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Time Below Range (TBR) and its Influence on Hypoglycemia Awareness and Severe Hypoglycemia - Insights from the Association of British Clinical Diabetologists (ABCD) Study

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Twitter Summary: Time Below Range (TBR) is effective in ruling out severe hypoglycemia, offering a valuable tool for better risk assessment in diabetes management. #DiabetesResearch #Hypoglycemia #CGM

Running Title: Time Below Range and Hypoglycemia Risk

Abstract

Objective: This study aimed to explore the relationship between Time Below Range (TBR), impaired Awareness of Hypoglycemia (IAH), and severe hypoglycemia (SH).

Research Design and Methods: This cross-sectional study analyzed data from people with diabetes using continuous glucose monitors (CGM) in the Association of British Clinical Diabetologists (ABCD) audit. Hypoglycemia awareness was assessed via the Gold score (≥4 denoting IAH), and SH was defined as hypoglycemia requiring third-party assistance. Logistic regression was used to determine the association between TBR% (<70 mg/dL, 3.9 mmol/L) at the first follow-up and follow-up Gold score and SH incidence. Youden's J index identified optimal TBR% cutoffs for detecting IAH and SH.

Results: The study included 15,777 participants, with follow-up TBR and SH data available for 5,029. The median TBR% was 4% (IQR 2%-6.6%), with 42% meeting the recommended TBR of ≤4%. Adjusted for age, gender, and BMI, TBR was significantly associated with SH (P<0.001) and IAH (P=0.005). Optimal TBR cutoffs for identifying IAH and SH were 3.35% and 3.95%, yielding NPV values of 85% and 97%, respectively.

Conclusions: Our findings support the international consensus recommending a TBR of <4% in type 1 diabetes, with high NPV values suggesting TBR's utility in screening for SH.

Article Highlights

- Why did we undertake this study?

  We aimed to explore whether Time Below Range (TBR) influences awareness of hypoglycemia and the occurrence of severe hypoglycemia (SH) in people with diabetes.

- What is the specific question we wanted to answer?

  Does a higher TBR impact hypoglycemia awareness and increase the risk of SH?

- What did we find?

  TBR was significantly associated with impaired Awareness of Hypoglycemia (IAH) and SH. Optimal TBR cutoffs were identified to detect these outcomes.

- What are the implications of our findings?

  A TBR threshold of <4% along with Gold score may serve as a valuable screening tool to exclude SH in individuals with type 1 diabetes.

Introduction

Diabetes mellitus, characterised by chronic hyperglycemia resulting from defects in insulin secretion, action, or both, poses significant challenges to healthcare systems worldwide due to its escalating prevalence and associated morbidity and mortality.(1, 2). Achieving optimal glycemic control, a cornerstone of diabetes management is paramount in mitigating the risk of microvascular and macrovascular complications.(1). However, the pursuit of tight glycemic targets is often associated with hypoglycemia, an acute complication of abnormally low blood glucose levels.(3-5). Hypoglycemia poses a substantial burden on individuals with diabetes, impairing quality of life, increasing healthcare utilisation, and, in severe cases, culminating in adverse cardiovascular outcomes and mortality.(3). Furthermore, impaired awareness of hypoglycemia (IAH), a state wherein individuals often fail to recognise hypoglycemic symptoms, exacerbates the risk of severe hypoglycemia (SH), which can be life-threatening and undermines efforts towards achieving glycemic targets.(6).

In recent years, the Time Below Range (TBR) percentage has emerged as a valuable metric of glycemic variability, offering insights into periods of hypoglycemia and glycemic fluctuations not captured by traditional glycemic indices(7-10). TBR percentage represents the proportion of time spent below a specified glucose threshold, defined through international consensus as 70 mg/dL or 3.9 mmol/L(10-14). This metric provides an easy-to-understand measure of total exposure to biochemical hypoglycaemia over a defined time period, thus complementing traditional measures such as HbA1c(10). Despite its growing recognition, the clinical implications of TBR percentage and its relationship with demographic and clinical factors such as IAH and SH remain underexplored. Therefore, we seek to explore the predictive utility of TBR percentage in identifying individuals at heightened risk of IAH and SH. By comprehensively examining these associations, we aim to advance our understanding of glycemic variability and its impact on diabetes outcomes, ultimately informing personalized diabetes management strategies tailored to individual risk profiles.

Methods

Study Design

This study constitutes a post-hoc analysis of data collected as part of the ongoing Nationwide FreeStyle Libre ABCD Audit.(15), an initiative to evaluate the real-world clinical utility and outcomes associated with FreeStyle Libre continuous glucose monitoring in individuals with diabetes. Data collection commenced in November 2017 through a secure online NHS tool, ensuring optimal security and enabling nationwide anonymized data analysis. Data were collected at baseline and follow-up during routine clinical care using secure NHS online tools in this nationwide audit. Baseline data included demographics, source of Freestyle Libre funding, previous structured diabetes education, HbA1c from the prior 12 months, Gold score for hypoglycaemia awareness, history of severe hypoglycaemia, paramedic callouts, and hospital admissions for hypoglycaemia, hyperglycaemia, or DKA. Data collection relied on both patient recall and medical records where available.

Data Collection

Demographic characteristics, pre and post FSL HbA1c levels, and TBR percentages were among the parameters collected. TBR percentage represents the proportion of time spent below a specified glucose threshold, defined as per the ATTD and IHSG consensus guidelines 70 mg/dL or 3.9 mmol/L(10, 16). Duplicates were meticulously removed, and those with paired baseline and follow-up data were included. Participants with complete loss of hypoglycaemia awareness, as indicated by a Gold score of seven, were also identified. Furthermore, severe

hypoglycemic episodes with decimal point numbers or those exceeding 20 were excluded from the analysis due to clinical non-viability and presumed errors. Hypoglycemia awareness was evaluated using the Gold score, with a score of ≥4 denoting Impaired Awareness of Hypoglycemia (IAH). SH was defined as at least one episode of hypoglycaemia necessitating third-party assistance. This was a cross-sectional study conducted at the first follow-up after the initiation of the Freestyle Libre (FSL). The study began in 2017 when isCGM in the UK did not have alerts for low glucose values. Therefore, the results presented reflect outcomes for isCGM use without the hypoglycaemia alert feature.

Statistical Analysis

Descriptive statistics, including means, standard deviations, and percentages, were employed to characterize baseline demographics between individuals. Logistic regression analysis was used to identify the independent effect of TBR on Hypoglycemia unawareness and severe hypoglycemia. Youden's J index(17) was used to identify the optimal TBR% cutoffs for detecting IAH and SH. Through its calculation, which considers both sensitivity and specificity, Youden's J index provides a single metric to assess the overall performance of a diagnostic test across various threshold values. This optimal threshold maximizes the discriminative ability of the test, ensuring both high sensitivity and specificity while minimizing misclassification errors(17).

Ethical Approval

Caldicott Guardian approval has been obtained for the ABCD Nationwide Audit Programme, designating it as audit work rather than research. Guided by established guidelines, all data collection occurred during routine clinical visits, with only anonymized data submitted to the central database to ensure patient confidentiality and privacy.

Results

Table 1 presents a comparative analysis of the demographics and clinical characteristics of individuals with diabetes stratified by, those achieving TBR < 4% (n=2132) and those with TBR ≥ 4% (n=2897). 42% of the study participants achieved a TBR < 4%. Patients with TBR ≥ 4% had a longer diabetes duration, with mean durations of 25.7 years for TBR ≥ 4% and 22.1 years for TBR < 4% ($p = 0.04$). Furthermore, individuals with TBR ≥ 4% were more likely to be using Continuous Subcutaneous Insulin Infusion (CSII) therapy (21% vs. 16%, $p < 0.0001$). Completion rates for structured education programs like Dose Adjustment for Normal Eating (DAFNE) did not significantly differ between the groups. Notably, those with TBR ≥ 4% had lower baseline HbA1c levels (65.9 mmol/mol vs. 75.3 mmol/mol, $p < 0.0001$). TBR ≥ 4% also correlated with a higher mean Gold score (2.34 vs. 2.11, $p < 0.0001$). A higher incidence of IAH was observed in the TBR ≥ 4% group (17% vs. 12%, $p < 0.0001$).

The prevalence of IAH and SH in this population was 17.2% and 4% respectively. We analysed factors associated with IAH and SH using logistic regression analysis, as shown in Table 2. For IAH, age was a weak but significant predictor, with an odds ratio (OR) of 1.020 (1.014 - 1.026, $p < 0.001$), indicating that each additional year of age increased the likelihood of hypoglycemia unawareness by 2%. Gender also showed a significant effect, with females being more likely to experience IAH compared to males (OR: 1.257, CI: 1.064 - 1.485, $p = 0.007$). The percentage TBR was another significant factor (OR: 1.014, CI: 1.004 - 1.024, $p = 0.005$) associated with

IAH, with a 1% increase in TBR associated with a 1% increase in IAH. Baseline Body Mass Index (BMI) and baseline HbA1c were not significant predictors of IAH. TBR was significantly associated with SH (OR: 1.013, CI: 1.016 - 1.052, $p < 0.001$); age and gender were not.

The optimal TBR cutoffs for identifying follow-up IAH and SH, as determined by Youden's J index were 3.35% and 3.95%, respectively. The Receiver Operating Characteristic curves ROC curves for detecting IAH and SH are shown in **Figure 1a**. The area under the curve (AUC) was 0.597 for IAH and 0.598 for SH, indicating that the model's poor discriminative ability is marginally better than random guessing (AUC = 0.5). Both ROC curves are close to the diagonal line, suggesting limited effectiveness in accurately predicting hypoglycaemic events. **Figure 1b** illustrates the impact of incorporating the Gold Score into the model predicting severe hypoglycemia (SH), resulting in an improved AUC of 0.74. This improvement suggests that combining Time Below Range (TBR) with the Gold Score could offer a synergistic benefit in predicting SH. In a model using only the Gold score as a predictor of severe hypoglycaemia, the area under the curve of the ROC analysis was 0.73 (**Figure 1c**). This demonstrates that the Gold score alone has a good predictive ability, and the increase in AUC compared to models incorporating additional factors, such as TBR, is modest.

Figure 2 shows diagnostic performance measures with TBR cut-off for the optimal TBR - cutoffs for SH and IAH. We observed that while the sensitivity for SH and IAH was moderate (65% and 73%, respectively), indicating the test's ability to correctly identify true positive cases, the specificity was relatively low (43% and 43%, respectively), reflecting the test's tendency to misclassify true negative cases. Interestingly, the positive predictive value (PPV) for IAH and SH was notably low (9% and 15%, respectively), indicating a high rate of false positives among individuals identified as positive for these conditions. Conversely, the negative predictive value (NPV) was high for both SH and IAH (97% and 85%, respectively),

suggesting a low rate of false negatives among individuals identified as negative for these conditions.

Discussion

In this nationwide study, we evaluated the link between TBR, IAH, and SH, finding that while TBR had a weak correlation with these outcomes, it has limited use in predicting them. However, its high negative predictive value provides reassurance in ruling out IAH and SH. The term "TBR" gained prominence with the widespread adoption of continuous glucose monitoring (CGM) technology in the late 2000s and early 2010s(18). The most significant formal recognition occurred with the International Consensus on Time in Range (TIR) publication in 2019(10) This consensus report standardised TBR and other CGM- TIR and time above range (TAR). Subsequently, TBR has been recognised as an important metric in managing people with diabetes.(8-10, 19).

The relationship between TBR and hypoglycaemic risk has been investigated previously. A study by Thomas et al.(20) showed that TBR on continuous CGM was significantly associated with a reduced epinephrine response during hypoglycaemic clamps, indicating impaired counter-regulation. This impaired epinephrine response may weaken the body's ability to defend against future hypoglycaemic episodes. The authors then conclude that CGM metrics, particularly TBR, can be valuable for identifying patients at heightened risk for severe hypoglycaemia and guiding preventative clinical interventions.

In this study, we show that 42% of individuals with diabetes managed to meet the TBR of less than or equal to 4%, indicating a prevalent issue of hypoglycemia within this population. These findings agree with another study conducted using de-identified user accounts from LibreView, where only 47% to 55% of participants achieved the recommended TBR of less than 4%(21).

Our analysis revealed a positive correlation between increased TBR and IAH and SH. This correlation persisted even after adjusting for confounding variables such as age, gender, and BMI. The results of our study are consistent with previous research, which showed that IAH is associated with higher percentages of values <3.9 mmol/L and <3.0 mmol/L compared to those with normal hypoglycemia awareness(11). Nevertheless, this study's findings contradict previous study(22), which indicated that CGM did not differentiate between individuals with impaired and normal awareness. The lack of correlation in this study might be attributed to the small sample size(22).

Youden's J index identified 3.35% and 3.9% cut-off values for IAH and SH, respectively. However, the specificity and predictive value of these cut-offs were low, approximately 50%, suggesting that TBR alone is insufficient to reliably predict individuals with IAH or those at high risk for SH. Despite this, the negative predictive value was high, indicating that a TBR of less than 4% correlates with a very low risk of SH. This discrepancy may be explained by the ability of CGM technology to enhance a user's awareness of glucose levels, enabling corrective actions to be taken before hypoglycaemia becomes severe, even when there is significant exposure to low glucose levels. Therefore, while TBR may not predict SH directly, it remains clinically valuable for identifying low-risk patients and guiding management strategies.

One reason for the weak association between TBR and SH or IAH might be that it could take longer for reductions in hypoglycaemia exposure from CGM interventions to affect impaired awareness of hypoglycaemia (IAH) in individuals with longer diabetes duration. A longitudinal follow-up study by Rickels et al. (23) demonstrated that while endogenous glucose production in response to insulin-induced hypoglycaemia in those using CGM did not change from baseline to 6 months, significant improvements were observed after 18 months. Furthermore another study(24) showed that intervention with automated insulin delivery improved the epinephrine response during hypoglycemic clamps in individuals with IAH, with reductions in

TBR contributing to this improvement. This highlights the potential of TBR not only as a risk marker but also as a modifiable target in clinical interventions to restore hypoglycemia counterregulation in individuals with IAH.

This study demonstrates that combining the Gold score with TBR resulted in the highest AUC for predicting severe hypoglycemia (SH). Prior research has shown that combining IAH and CGM metrics significantly improves the prediction of individuals with absent autonomic symptom recognition during insulin-induced hypoglycemia. A. J. Flatt et al(25). demonstrated that the Clarke score, combined with CGM measures of hypoglycemia exposure, had a strong predictive ability (AUC $\geq$ 0.80) for identifying absent AS recognition during hypoglycemic clamp experiments. Importantly, a composite threshold of IAH (Clarke score $\geq$ 4) alongside CGM measures of hypoglycemia exposure increased specificity and predictive value for identifying individuals at risk of severe hypoglycemia (SH). This aligns with our findings, which highlight that the combination of TBR measurement and IAH assessment provides enhanced prediction of SH. However, our analysis also shows that the Gold score alone could predict SH and there is modest improvement in the AUC with the addition of TBR.

It is clear that the Gold score and TBR do not capture the full complexity of hypoglycemia risk. Future research should assess how these measures can work synergistically to improve the accuracy of hypoglycemia risk prediction and guide better clinical decision-making. Recent data from the HypoMETRICS study (26) found similar rates of time below range (TBR) between individuals with and without impaired awareness of hypoglycemia (IAH). Notably, even among those with good hypoglycemia awareness as indicated by low Gold scores (1-2), up to half of CGM-detected low glucose events were asymptomatic. This high rate of asymptomatic hypoglycemia, even in individuals classified as low risk for severe hypoglycemia (SH) based on the Gold score, may explain the low predictive value of TBR alone in identifying those with IAH or SH.

Exploring additional metrics and approaches may provide greater predictive accuracy to improve the PPV of TBR. These could include incorporating a more comprehensive analysis of glycemic variability using Time in Range (TIR) and Time Above Range (TAR), alongside TBR, to enhance the prediction of hypoglycemia and overall glycemic control. Advances in machine learning and predictive algorithms that factor in glucose variability, insulin dosing patterns, and meal timing may also offer more precise predictive metrics than relying on TBR alone. Additionally, combining CGM data with physiological parameters such as heart rate variability, skin temperature, and electrodermal activity, available from wearable devices, could further improve real-time hypoglycaemia predictions.

We also explored the relationship between age, duration of diabetes and risk of severe hypoglycaemia. The relationship between TBR%, age, and duration of type 1 diabetes suggests a nuanced interaction between glycaemic targets and hypoglycaemia risk. Older patients may have higher A1c goals to reduce the risk of hypoglycaemia, which could explain the association with lower TBR%. On the other hand, patients with longer disease duration, who may be more adept at managing tight glucose control, tend to have higher TBR%. This could also be influenced by impaired awareness of hypoglycaemia (IAH), which becomes more prevalent with longer diabetes duration. The competition between these two effects—higher A1c targets for older patients and tighter glucose management for long-term patients—may play a key role in hypoglycaemia risk as patients age. Future research should further explore these dynamics to inform better personalised glycaemic targets that account for both age and disease duration while minimising hypoglycaemia risk.

Two important limitations of the FreeStyle Libre system must be acknowledged. First, as an intermittently scanned CGM, the FreeStyle Libre requires the user to scan the sensor to capture glucose data manually. This reliance on user interaction may lead to significant data gaps when scans are infrequent, potentially introducing errors in the calculation of time TBR and leading

to an inaccurate assessment of hypoglycemic exposure. Second, evidence suggests that the FreeStyle Libre system is less accurate in detecting glucose levels in the hypoglycemic range. Galindo et al.(27) have shown that that the FreeStyle Libre system tended to overestimate hypoglycemia compared to capillary glucose testing in hospitalised patients with Type 2 diabetes. Similarly, Alitta et al. (28) demonstrated an overestimation of hypoglycemia in long-term care home residents using the system. These inaccuracies may result in inflated TBR values and limit the precision of TBR as a standalone metric for assessing hypoglycemic risk. When interpreting our findings, these limitations should be considered and underscore the importance of combining CGM data with clinical judgment in hypoglycemia management.

This study provides valuable insights into the relationship between TBR, IAH, and SH; however, several limitations warrant consideration. Firstly, our study relies on retrospective analysis of data collected from the Nationwide FreeStyle Libre ABCD Audit, introducing the possibility of selection bias and incomplete data capture. Furthermore, the determination of optimal TBR cutoffs for identifying IAH and SH may be influenced by the study population's characteristics and may not be generalised to other populations. Finally, the observational nature of our study precludes causal inference, and further prospective studies are warranted to validate our findings and elucidate the mechanistic underpinnings of the observed associations. Despite these limitations, our study offers several strengths that enhance its clinical relevance and utility. Leveraging real-world data from a large cohort of individuals with diabetes using continuous glucose monitoring provides valuable insights into glycemic control patterns and hypoglycemia risk in routine clinical practice. By identifying optimal TBR cutoffs for detecting IAH and SH and evaluating diagnostic performance measures, our study contributes to the refinement of hypoglycemia risk assessment tools and informs clinical decision-making in diabetes management. Moreover, our findings underscore the importance of minimising

TBR to reduce the incidence of IAH and SH, highlighting the clinical significance of glycemic variability metrics in optimising diabetes care and improving outcomes.

In conclusion, our study highlights the critical role of TBR in managing diabetes and preventing hypoglycemic events. By understanding the factors contributing to increased TBR and implementing targeted interventions, healthcare providers can better manage those at risk for IAH and SH, ultimately improving the outcomes of people living with diabetes.

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Table 1: Demographic and clinical characteristics of people with diabetes achieving TBR<4% vs TBR>=4%

	TBR >=4% (2897)	**TBR<4% (2132)**	P-value
Age (years)	44.9 (15.6)	46.6 (16.4)	<0.0001
Sex, % female	1455 (50.2%)	1068 (50%)	0.94
Ethnicity			
British	2456(84%)	1764 (82%)	
All other ethnicities	441 (16%)	368 (18%)	0.13
Baseline BMI (kg/m^2)	26.8 (±5.9)	26.5 (±6.2)	0.14
Duration of diabetes (years)	25.7 (±40)	22.1 (±75.7)	0.04
Type 1 diabetes	2836	2024	
Type 2 diabetes	8	67	
Others	53	41	<0.0001
CSII	627 (21%)	349 (16%)	<0.0001

Completion of structured education (DAFNE)	939 (32%)	677 (31%)	0.9
Average pre-FSL HbA1c (mmol/mol) (%)	65.9 (±18.8) 8.2%	75.3(±15.3) 9%	<0.0001
Gold score			
Mean	2.34 (±1.54)	2.11 (±1.46)	<0.0001
≥4 (IAH)	498 (17%)	263 (12%)	<0.0001

Table 2: Multivariate Logistic Regression Analysis for examining association of TBR with of IAH and SH

	Impaired Awareness of Hypoglycaemia		Severe Hypoglyceamia	
	OR (CI)	P-value	OR (CI)	P-value
Age	1.020 (1.014 - 1.026)	<0.001	1.008 (0.999 - 1.015)	0.160
Gender	1.257 (1.064 - 1.485)	0.007	1.147 (0.847 - 1.555)	0.441
Baseline BMI	1.008 (0.995 - 1.021)	0.278	1.147 (0.847 - 1.555)	0.352
Time Below Range (% <3.9mmol/l)	1.014 (1.004 - 1.024)	**0.005**	1.013 (1.016 - 1.052)	**<0.001**
Baseline HbA1c	1.002 (0.996 - 1.008)	0.380	1.017 (1.007 - 1.027)	0.380

Figure Legends

Figure 1a: The Receiver Operating Characteristic curves ROC curves for detecting IAH and SH with TBR and baseline covariates

Figure 1b: The Receiver Operating Characteristic curves ROC curves for detecting SH with TBR and GOLD score and baseline covariates

Figure 1c: The Receiver Operating Characteristic curves ROC curves for detecting SH with GOLD score and baseline covariates

Figure 2: Diagnostic performance measures with TBR cut-off for the optimal TBR -cutoffs for IAH and SH