and GV in insulin-treated patients. Future studies will need to be conducted to determine if routine assessment of the CPGV by CGMS adds to the prediction of future hypoglycemia or the increased risk for long-term complications, which have been suggested in both forms of diabetes.

The major limitation of this study is the small sample size, which limits the statistical power of this study and makes generalization to other populations more difficult. We did not have a large enough sample size to see if there were differences in the risk for hypoglycemia or CPGV among the various medications or medication combinations other than insulin and hypoglycemic agents. The accuracy of both SGM and CGMS is still a major issue of concern in the diabetes research literature, especially with hypoglycemia. This is particularly important when we are using hard cutoffs for hypoglycemia that may exceed the accuracy of the outpatient gold standard SGM. This study reemphasizes the need for a better gold standard. Finally many of these participants had changes in their treatments in response to this study. The investigators did not elaborate on the changes and if they worked in this study as it was beyond the scope of this study.

Klonoff[36] advocates that CGMS should become an integral part of diabetes management. CGM provides much greater insight into glucose excursions throughout the day and can help identify and prevent unwanted episodes of hypoglycemia and hyperglycemia. This can be utilized initially for patients with difficult-to-control diabetes and eventually for routine use in most patients with diabetes. The authors believe that routine, intermittent use of CGM should be considered for all patients with T2DM, especially those on any medication that causes hypoglycemia.

## Conclusion

Hypoglycemia is much more frequent in asymptomatic patients with T2DM than is generally appreciated. Hypoglycemia increases T2DM patient risk for acute injuries (falls or motor vehicle accidents), medical visits/hospitalizations, and acute macrovascular complications. It can be a nuisance, cause distraction, and be embarrassing at times. Fear of an episode can cause a major barrier to glycemic control.

Intermittent use of CGM should be considered in all T2DM patients who are taking medications that can cause hypoglycemia. Finally, once hypoglycemia has been detected, a renewed emphasis on diabetes education regarding the symptoms, treatment, and prevention of hypoglycemia should be initiated in addition to medication changes.

### Abbreviations

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ANOVA, analysis of variance; A1C, glycosylated hemoglobin; CGM, continuous glucose monitor; CGMS, continuous glucose monitoring system; CI, confidence interval; CPGV, consensus perceived glycemic variability; DPP-4, dipeptidyl-peptidase-4 inhibitors; FDA, Food and Drug administration; GLP-1, glucagon-like peptide-1 receptor agonists; GV, glycemic variability; MAGE, mean amplitude of glycemic excursion; SGLT2, sodium-glucose cotransporter 2 inhibitors; SGM, self-glucose monitoring; T1DM, type 1 diabetes; T2DM, type 2 diabetes; TZDs, thiazolidinediones; UKPDS, United Kingdom Prospective Diabetes Study; VA SCDM, Veterans Affairs Cooperative Study on Type 2 Diabetes.

### Acknowledgments

The authors acknowledge Cammie Starner RN, CCRC, Lynn Petrik, RN, BSN, CCRC, and Shandra Hamilton.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FLS has a Medtronic research grant and is a Sanofi consultant. CRM has a Medtronic research grant. JHS has research grants from Sanofi and Medtronic and is on the Advisory Board for Eli Lilly, Astra Zeneca, and NovoNordisk.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: OUHCOM/O'Bleness Memorial Hospital.

### References

1. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia*. 2002;45:937-948.
2. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care*. 2005;28:2948-2961.
3. Gerstein HC, Miller ME, Byington RP, et al. Action to control cardiovascular risk in diabetes study group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
4. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909.
5. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann Intern Med*. 2011:154:554-559.

6. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. *Endocr Pract*. 2011;17(2):287-302.
7. Bron M, Marynchenko M, Yang H, Yu AP, Wu EQ. Hypoglycemia, treatment discontinuation, and costs in patients with type 2 diabetes mellitus on oral antidiabetic drugs. *Postgrad Med*. 2012;124(1):124-132.
8. Lopez J, Annunzita K, Bailey RA, Rupnow M, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. *Patient Prefer Adherence*. 2014;8:683-692.
9. Green AJ, Fox KM, Grandy S, SHIELD Study Group. Self-reported hypoglycemia and impact on quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;96(3):313-318.
10. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med*. 2014;174(7):1116-1124.
11. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med*. 1997;157(15):1681-1686.
12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853.
13. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. *Diabetes Care*. 1995;18(8):1113-1123.
14. Deiss D, Kordonouri O, Meyer K, Danne T. Long hypoglycaemic periods detected by subcutaneous continuous glucose monitoring in toddlers and pre-school children with diabetes mellitus. *Diabet Med*. 2001;18(4):337-338.
15. McGarraugh G, Bergenstal R. Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator Continuous Glucose Monitoring System. *Diabetes Technol Ther*. 2009 Mar;11(3):145-150.
16. Ahmet A, Dagenais S, Barrowman NJ, Collins CJ, Lawson ML. Prevalence of nocturnal hypoglycemia in pediatric type 1 diabetes: a pilot study using continuous glucose monitoring. *J Pediatr*. 2011;159(2):297-302.e1.
17. Weber KK, Lohmann T, Busch K, Donati-Hirsch I, Riel R. High frequency of unrecognized hypoglycaemias in patients with Type 2 diabetes is discovered by continuous glucose monitoring. *Exp Clin Endocrinol Diabetes*. 2007;115(8):491-494.
18. McNally PG, Dean JD, Morris AD, Wilkinson PD, Compion G, Heller SR. Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: a double-blind crossover study in individuals with type 2 diabetes. *Diabetes Care*. 2007;30(5):1044-1048.
19. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes*. 1970;19(9):644-655.
20. Rodbard D, Bailey T, Jovanovic L, Zisser H, Kaplan R, Garg SK. Improved quality of glycemic control and reduced glycemic variability with use of continuous glucose monitoring. *Diabetes Technol Ther*. 2009;11(11):717-723.
21. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57(5):1349-1354
22. Joy NG, Tate DB, Younk LM, Davis SN. Effects of acute and antecedent hypoglycemia on endothelial function and markers of atherothrombotic balance in healthy man [published online ahead of print February 18, 2015]. *Diabetes*.
23. Ceriello A, Novials A, Ortega E, et al. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. *Diabetes*. 2012;61(11):2993-2997.
24. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther*. 2011;13(8):813-818.
25. Hermanides J, Bosman RJ, Vriesendorp TM, et al. Hypoglycemia is associated with intensive care unit mortality. *Crit Care Med*. 2010;38(6):1430-1434.
26. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med*. 2010;38(3):838-842.
27. Wright RJ, Newby DE, Stirling D, Ludlam CA, Macdonald IA, Frier BM. Effects of acute insulin-induced hypoglycemia on indices of inflammation: putative mechanism for aggravating vascular disease in diabetes. *Diabetes Care*. 2010;33(7):1591-1597.
28. Gogitidze JN, Hedrington MS, Briscoe VJ, Tate DB, Ertl AC, Davis SN. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. *Diabetes Care*. 2010;33(7):1529-1535.
29. Nalysnyk L, Hernandez-Medina M, Krishnareajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes Obes Metab*. 2010;12:288-298.
30. Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. *Diabetes Technol Ther*. 2009;11(9):551-565.
31. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther*. 2009;11(suppl 1):S55-S67.
32. Marling CR, Shubrook JH, Vernier SJ, Wiley MT, Schwartz FL. Characterizing blood glucose variability using new metrics with continuous glucose monitoring data. *J Diabetes Sci Technol*. 2011;5(4):871-878.
33. Marling CR, Struble NW, Bunescu RC, Shubrook JH, Schwartz FL. A consensus perceived glycemic variability metric. *J Diabetes Sci Technol*. 2013;7(4):871-879.
34. Hessler D, Fisher L, Glasgow RE, et al. Reductions in regimen distress are associated with improved management and glycemic control over time. *Diabetes Care*. 2014;37(3):617-624.
35. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med*. 2003;20(12):1016-1021.
36. Klonoff DC. Continuous glucose monitoring roadmap for 21st century diabetes therapy. *Diabetes Care*. 2005;28(5):1231-1239.