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Nocturnal Hypoglycemia in the Era of Continuous Glucose Monitoring

Bernhard Kulzer, PhD[1,2,3], Guido Freckmann, MD[4], Ralph Ziegler, MD[5], Oliver Schnell, MD[6], Timor Glatzer[7], and Lutz Heinemann, PhD[8]

Abstract
Nocturnal hypoglycemia is a common acute complication of people with diabetes on insulin therapy. In particular, the inability to control glucose levels during sleep, the impact of external factors such as exercise, or alcohol and the influence of hormones are the main causes. Nocturnal hypoglycemia has several negative somatic, psychological, and social effects for people with diabetes, which are summarized in this article. With the advent of continuous glucose monitoring (CGM), it has been shown that the number of nocturnal hypoglycemic events was significantly underestimated when traditional blood glucose monitoring was used. The CGM can reduce the number of nocturnal hypoglycemia episodes with the help of alarms, trend arrows, and evaluation routines. In combination with CGM with an insulin pump and an algorithm, automatic glucose adjustment (AID) systems have their particular strength in nocturnal glucose regulation and the prevention of nocturnal hypoglycemia. Nevertheless, the problem of nocturnal hypoglycemia has not yet been solved completely with the technologies currently available. The CGM systems that use predictive models to warn of hypoglycemia, improved AID systems that recognize hypoglycemia patterns even better, and the increasing integration of artificial intelligence methods are promising approaches in the future to significantly minimize the risk of a side effect of insulin therapy that is burdensome for people with diabetes.

Keywords
diabetes, nocturnal hypoglycemia, continuous glucose monitoring, predictive models

Introduction

Hypoglycemia is a common side effect of diabetes treatment with insulin or sulfonylureas and an important limiting factor in glycemic management of people with diabetes (PwD). Although daytime hypoglycemia (DH) and nocturnal hypoglycemia (NH) have the same causative factors and no differences in treatment, there are some important differences between DH and NH.[1,2]

Sleep limits the ability of PwD to recognize and respond appropriately to asymptomatic NH. The results from the Diabetes Control and Complications Trial (DCCT) showed that in type 1 diabetes (T1D), 43% of all hypoglycemic episodes and 55% of severe hypoglycemic episodes occurred at night, with 51% of severe hypoglycemic episodes not detected during sleep.[3,4] Although DH can be dangerous, especially due to potentially dangerous situations (eg, falls and car accidents), severe hypoglycemia with seizures can be particularly dangerous at night. Dead-in-bed syndrome is likely to be the result of severe NH and is thought to be responsible for about 5% to 6% of deaths in PwD with T1D under 40 years.[5,6]

The NH is often a consequence of the previous day's activities (eg, exercise, food, and alcohol). Because of sleep and the fact that night is usually the longest period between meals, NH is generally more difficult to prevent. Glycemic control is further complicated by the fact that periods of high and low insulin sensitivity alternate during the night due to

[1]Research Institute Diabetes Academy Mergentheim, Bad Mergentheim, Germany
[2]Diabetes Center Mergentheim, Bad Mergentheim, Germany
[3]Department of Clinical Psychology and Psychotherapy, University of Bamberg, Bamberg, Germany
[4]Institut für Diabetes-Technologie, Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm, Germany
[5]Diabetes Clinic for Children and Adolescents, Muenster, Germany
[6]Forschergruppe Diabetes e.V., Helmholtz Zentrum, Munich, Germany
[7]Roche Diabetes Care GmbH, Mannheim, Germany
[8]Science Consulting in Diabetes GmbH, Düsseldorf, Germany

Corresponding Author:
Bernhard Kulzer, PhD, Research Institute Diabetes Academy Mergentheim, Johann Hammer Straße. 24, 97980 Bad Mergentheim, Germany.
Email: kulzer@fidam.de

hormonal circadian rhythms. Periods of NH are also generally longer than those of DH.[1,2] The NH also has a number of specific adverse effects that differ from DH, which are described in this review.

Continuous glucose monitoring (CGM) has led to new insights into NH, providing the first valid data on the true incidence, duration, and severity of NH.[7] It has also verified and corrected previous theories of NH, such as the so-called "Somogyi effect" (increased fasting glucose [FG] levels due to hypoglycemia).[8] Although CGM systems are used by many PwD, and despite the considerable progress made with new technologies such as automatic glucose adjustment (AID) systems, the problem of NH is still not solved.[9,10] In addition, the use of CGM at night may lead to new challenges (eg, sleep disturbances and alarm fatigue), as well as methodological problems that have not yet been fully resolved (eg, false alarms due to movement during sleep or lying on the sensor).[11,12]

The aim of this review is to outline the impact of NH on glycemic control and the somatic, psychological, social, and economic impact of NH. In addition, the progress and limitations of existing solutions such as CGM or AID systems in preventing NH will be highlighted and new solutions will be outlined.

Pathophysiology

The main pathophysiological factors of NH are the same as those of DH, eg, insulin overdose, physical exercise, and alcohol with a few exceptions. However, in hypoglycemia during sleep and due to the supine position, the counterregulatory responses are significantly attenuated, especially in the second half of the night.[1,2,13,14] Studies in healthy people and PwD have shown that the autonomic and symptomatic response to hypoglycemia is attenuated during sleep compared with wakefulness, which contributes to impaired hypoglycemia perception during sleep. This is more pronounced in PwD, making it more difficult to recognize hypoglycemia or to wake up.[14] Counterregulatory hormones such as epinephrine, norepinephrine, adrenocorticotropic hormone (ACTH), cortisol, or growth hormones are less pronounced during the late sleep phase (03:00-07:00) than during the early sleep phase (24:00-03:00). This also may also explain why about 60% to 70% of NH episodes in PwD occur in the late sleep phase.[15-17]

The NH, which often lasts longer than DH, can be a significant factor in the development of hypoglycemia awareness disorder. This is a significant risk factor for recurrent hypoglycemia due to impaired hormonal counter regulation, and particularly a lowering of the perception threshold for autonomic symptoms.[17] It is particularly challenging for the elderly, who already have limited hypoglycemia awareness due to their age.[18]

Continuous Glucose Monitoring–Based Detection of Nocturnal Hypoglycemia

There are a number of issues with estimating the frequency of NH events that make it difficult to quantify the exact number of these. In studies prior to the introduction of CGM, estimates were based on reports from PwD who woke up due to hypoglycemia and, if necessary, performed a blood glucose test for quantification. They were therefore quite inaccurate and, as known now from studies with CGM, this diagnostic approach significantly underestimated the number of NH events.[19,20] A recent study in elderly people showed that, regardless of geriatric status and frailty, only every second hypoglycemic episode was detected by self-monitoring of blood glucose (SMBG) compared with CGM, the time below range (TBR) >15 minutes during the night, during the 28-day study period.[21]

Owing to the lack of a precise definition of NH, studies have reported different time intervals for the duration of NH. In the Hypo-METRICS study, sleep trackers were used to compare the rate of NH of adults with T1D or insulin-treated type 2 diabetes (T2D) during actual sleep time with the rate of NH during the commonly used time period between 00:00 and 06:00. It was observed that the median time to go to bed and wake up was 23:30 and 07:30, respectively. The weekly rates of NH were significantly higher in both PwD with T1D and T2D when actual sleep time was examined. Using time of day to estimate NH underestimates hypoglycemia during sleep by up to a third.[22] Furthermore, when interpreting prevalence data, both the methodology (observational studies vs randomized trials) and, given the rapid advances in diabetology regarding new insulins, drugs, and new technologies, the date of publication are essential. The use of insulin pumps or AID is associated with a lower number of NH episodes compared with multiple daily injection (MDI) users.[23] The usage of CGM systems has also improved detecting low-glucose levels.[24]

However, there are still several unresolved issues regarding the accuracy of low-glucose measurement. It is interesting to note that even in people without diabetes, who by definition are not at risk of hypoglycemic events, (false) hypoglycemic events occur much more frequently than would be expected, even at night.[25,26] Compression artifacts describe the decrease in glucose concentration in the interstitial fluid near the sensor tip when the CGM system user sleeps on the CGM sensor, reducing or even blocking blood flow and glucose exchange. Such a drop in glucose levels is accurately measured by the CGM system but does not match the glucose levels in the rest of the body, resulting in a false alarm for hypoglycemia. This can lead to alarm fatigue, ie, users tend to ignore or turn off alarms during the night, compromising one of the main benefits of using a CGM system to prevent NH. Facchinetti et al[12] showed that in a sample of people with T1D and T2D using a Dexcom G4 sensor, the mean duration of the compression artifact was 45 (30-70) minutes and the mean glucose drop was 24 (10-48) mg/dL. They proposed to detect these compression artifacts using a specific algorithm, thus avoiding false alarms.[27] Whether the algorithms of current systems are better at detecting pressure-induced hypoglycemia is currently unknown.

Prevalence

The prevalence of NH depends on a variety of factors, such as the type of therapy (eg, basal only, MDI, continuous subcutaneous insulin infusion [CSII], AID), the CGM measurement system used (eg, sensor type, type of insulin), the type of study (eg, randomized controlled trial [RCT] and real-world data), the time at which the study was conducted (eg, publication date), and the sample studied (eg, people with or without specific hypoglycemia problems). The largest observational study of NH is the international self-report HAT study. It included 27 585 PwD with T1D and T2D and insulin therapy from 24 countries. The study identified a rate of 11.3 NH events/patient-year (95% confidence interval [CI] = 11.0-11.6) in PwD with T1D and a rate of 3.7 events/patient-year (95% CI = 3.6-3.8) in PwD with T2D.[28] The prevalence of NH with CGM (as annual incidence as a percentage of the patient population) is up to 73% in people with type 1 diabetes mellitus (T1DM) and up to 43% in people with type 2 diabetes mellitus (T2DM), according to the review by Siamashvili et al.[18] In the INCONTROL study, in which PwD with T1D and hypoglycemia problems were enrolled, the percentage of glucose values <70 mg/dL during the night (00:00-06:00) was lower (7.6%) than during the entire day (6.8%). The rate of CGM-recorded hypoglycemic events per night was 0.26 (0.21-0.31), and the duration per event was 78.7 minutes (69.3-88.1).[29] Although in the HypoDE study, which had similar inclusion criteria to the INCONTROL study, the rate of NH <70 mg/dL was lower (2.8%).[30,31] In the DIAMOND study of PwD and T1D on MDI therapy, the number of nighttime glucose values <70 mg/dL was reduced at 24 weeks from 5.5% to 1.8% in the CGM group (7.2%-5.2% in the SMBG group) and from 1.1% to 0% in the <50 mg/dL group (1.8%-0.3% in the SMBG group).[32]

Conflicting results have been reported regarding the difference between the incidence of NH and DH. In the GOLD-3 study (MwTD1), there was no difference between daytime and nocturnal glucose levels <70 mg/dL in the CGM group at baseline (2.73 vs 2.82). However, after 63 weeks, the number of nighttime events was reduced compared with daytime events (3.50 vs 1.03).[33] A somewhat similar conclusion was reached by Eisenlaub et al[34] published in the same special issue as this article. In his analysis, the frequency of hypoglycemic events <70 mg/dL was significantly lower at night than during the day, with 0.8 and 3.8 events per week, respectively. However, the frequency of hypoglycemic events with CGM readings <54 mg/dL did not differ significantly between day and night.

Risk Groups and Risk Factors

Similar to DH, there are specific risk groups with an increased risk of mild and severe hypoglycemia during the night. This is important for clinical practice to identify individuals at increased risk. The most important risk factor for NH is unawareness of hypoglycemia, which is also an important risk factor for severe hypoglycemia. Other risk factors include T1D, older age, adolescent age, female gender, longer duration of diabetes, high glucose variability (GV), and the presence of comorbidities such as autonomic neuropathy.[1,2,18,34]

In a sample of PwD T1D, Calhoun and colleagues were able to show that glycated hemoglobin (HbA_{1c}), bedtime glucose levels, insulin use, activated timers, exercise intensity, and hypoglycemia on the previous day were significant predictors of NH.[35] The increased risk of NH correlated with lower HbA_{1c}, glycated albumin, and mean glucose levels, as well as higher standard deviation, mean amplitude of glycemic excursions, and lower glucose index in the Lin et al's[36] study of PwD and T1D after adjustment for age and duration. Based on an analysis of more than 1 million glucose data points from individuals with T1D, Vu et al[37] found that lower glucose levels at midnight, the average downward trend in glucose before midnight, and the number of recent hypoglycemic events were the most important predictors of NH. In PwD and T2D, according to the study by Klimontov and Myakina, lower mean daytime glucose values, a 2-hour continuous overlapping glycemic effect (CONGA2), a higher mean glucose value at daytime, and a lower mean glucose before midnight are risk factors for NH. Previous daytime hypoglycemia significantly increased the risk of NH.[38]

Consequences of Nocturnal Hypoglycemia

Glycemic Control

The effect of NH on glycemic control has not been studied in detail. It has long been thought that NH may be the cause of high FG levels the next morning due to the excessive release of counterregulatory hormones, known as the "Somogyi effect." However, this has not been demonstrated average with CGM data, although there is evidence that this may be the case in subgroups of PwD and T1D.[8] Shah et al[39] examined CGM data from 407 adults with T1D with daytime and nighttime glucose characteristics in five HbA_{1c} categories (<7%, 7%-7.9%, 8%-8.9%, 9%-9.9%, and ≥10%) and concluded that overall, daytime and nighttime glucose levels and hypoglycemia rate have a similar effect on HbA_{1c}.[40]

Glucose Variability

Elevated GV and FG variability are risk factors for NH.[41] In addition, many studies have shown an association between long-term elevated GV (HbA_{1c}/FG) and the risk of cardiovascular disease, including myocardial infarction, stroke, and increased mortality.[42-44] Increased glycemic variability detected by CGM is associated with increased coronary plaque vulnerability and increased risk of major cardiovascular events in patients with myocardial infarction.[45,46] The GOLD-3 study showed that both the number of NH episodes and nocturnal GV were significantly reduced in the CGM group compared with the SMBG group in PwD with T1D.[47]

Cardiovascular Disease

Insulin-treated PwD with T2D have an increased risk of hypoglycemia, which is associated with an excess risk of cardiovascular disease and mortality.[1,2] In a complex 1-year study, a research group at the Steno Center in Denmark used CGM and an implantable cardiac monitor to investigate the relationship between episodes of hypoglycemia, CV, and cardiac arrhythmias in insulin-treated PwD with T2D in a real-world setting. Glucose levels <70 mg/dL were higher in PwD treated with basal/bolus or mixed insulin compared with those treated with basal insulin alone (1.8% [0.5-4.2] and 0.3% [0.1-0.8], respectively). Time in hypoglycemia was higher during nighttime when compared with daytime (0.7% [0.7-2.7] and 0.4% [0.2-0.8]). Although there was no correlation between hypoglycemia and arrhythmias during the day and night, the incidence of arrhythmias tended to increase with the onset of NH.[47] The different effects of NH and DH are probably the result of a weakened sympathetic response at night with a compensatory effect of parasympathetic activity.

Mortality

Severe NH is associated with an increased risk of death over the next 5 years in both PwD with T1DM or T2DM.[48] Hypoglycemia is known to be the leading cause of death, especially in young PwD with T1D, although the proportion of NH is unclear.[1] In a retrospective Chinese cohort study of 1520 PwD with T2D, the number and severity of hypoglycemic episodes were determined using CGM. Both DH and NH are associated with an increased risk of cardiovascular death (hazard ratio [HR] = 2.6 [95% CI = 1.398-4.994]), non-fatal stroke (HR = 1.8 [95% CI = 1.110-2.960]), and all-cause mortality (HR = 2.0 [95% CI = 1.124-3.418]) after full adjustment.[49] The ORIGIN (Outcome Reduction With Initial Glargine Intervention) study also demonstrated that elevated NH in PwD with T2D significantly increased the risk of cardiovascular events and all-cause mortality.[50]

Cognitive Impairment and Dementia

To investigate the effects of nocturnal glycemia on next-day cognitive performance in adults with T1D, researchers used a novel Ecological Momentary Assessment (EMA) approach to directly examine cognitive effects following NH.[51] The results showed that an increase in NH was associated with slower cognitive processing speed the next day, which was not due to negative effect, sleepiness, or sleep quality. Although the role of hypoglycemia in regard to cognitive decline has long been controversial, more recent studies have been able to demonstrate this association. In a recent meta-analysis that included studies of NH, PwD with T2D and severe hypoglycemic events had a 54% higher risk of dementia than PwD without severe hypoglycemia. The risk of dementia increased with the number of severe events: odds ratio [OR] = 1.29 (95% CI = 1.15-1.44) for one hypoglycemic event, OR = 1.68 (95% CI = 1.38- .04) for two hypoglycemic events, and OR = 1.99 (95% CI = 1.48-2.68) for three or more hypoglycemic events.[51] The meta-analysis also included studies on NH. The NH was an independent risk factor for cognitive impairment and dementia in PwD, along with a number of other factors (eg, arterial hypertension, chronic hyperglycemia, comorbid depression, physical inactivity, and microvascular and macrovascular diseases).[52]

Sleep

The NH worsens sleep quality, which was shown for all dimensions of sleep quality (eg, sleep duration, sleep depth, time to fall asleep, and time to wake up).[53] It can cause daytime sleepiness, lack of concentration, poor mental performance, and risk of accidents. In children with diabetes, NH affects not only the child's sleep, but more importantly, the parents' sleep, which is a major factor in parental stress and exhaustion.[54] Disturbed sleep has negative effects on insulin action in the form of increased insulin resistance. It also increases the risk of obesity. Studies on CGM and NH does not show a consistent picture, because, on one hand, CGM leads to more safety from hypoglycemia, but, on the other hand, frequent alarms can also disturb sleep. In contrast, studies in children with AID, which is particularly effective at night, have shown improvements in parental sleep, fear of hypoglycemia, and a reduction in diabetes-related stress.[55]

Quality of Life, Diabetes Distress

Hypoglycemia is one of the greatest burdens of diabetes. The NH can be particularly distressing and reduce quality of life because it may not be detected and treated in time. They can cause anxiety, sleep disturbances, morning headaches, fatigue, and mood swings.[56] Daytime quality of life decreases after asymptomatic NH compared with nights without hypoglycemia, especially if the NH lasted longer.[57] In a meta-analysis of the effects of hypoglycemia, all studies that included NH reported significantly worse mood, fatigue, less deep sleep, and greater arousal during and after nights of hypoglycemia.[14,58,59] Compared with SMBG, CGM users report greater confidence in their ability to avoid hypoglycemia or difficult social situations due to hypoglycemia, greater confidence in their ability to detect hypoglycemia earlier, and fewer life limitations due to hypoglycaemia.[32] The CGM and advanced diabetes technologies were also found to improve hypoglycemia, diabetes-specific symptoms, and quality of life.[60]

Impact on Family Members

Relatives, especially parents of children with T1D, are also affected by NH.[55] A nine-country study with 4300 family members of PwD, almost all of whom were treated with insulin (T1D = 29%, T2D = 46%), found that 30% of respondents had experienced hypoglycemia in their relatives in the past month.[61] Nearly two out of three family members (66%) said they think about their relatives' hypoglycemia monthly, and 64% are concerned about the risk of hypoglycemia.[62] In the international DAWN study, concerns about NH were assessed in the same way in PwD and in their family members. Similar to the overall evaluation, the proportion of relatives with a high level of concern about NH (63.4%) was significantly higher than in the PwD (39.4%). Interestingly, relatives were slightly more concerned about NH than about daytime hypoglycaemia.[63] This may be related to the fact that relatives feel more helpless in the face of hypoglycemia, which they cannot control and monitor, but nevertheless, experience the possible consequences with the person affected.

Costs

Not only is NH associated with personal financial costs, loss of performance, and reduced productivity, but it is also associated with increased costs to the health care system due to the cost of treatment. Two large studies found that people often have difficulty concentrating at work, are less productive, and have more absences after experiencing NH. The NH has a negative impact on well-being, concentration, and executive function the next day. About 39% of respondents with T1D and T2D report a severely impaired sense of well-being. The average duration of treatment for NH is 32 minutes; the subsequent recovery phase is a further 205 minutes. Sleep loss averages 2 hours; 12% of those affected are unable to fall back asleep afterwards. One in four people consulted a doctor because of NH.[64] Participants who had recently experienced NH reported decreased sleep quality (44%), arriving late to work (29%), leaving work early (16%), or missing an entire day of work (12%). Mean working time lost per NH was 14.7 hours. The cost of absence from work was estimated in this study to be €35.58 ± €130.27.[65] According to a review, which also included studies on NH, the direct costs of hypoglycemia per episode were on average $66 (T1D) and $11 (T2D) for self-help and $1161 for third-party help by medical professionals.[66]

Treatment Strategies

Treatment strategies are varied and include diabetes education to better understand the influence of factors that cause NH (eg, physical activity, diet, alcohol, and stress), strategies to optimize therapy (eg, change in insulin, medication, or adjustment), and technology support. The CGM alone or in combination with an AID system has been shown to reduce NH.[67,68]

However, existing CGM systems can mainly analyze the previous history of glucose values (eg, the extent of TBR) or warn with alarms when hypoglycemia occurs which causes a sleep disruption by itself with a potential impact on sleep quality. Current research on the prevention of NH attempts to develop prospective prediction models for the prevention of hypoglycemia. To this end, glucose levels measured by CGM systems were evaluated, and the occurrence of NH was predicted using algorithms that also take into account clinical characteristics. For example, Cichosz et al[69] extracted 26 variables for the prediction of NH using an AI approach. The variables contain clinical (eg, time in range [TIR], time above range [TAR], and TBR), statistical (eg, mean, variance, and skewness), time (eg, zero crossing rate, signal energy, and autocorrelation), frequency (eg, spectral power density, center of gravity, and entropy), and waveform characteristics (eg. peak-to-peak amplitude, crest factor, and waveform length). Overall, the systematic review showed that such integrative machine learning (ML) approaches achieved a sensitivity ranging between 71.0% and 95.6%, a specificity between 62.1% and 91.4%, and an overall receiver operating characteristic (ROC) with an overall area under the curve (AUC) between 0.62 and 0.97 in predicting NH. Predictive performance was generally higher in studies using a smaller prediction horizon during the night (15 minutes, 30 minutes, 3 hours) compared with studies predicting the whole nighttime.[70]

Most of the proposed models take a data-driven approach, relying on ML.[71,72] Models that predicted the risk of hypoglycemia in the short term (less than 60 minutes) were relatively accurate.[73,74] Dave et al[75] demonstrated that their feature-based ML model achieved a sensitivity of 93.9% and a specificity of 94.0%. Nevertheless, there are now also promising approaches for medium-term prediction of glucose levels in the range of 60 to 240 minutes[76-78] and for the use of AI-based glucose prediction to predict hypoglycemia in long-term periods such as at night.[79,80] For example, the Mosquera-Lopez et al[81] algorithm predicted 94.1% of NH events (<3.9 mmol/L, 95% CI = 71.3-99.9) from PwD T1D with an AUC of 0.86 (95% CI = 0.75-0.98). In summary, with advanced ML algorithms, the prediction of NH is possible with very good sensitivity and specificity. Generally, the addition of other clinical and demographic information improves predictive performance over just CGM-based prediction. The next step is to make these findings available to PwD and to bring to market modern CGM systems that reliably predict NH. These should warn PwD on basal therapy or MDI of NH in time for proactive prevention. In AID systems, this would lead to an optimization of the control algorithms. However, it is important to determine the appropriate messages and desired response to the predictive alert. How should PwD react to the glucose prediction? How will missing predictions affect confidence in the prediction and in the CGM? Will glucose control deteriorate because of the response to the prediction? A lot of work, outside of the algorithm development, needs to be done to have these predictive algorithms implemented on a commercial device.

Conclusion

The NH remains a major obstacle to diabetes management, with a variety of negative consequences for PwD. The CGM and related new technologies such as AID systems represent an important advancement in the prevention and timely treatment of NH but leave room for improvement. Future developments will be based on additional analysis of CGM data in combination with clinical parameters to use algorithms to predict and prevent the occurrence of NH. However, significant human factors and clinical work are needed to develop and optimize hypoglycemia prediction messaging. This would make a significant difference in the lives of PwD who are treated with insulin and may allow them to worry less about nocturnal hypoglycemia and to experience relief from their diabetes routines.

Abbreviations

ACTH, adrenocorticotropic hormone; AID, automated insulin delivery; AUC, area under the curve; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DH, daytime hypoglycemia; EMA, Ecological Momentary Assessment; FG, fasting glucose; GV, glucose variability; LBGI, low blood glucose index; MDI, multiple daily injections; NH, nocturnal hypoglycemia; PwD, people with diabetes; SMBG, self-monitoring of blood glucose; TAR, time above range; TB54, time <below 54 mg/dL; TBR time below range; T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time in range; ROC, receiver operating characteristic.

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ORCID iDs

Bernhard Kulzer https://orcid.org/0000-0001-9120-4479
Guido Freckmann https://orcid.org/0000-0002-0406-9529
Ralph Ziegler https://orcid.org/0000-0002-2373-3720
Timor Glatzer https://orcid.org/0009-0009-5644-2098
Lutz Heinemann https://orcid.org/0000-0003-2493-1304

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