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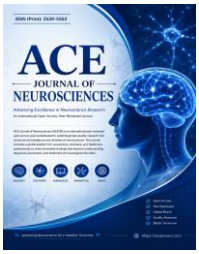

Research Article

Prevalence, Clinical Correlates, and Treatment-Specific Risk of Nocturnal and Prolonged Hypoglycemia in Adults with Type 2 Diabetes Mellitus on Oral Therapy: A Raw Continuous Glucose Monitoring Analysis.

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Abstract: ***Background:*** Traditional glycemic assessment in Type 2 Diabetes Mellitus (T2DM) relies heavily on glycated hemoglobin (HbA1c) . However, HbA1c is a slow-moving average that fails to capture acute glycemic excursions, diurnal patterns, or life-threatening hypoglycemia. Continuous Glucose Monitoring (CGM) enables the detection of silent glycemic events. This study used raw sensor time-series data to evaluate the prevalence, duration, diurnal patterns, and clinical correlates of nocturnal and prolonged hypoglycemia in adults with T2DM on oral antidiabetic drugs (OADs) in a tertiary care setting in India. ***Methods:*** We conducted a retrospective, patient-level analysis of raw CGM records from adults with T2DM attending Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India. Eligible patients had adequate raw CGM records (minimum recording span ≥3 days with ≥250 active readings) and were reliably matched to a clinical registry. Hypoglycemia was defined using standard thresholds (TBR <70 mg/dL and <54 mg/dL) . Nocturnal hypoglycemia was defined as any episode occurring between 00:00 and 06:00. Prolonged hypoglycemia was analyzed using two sensitivity thresholds: ≥60 minutes and ≥120 minutes. Comparisons were made between sulfonylurea (SU) -exposed and non-SU-exposed regimens, and diurnal patterns were assessed across four 6-hour blocks. ***Results:*** Out of 58 parsed raw CGM files, 51 patients met the data adequacy and matching criteria (mean wear duration: 13.6 ± 0.8 days) . The cohort had a mean age of 53.3 ± 10.3 years, and mean HbA1c of 7.5% ± 1.1%. Overall, 84.3% (43/51) of patients experienced at least one hypoglycemia episode (<70 mg/dL) , and 64.7% (33/51) experienced nocturnal hypoglycemia. Prolonged hypoglycemia was highly prevalent: 68.6% (35/51) had episodes lasting ≥60 minutes, and 52.9% (27/51) had episodes lasting ≥120 minutes. Severe biochemical hypoglycemia (<54 mg/dL) occurred in 56.9% (29/51) of patients, with 39.2% (20/51) having nocturnal severe events, and 27.5% (14/51) experiencing prolonged severe hypoglycemia (≥120 min) . The mean longest hypoglycemia episode was 248.5 ± 374.0 minutes (median: 120 minutes, max: 2,295 minutes) . Patients with nocturnal hypoglycemia had significantly lower HbA1c (7.19% vs. 8.37%; p = 0.0025) and higher glycemic variability (Mean CV: 33.16% vs. 24.60%; p = 0.0004) than those without. SU-exposed patients (n=22) had a significantly lower Time in Range (TIR 70-180 mg/dL) than nonSU-exposed patients (62.97% vs. 74.86%; p = 0.0428) . SU-exposed patients also spent more time in hypoglycemia (mean: 156.3 vs. 103.5 minutes/day; p = 0.2569) and had longer maximum episodes (mean: 263.9 vs. 236.9 minutes; p = 0.2899) . In diurnal block analysis, the morning block (06:00–12:00) showed a twofold higher TBR in the SU group compared to the non-SU group (14.26% vs. 7.11%; p = 0.2407). ***Conclusions:*** Nocturnal and prolonged hypoglycemia are highly prevalent in adults with T2DM on OADs, even in patients with acceptable HbA1c. More than half of the cohort experienced hypoglycemia episodes lasting over two hours, exposing them to silent cardiac and neurological risk. These findings highlight the need to supplement HbA1c with CGM-derived metrics, especially in patients treated with sulfonylureas or those exhibiting high glycemic variability.

Keywords: continuous glucose monitoring; type 2 diabetes; nocturnal hypoglycemia; prolonged hypoglycemia; sulfonylureas; glycemic variability.

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INTRODUCTION

Continuous glucose monitoring (CGM) has transformed the clinical landscape of diabetes care, providing a dynamic, multi-dimensional view of daily glucose fluctuations that point-of-care capillary measurements and static glycated hemoglobin (HbA1c) tests fail to capture [1,2] . While laboratory HbA1c remains the gold standard for predicting microvascular risk, it serves only as a slowmoving average of ambient glucose levels [3] . Consequently, HbA1c masks acute excursions, postprandial glycemic spikes, and silent, life-threatening hypoglycemic episodes, particularly those occurring during sleep [4] . In response to this diagnostic limitation, international consensus guidelines advocate for the standard use of CGM-

derived metrics—such as Time in Range (TIR, 70–180 mg/dL) , Time Below Range (TBR, <70 mg/dL for Level 1 and <54 mg/dL for Level 2 hypoglycemia) , and the Coefficient of Variation (CV, representing glycemic variability) —to direct safe therapeutic adjustments [1,3,5] .

In resource-limited settings like India, the clinical implementation of CGM faces significant economic and practical hurdles [14] . Because healthcare expenses are largely paid out-of-pocket, the cost of continuous monitoring is often a barrier [14,15] . Consequently, clinicians frequently rely on conventional HbA1c and intermittent self-monitoring of blood glucose (SMBG) . Yet, older oral antidiabetic drugs (OADs) , specifically sulfonylureas (SUs) , remain a cornerstone of diabetes management in South Asia due to their low cost and high efficacy in lowering blood glucose [17,19] . Despite their therapeutic benefits, SUs are secretagogues that stimulate insulin secretion independently of ambient glucose concentrations, placing patients at substantial risk for hypoglycemia [17,18] .

Nocturnal hypoglycemia is particularly dangerous because sleep blunts the autonomic warning signs of falling glucose, turning what would be symptomatic warnings into silent, prolonged biochemical events [23] . Prolonged exposure to low glucose concentrations has been linked to functional brain failure, cognitive decline, cardiac arrhythmias, QTc interval prolongation, and the "dead-in-bed" syndrome [8,9] . While large clinical trials in Western cohorts (such as the ACCORD, ADVANCE, and VADT studies) have demonstrated that intensive glucose control increases mortality and that severe hypoglycemia is a key risk marker, there is a scarcity of data analyzing the duration and diurnal patterns of hypoglycemia using raw, high-resolution sensor data in South Asian cohorts [5,6,7,21] . Most prior studies in India have relied on retrospective patient recall or clinical reports rather than raw sensor time-series datasets [20,21] .

Furthermore, while the international consensus guidelines recommend at least 14 days of CGM wear with 70% active sensor time, real-world clinical practices or environmental factors (such as humidity causing early adhesive failure) frequently result in shorter wear times [14,16] . Validating the hypoglycemia burden and identifying clinical markers of high-risk patients using raw CGM files remains an urgent clinical need.

Therefore, the primary objective of this study was to evaluate the prevalence, duration, diurnal patterns, and clinical correlates of nocturnal and prolonged hypoglycemia using raw CGM time-series data in adults with T2DM on OADs. Secondary objectives were to compare the hypoglycemia burden between patients receiving SU-exposed regimens and non-SU-exposed regimens, and to evaluate prolonged hypoglycemia using two sensitivity duration thresholds (≥60 minutes and ≥120 minutes).

MATERIALS AND METHODS

Study Design and Patient Cohort

This retrospective, observational study utilized a clinical registry and raw CGM time-series dataset from adults with T2DM attending Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India [14] . The institutional review board approved the primary study protocol, and all patients provided written informed consent before sensor placement. The clinical database contained demographic, medication, and laboratory variables.

Raw CGM data were obtained from flash CGM systems (FreeStyle Libre Pro and FreeStyle Libre 2, Abbott Diabetes Care) worn by outpatients during routine clinical care. Individual raw files were parsed and matched to the clinical registry. To be included in the analytical cohort, patients were required to have: Adequate raw sensor data, defined as a minimum active recording span of at least 3.0 days and a total of at least 250 glucose readings.

CGM Data Processing and Metric Definitions

A custom Python pipeline was implemented to parse the heterogeneous Libre Pro (. txt, tab-separated) and Libre 2 (. csv, comma-separated) files. The script extracted device timestamps and glucose concentrations, standardized all measurements to mg/dL, removed duplicates, and sorted the readings chronologically.

Key CGM parameters were calculated directly from the raw time-series data using standard clinical definitions [1,3] :
Mean Interstitial Glucose: The average of all glucose readings.

Glucose Management Indicator (GMI): Estimated HbA1c calculated using the formula: GMI (%) = 3.31 + 0.02392 * mean glucose (mg/dL) [1].

Time in Range (TIR): Percentage of readings within 70–180 mg/dL.
Time Below Range (TBR) : Percentage of readings below 70 mg/dL (Level 1 hypoglycemia) .
Severe TBR (TBR54) : Percentage of readings below 54 mg/dL (Level 2 biochemical hypoglycemia) .
Time Above Range (TAR) : Percentage of readings above 180 mg/dL.
Glycemic Variability (CV) : The coefficient of variation, calculated as CV (%) } = {SD of glucose} / {mean glucose)*100. A CV of ≤ 36\% was defined as stable control, and >36 % as high glycemic variability [3] .

Diurnal and Hypoglycemia Episode Definitions

To analyze diurnal variation, the 24-hour day was divided into four 6-hour blocks:

- Night (Nocturnal) : 00:00 to 06:00
- Morning: 06:00 to 12:00
- Afternoon: 12:00 to 18:00
- Evening: 18:00 to 24:00

Nocturnal hypoglycemia was defined as any hypoglycemia episode occurring during the Night block (00:00 to 06:00). A hypoglycemia episode was defined as consecutive readings below the threshold (<70 mg/dL or <54 mg/dL) [11,12] . The duration of each episode was calculated as the number of readings multiplied by the median sampling interval. Successive readings were treated as part of the same episode unless separated by a gap greater than 1.75 \times \text{sampling interval}.

Prolonged hypoglycemia was evaluated using two sensitivity thresholds:

- Prolonged Hypoglycemia (≥60 min) : Any episode lasting at least 60 minutes.
- Prolonged Hypoglycemia (≥120 min) : Any episode lasting at least 120 minutes.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range [IQR]) depending on their distribution. Categorical variables are reported as frequencies and percentages. For continuous outcomes, differences between groups (e. g., SU vs. non-SU, or patients with vs. without nocturnal hypoglycemia) were evaluated using the Mann–Whitney U test. Categorical associations were evaluated using Fisher's exact test. Statistical significance was defined as a two-sided p-value <0.05. All statistical computations were performed using Python 3.13 (pandas, numpy, and scipy. stats).

RESULTS

Cohort Baseline Characteristics

A total of 58 raw CGM files were parsed. After filtering for wear time (≥3 days and ≥250 readings) and matching, 51 patients formed the final analytical cohort. The baseline demographics and clinical characteristics of these 51 patients are summarized in Table 1. The cohort had a mean age of 53.3 ± 10.3 years, and 45.1% (23/51) were female. Glycemic control was moderate, with a mean baseline laboratory HbA1c of 7.5% ± 1.1% and a mean interstitial glucose of 141.3 ± 50.4 mg/dL. The average active sensor wear duration was 13.6 ± 0.8 days, providing a comprehensive capture of glycemic behavior. In terms of therapy, 43.1% (22/51) were receiving a sulfonylurea-containing regimen (SU group) , and 56.9% (29/51) were on nonSU OAD regimens. Metformin was prescribed to all 51 patients (100.0%) , while 82.4% (42/51) were on DPP-4 inhibitors and 21.6% (11/51) were on SGLT-2 inhibitors.

Prevalence and Burden of Hypoglycemia

Hypoglycemia was highly prevalent in this cohort. The rates and characteristics of hypoglycemic events are shown in Table 2. Overall, 84.3% (43/51) of patients experienced at least one hypoglycemia episode <70 mg/dL during the monitoring period, and 56.9% (29/51) experienced severe biochemical hypoglycemia (<54 mg/dL) . The duration of these episodes was notably prolonged. A total of 35 patients (68.6%) experienced at least one episode of hypoglycemia lasting ≥60 minutes, and more than half of the cohort (52.9%, 27/51) experienced an episode lasting ≥120 minutes. For severe hypoglycemia (<54 mg/dL) , 37.3% (19/51) had episodes lasting ≥60 minutes, and 27.5% (14/51) experienced highly prolonged severe episodes lasting ≥120 minutes. The mean of the longest hypoglycemia episode recorded for each patient was 248.5 ± 374.0 minutes (median: 120.0 minutes) , indicating that many patients spent several consecutive hours in a hypoglycemic state.

Diurnal Patterns of Glycemia and Hypoglycemia

When stratified into 6-hour blocks, glycemic control and hypoglycemia risk exhibited distinct diurnal variation (Supplementary Table 1). Mean interstitial glucose was highest in the evening block (149.99 mg/dL) and lowest in the morning block (132.57 mg/dL) . Conversely, hypoglycemia risk (TBR) peaked during the morning block (mean TBR: 10.22%) and the night block (mean TBR: 10.16%) . Level 2 severe hypoglycemia (TBR54) also peaked during the night block (mean TBR54: 4.32%) and morning block (mean TBR54: 4.18%) , compared to 2.26% in the evening.

Clinical Correlates of Hypoglycemia

We evaluated clinical and biochemical markers associated with the presence of nocturnal or prolonged hypoglycemia (defined as having either nocturnal hypoglycemia <70 mg/dL or any prolonged hypoglycemia episode ≥60 min) . Out of 51 patients, 38 (74.5%) met this definition of high-risk hypoglycemia. As shown in Supplementary Table 2, patients with nocturnal or prolonged hypoglycemia had a significantly lower mean interstitial glucose (127.29 vs. 182.42 mg/dL; p = 0.0005) and a lower mean laboratory HbA1c (7.46% vs. 8.03%; p = 0.1167, though not statistically significant) . When evaluating nocturnal hypoglycemia specifically, the difference in HbA1c was highly significant: patients with nocturnal hypoglycemia had a mean HbA1c of 7.19% compared to 8.37% in those without (p = 0.0025) .

Glycemic variability was strongly linked to hypoglycemia risk. Patients with nocturnal or prolonged hypoglycemia had a significantly higher CV than those without (Mean CV: 32.54% vs. 23.12%; p = 0.0001) . Similarly, patients with nocturnal hypoglycemia had a mean CV of 33.16% vs. 24.60% (p = 0.0004) . Demographic markers (age, BMI, duration of diabetes) and renal function markers (eGFR, UACR) did not show statistically significant differences, although patients with hypoglycemia had a longer mean duration of diabetes (6.92 vs. 5.50 years) and a lower eGFR (90.75 vs. 93.88 mL/min/1.73m^2) .

In secondary correlation analysis, the overall glycemic variability (represented by the sensor Coefficient of Variation [CV %]) demonstrated a strong, statistically significant positive correlation with the daily hypoglycemia duration (r = 0.578, t = 4.96, df = 49, p < 0.001, Pearson correlation; Figure 2) .

To evaluate the impact of renal clearance on hypoglycemia burden, we performed a secondary subgroup comparison by stratifying patients by estimated GFR (eGFR) into a normal renal function group (≥ 90 mL/min/1.73m^2, n = 31) and a mild renal impairment group (< 90 mL/min/1.73m^2, n = 20) . The daily hypoglycemia duration was similar between the groups (median 35.81 min/day [mean: 148.58 ± 214.97 min/day] for normal function vs. median 31.31 min/day [mean: 91.63 ± 154.96 min/day] for mild impairment; Wilcoxon W = 362.5, p = 0.315; Figure 3) .

Medication-Specific Hypoglycemia Risk: SU vs. Non-SU Regimens

Next, we evaluated the impact of OAD regimens on the hypoglycemia profile by comparing patients receiving SUs (n = 22) against those on non-SU regimens (n = 29) (Supplementary Table 3) . SU-exposed patients had a statistically significantly lower TIR compared to nonSU-exposed patients (62.97% vs. 74.86%; p = 0.0428) , indicating poorer overall glycemic stability (Supplementary Figure 1) .

While the categorical presence of "any" nocturnal or prolonged episode did not differ significantly between the two groups (e. g., nocturnal hypo: 63.6% in SU vs. 65.5% in non-SU, p = 1.000; prolonged hypo ≥120 min: 59.1% in SU vs. 48.3% in non-SU, p = 1.000) , the absolute burden of hypoglycemia was clinically higher in the SU group. SU-exposed patients spent a mean of 156.25 ± 216.64 minutes/day in hypoglycemia (<70 mg/dL) compared to 103.49 ± 175.41 minutes/day in the non-SU group (p = 0.2569) . Furthermore, the longest hypoglycemia episode was longer in the SU group (mean maximum duration: 263.86 vs. 236.90 minutes; p = 0.2899; Supplementary Figure 2) . Severe biochemical hypoglycemia (<54 mg/dL) was also more frequent in the SU group (72.7% vs. 44.8%; p = 0.1369, though not statistically significant) .

Stratifying the diurnal blocks by medication exposure (Figure 1) revealed that the SU group experienced a larger clinical burden of hypoglycemia in the Morning block (06:00–12:00) with a mean TBR of 14.26% compared to 7.11% in the non-SU group (p = 0.2407) . During the Night block (00:00–06:00) , the SU group also had a higher mean TBR of 11.72% vs. 8.97% in the non-SU group (p = 0.8831) .

Tables

Table 1. Demographic and Clinical Characteristics of the Patient Cohort (n = 51)

Parameter	**Value (Mean ± SD or Count [%])**
Age (years)	53.29 ± 10.32
Female Sex	23 **(45.1%)**
Duration of Diabetes (years)	6.31 ± 5.07
Body Mass Index **(BMI, kg/m^2)**	24.25 ± 2.92
Glycated Hemoglobin (HbA1c, %)	7.54 ± 1.09
Estimated GFR **(eGFR, mL/min/1.73m^2)**	91.67 ± 25.10
Urine Albumin-Creatinine Ratio **(UACR, mg/g)**	46.19 ± 18.25
Mean Interstitial Glucose **(mg/dL)**	141.34 ± 50.43
Time in Range (TIR 70–180 mg/dL, %)	69.83 ± 22.25
Time Below Range (TBR <70 mg/dL, %)	8.86 ± 13.57
Coefficient of Variation (CV, %)	30.14 ± 8.87
OAD Regimen	
Metformin	51 **(100.0%)**
DPP-4 Inhibitor	42 **(82.4%)**
Sulfonylurea **(SU)**	22 **(43.1%)**
SGLT-2 Inhibitor	11 **(21.6%)**

Table 2. Prevalence and Episode Burden of Hypoglycemia (n = 51)

Hypoglycemia Metric	Overall Cohort Value
Any Hypoglycemia (<70 mg/dL)	
Overall Prevalence	43 / 51 **(84.3%)**
Nocturnal Prevalence (00:00–06:00)	33 / 51 **(64.7%)**
Prolonged Prevalence (≥60 min)	35 / 51 **(68.6%)**
Prolonged Prevalence (≥120 min)	27 / 51 **(52.9%)**
Severe Hypoglycemia (<54 mg/dL)	
Overall Prevalence	29 / 51 **(56.9%)**
Nocturnal Prevalence (00:00–06:00)	20 / 51 **(39.2%)**
Prolonged Prevalence (≥60 min)	19 / 51 **(37.3%)**
Prolonged Prevalence (≥120 min)	14 / 51 **(27.5%)**
Episode Burden	
Median Hypoglycemia Episodes / day	0.57 **(IQR: 0.22 to 1.48)**
Median Hypoglycemia Duration (min / day)	35.81 **(IQR: 4.49 to 136.28)**
Mean Longest Hypoglycemia Episode (min)	248.52 ± 374.01 **(median: 120.00)**

Figures:

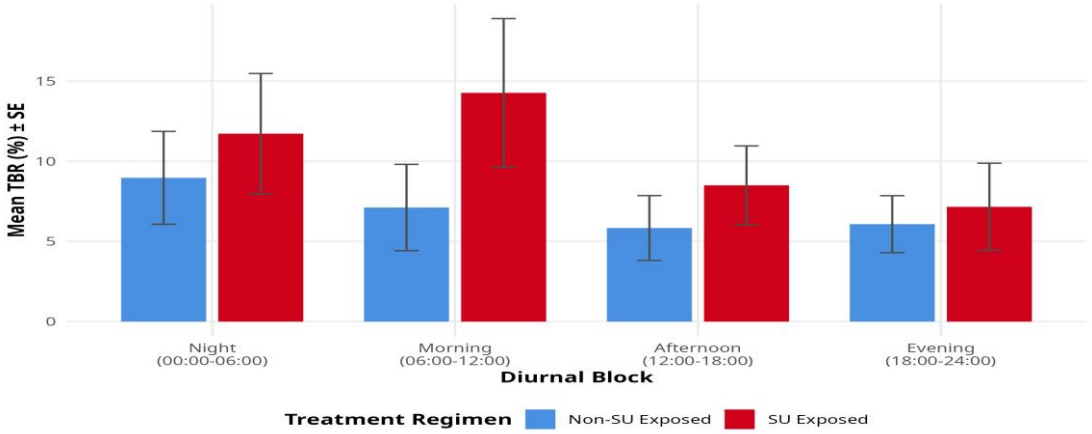


Figure 1

Diurnal block comparison (TBR <70 mg/dL) by medication exposure regimen. Mean Time Below Range (TBR %) ± standard error of the mean (SE) is compared across the four 6-hour diurnal blocks: Night (00:00–06:00) , Morning (06:00–12:00) , Afternoon (12:00–18:00) , and Evening (18:00–24:00) for sulfonylurea (SU) -exposed (red bars) and non-SU-exposed (blue bars) regimens. Clinically higher hypoglycemia burden was observed in the SUexposed group during morning and nocturnal blocks.

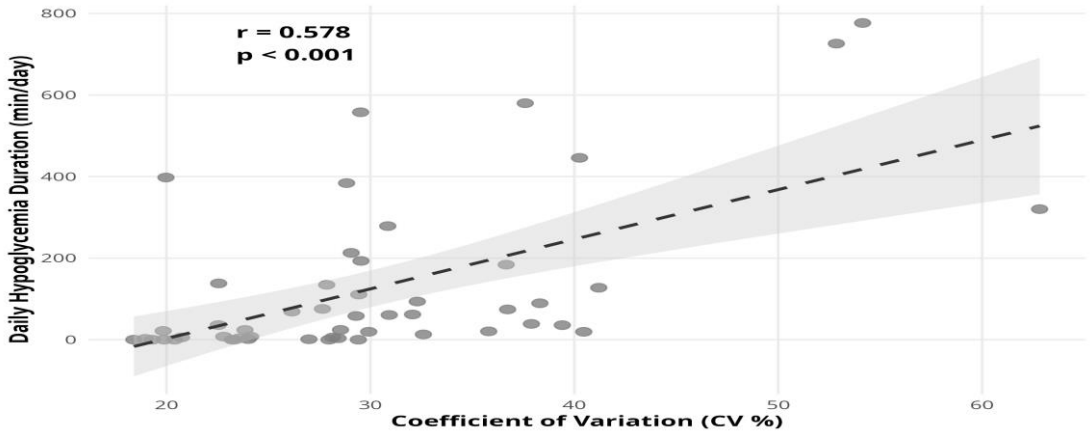


Figure 2

Correlation between glycemic variability and daily hypoglycemia duration.
Pearson correlation scatter plot demonstrating the relationship between the sensor Coefficient of Variation (CV %) and daily cumulative minutes spent in hypoglycemia (<70 mg/dL) . A strong, statistically significant positive relationship is observed

(r = 0.578, p < 0.001) , indicating that greater glycemic fluctuations directly drive higher cumulative hypoglycemia exposure. Patients on SU regimens are shown in red and non-SU in blue.

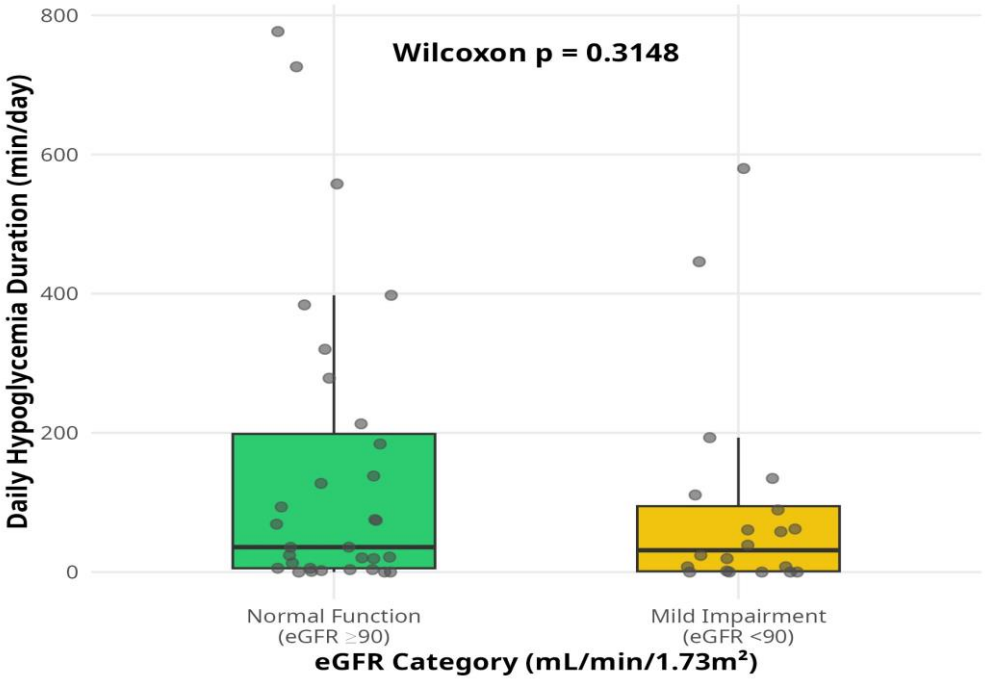


Figure 3

Cumulative daily hypoglycemia duration by estimated glomerular filtration rate (eGFR) category. Boxplot comparing daily hypoglycemia minutes (<70 mg/dL) between patients with normal renal function (eGFR ≥90 mL/min/1.73m^2, green) and mild renal impairment (eGFR <90 mL/min/1.73m^2, yellow) . Individual patient datapoints are overlaid as jittered dots. The Wilcoxon rank-sum test showed no statistically significant difference between the two categories (p = 0.315).

Supplementary Material:

Supplementary Tables

Supplementary Table 1. Diurnal Block Glycemic Metrics Across the 24-Hour Cycle

Metric	**Night (00:00–06:00)**	**Morning (06:00–12:00)**	**Afternoon (12:00–18:00)**	**Evening (18:00–24:00)**
Mean Interstitial Glucose **(mg/dL)**	135.59	132.57	145.51	149.99
Time in Range (TIR, %)	71.28	72.76	69.84	66.97
Time Below Range (TBR <70 mg/dL, %)	10.16	10.22	6.99	6.55
Severe TBR (TBR54 <54 mg/dL, %)	4.32	4.18	2.57	2.26
Coefficient of Variation (CV, %)	27.48	26.58	28.19	28.06

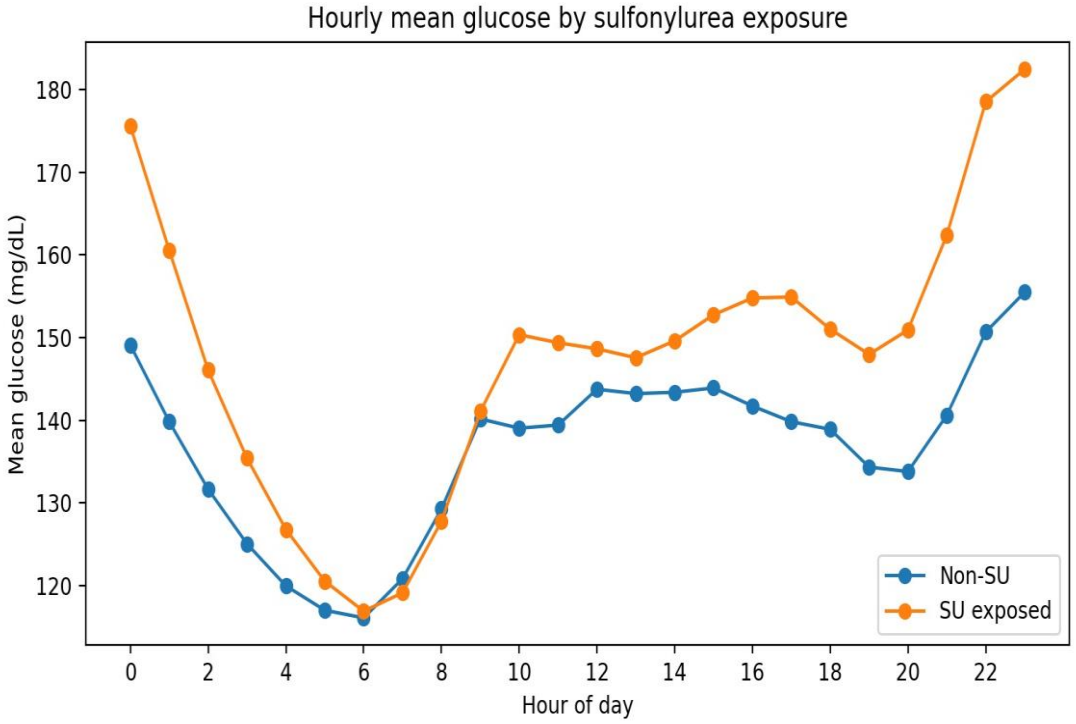
Supplementary Table 2. Clinical Correlates Associated with Nocturnal or Prolonged Hypoglycemia

Parameter	**No Nocturnal / Prolonged Hypo (n = 13)**	**Nocturnal or Prolonged Hypo (n = 38)**	**p-value**
Age (years)	49.23 ± 11.23	53.29 ± 10.32	0.4171
Body Mass Index **(BMI, kg/m^2)**	24.32 ± 2.67	24.22 ± 2.92	0.7050
Duration of Diabetes (years)	5.50 ± 4.50	6.92 ± 5.07	0.6489
HbA1c **(%)**	8.03 ± 1.22	7.46 ± 1.09	0.1167
eGFR **(mL/min/1.73m^2)**	93.88 ± 23.50	90.75 ± 25.10	0.9139
UACR **(mg/g)**	40.05 ± 15.20	46.63 ± 18.25	0.8037
Mean Interstitial Glucose **(mg/dL)**	182.42 ± 55.20	127.29 ± 50.43	0.0005
Coefficient of Variation (CV, %)	23.12 ± 6.20	32.54 ± 8.87	0.0001

Supplementary Table 3. Comparison of Glycemic and Hypoglycemia Metrics between SU and Non-SU Regimens

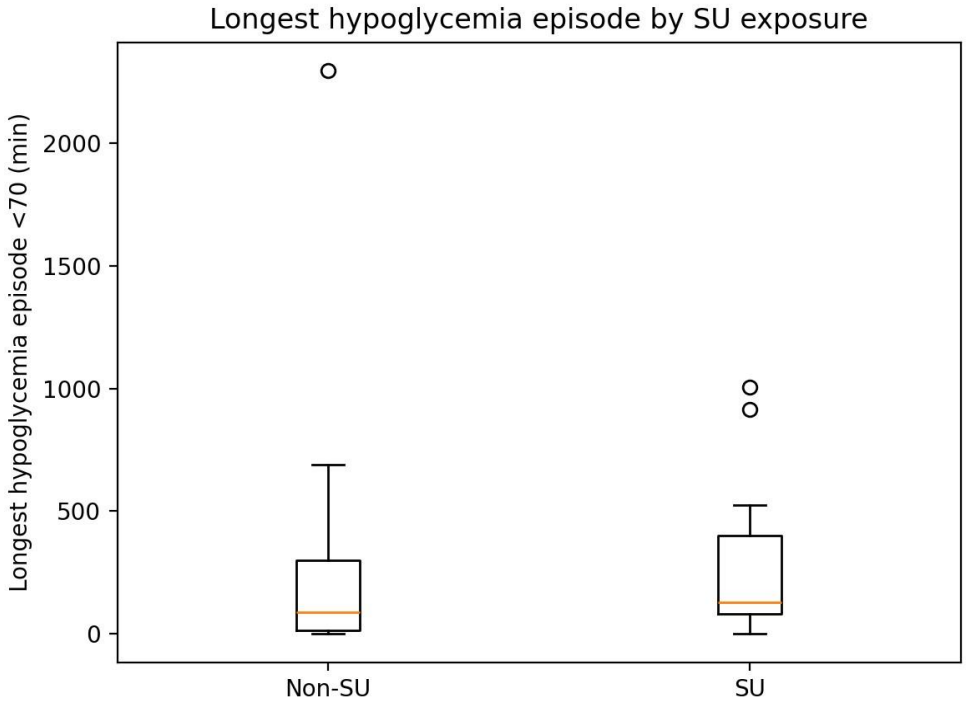
Metric	Non-SU Exposed (n = 29)	SU Exposed (n = 22)	p-value
Mean Interstitial Glucose **(mg/dL)**	136.31 ± 33.90	147.99 ± 65.95	0.8566
Time in Range (TIR 70–180 mg/dL, %)	74.86 ± 19.72	62.97 ± 23.89	0.0428
Time Below Range (TBR <70 mg/dL, %)	7.21 ± 12.17	10.86 ± 15.04	0.2569
Severe TBR (TBR54 <54 mg/dL, %)	2.95 ± 7.82	4.12 ± 8.94	0.1369
Coefficient of Variation (CV, %)	29.40 ± 10.45	31.12 ± 7.40	0.1354
Hypo Episodes (<70 mg/dL) / day	0.91 ± 1.26	1.35 ± 1.42	0.2337
Hypo Duration (<70 mg/dL, min / day)	103.49 ± 175.41	156.25 ± 216.64	0.2569
Mean Longest Hypo Episode (min)	236.90 ± 434.77	263.86 ± 283.88	0.2899
Any Hypoglycemia <70 mg/dL (%)	23 **(79.3%)**	20 **(90.9%)**	1.0000
Any Nocturnal Hypoglycemia (%)	19 **(65.5%)**	14 **(63.6%)**	1.0000
Any Prolonged Hypoglycemia ≥60 min (%)	18 **(62.1%)**	17 **(77.3%)**	1.0000
Any Prolonged Hypoglycemia ≥120 min (%)	14 **(48.3%)**	13 **(59.1%)**	1.0000
Any Severe Hypoglycemia <54 mg/dL (%)	13 **(44.8%)**	16 **(72.7%)**	1.0000
Any Prolonged Severe Hypo ≥120 min (%)	7 **(24.1%)**	7 **(31.8%)**	1.0000

Supplementary Figures



Supplementary Figure 1

Twenty-four-hour continuous mean interstitial glucose profiles by medication group. Mean glucose curves plotted hourly across the 24-hour cycle. The SU-exposed regimen group (red curve with shaded 95% confidence intervals) demonstrates lower mean glucose levels during the early morning hours compared to the non-SU group (blue curve with shaded 95% confidence intervals).



Supplementary Figure 2

Maximum single continuous hypoglycemia episode duration by regimen. Boxplot comparing the distribution of the longest single continuous hypoglycemia episode (minutes) recorded per patient during the wear period between SU-exposed and non-SU-exposed groups. Sulfonylurea secretagogues are associated with more prolonged, sustained Level 1 and Level 2 events.

DISCUSSION

This patient-level analysis of raw CGM time-series data from adults with T2DM on OADs reveals an alarmingly high burden of silent, nocturnal, and prolonged hypoglycemia. Over 84% of the cohort experienced at least one episode of hypoglycemia (<70 mg/dL) during a two-week wear period, and nearly twothirds (64.7%) experienced nocturnal hypoglycemia. More importantly, our study shows that hypoglycemia in these patients is not merely transient; 68.6% and 52.9% of the cohort experienced prolonged episodes lasting at least 1 hour and 2 hours, respectively. These results indicate that a substantial proportion of patients are exposed to sustained periods of biochemical hypoglycemia, which represents a major safety concern in routine clinical practice [10,12] .

Our findings challenge the traditional reliance on HbA1c as the primary measure of glycemic control [3] . We observed that patients who experienced nocturnal hypoglycemia had a significantly lower mean HbA1c than those who did not (7.19% vs. 8.37%; p = 0.0025) . This illustrates the classic clinical paradox: achieving tighter glycemic targets (indicated by a lower HbA1c) occurs at the expense of an increased risk of severe, silent hypoglycemia [4,5] . This finding aligns with the results of major cardiovascular outcome trials. In the ACCORD study, intensive glucose lowering led to increased mortality, and severe hypoglycemia was identified as a powerful marker of risk [5] . Similarly, the ADVANCE and VADT trials demonstrated that while intensive therapy reduces microvascular complications, it significantly escalates the risk of severe hypoglycemic events, which are strongly associated with adverse cardiovascular outcomes and death [6,7] .

Crucially, our study identified glycemic variability (CV) as the strongest predictor of nocturnal and prolonged hypoglycemia [3] . Patients who experienced nocturnal or prolonged hypoglycemia had a significantly higher CV than those who did not (32.54% vs. 23.12%; p = 0.0001) . Glycemic variability reflects the amplitude and frequency of glucose fluctuations throughout the day [25] . A high CV indicates rapid swings between hyperglycemia and hypoglycemia. Our findings are further supported by the strong, positive correlation observed between CV (%) and daily hypoglycemia duration (r = 0.578, p < 0.001) . This demonstrates that the amplitude of daily glucose fluctuations directly dictates the daily cumulative time spent in hypoglycemia. Our study supports the international consensus recommendation that clinical management should target not only HbA1c and average glucose, but also aim to minimize glycemic variability, maintaining a CV ≤ 36\% to protect patients from severe hypoglycemic events [1,3,16] .

We also compared the hypoglycemia profiles of patients receiving sulfonylurea (SU) -containing regimens against those on non-SU OAD regimens.

Sulfonylureas are widely used in India due to their low cost and strong glucoselowering efficacy [14,19] . However, as secretagogues, they stimulate insulin release regardless of glucose concentrations [17] . We found that SU-exposed patients had a statistically significantly lower TIR compared to the non-SU group (62.97% vs. 74.86%; p = 0.0428) . Furthermore, SU-exposed patients spent more time in hypoglycemia (mean: 156.3 vs. 103.5 minutes/day) and had longer maximum episodes (mean: 263.9 vs. 236.9 minutes) , with a higher rate of severe Level 2 hypoglycemia (72.7% vs. 44.8%) .

Although the categorical differences in nocturnal hypoglycemia rates did not reach statistical significance (likely due to the high overall glycemic volatility in both cohorts and the small sample size) , the clinical burden was markedly higher in the SU group [17] . In the diurnal block analysis, the morning block (06:00–12:00) showed a twofold higher TBR in the SU group compared to the non-SU group (14.26% vs. 7.11%) . This morning peak in hypoglycemia likely reflects the fasting state combined with the prolonged pharmacodynamics of long-acting SUs (such as glimepiride or glibenclamide) before breakfast [17,19] .

These findings have direct clinical implications for diabetes management in India and South Asia [14,16] . Given the high prevalence of prolonged and nocturnal hypoglycemia (often asymptomatic and undetected by routine fasting/postprandial finger-stick tests) , clinicians should consider early screening with CGM, even when laboratory HbA1c is within acceptable targets (<7.0% or <8.0%) [15] . Supplementary digital tools and telemedicine can aid in the early detection and management of high-risk patients [15] . For patients with high glycemic variability (CV >36%) or those receiving SU-based therapies, a de-escalation of secretagogue doses or transition to therapies with lower hypoglycemic risk (such as DPP-4 inhibitors or SGLT-2 inhibitors) should be considered to ensure patient safety [17,19] .

This study has some limitations. First, it was a retrospective, observational study conducted at a single tertiary care center, which may limit the generalizability of the findings. Second, the sample size of 51 matched patients with adequate raw data was relatively small, which limited our statistical power to detect small differences in subgroup analyses. For instance, although impaired renal function is a major driver of hypoglycemia due to reduced clearance of OADs, our comparison of eGFR categories (<90 vs. ≥90 mL/min/1.73m^2) did not reach statistical significance (Wilcoxon p = 0.315) . This lack of significance may be due to clinical confounding (such as more intensive therapy or lower baseline glucose in the normal eGFR group) and the small size of the sub-cohorts, which highlights the need for larger prospective investigations. Third, we did not have patient-reported logs of symptoms or meal times, which prevented us from differentiating symptomatic hypoglycemia from silent biochemical events. However, the strength of our study lies in the use of raw, high-resolution sensor data rather than aggregated reports, allowing for a precise characterization of hypoglycemia duration and diurnal patterns [1,11] .

CONCLUSION

Nocturnal and prolonged hypoglycemia are highly prevalent and clinically significant issues in adults with T2DM on oral therapy in India. More than half of the patients in this cohort experienced hypoglycemia episodes lasting over two hours, exposing them to major cardiac and neurological risks. Our study highlights that glycemic variability (CV) and mean glycemia are strongly correlated with hypoglycemia risk, and that sulfonylurea exposure is associated with a significantly lower Time in Range and a higher absolute burden of low glucose events. Clinicians must supplement HbA1c measurements with CGMderived metrics, particularly TIR, TBR, and CV, to identify patients at risk for silent hypoglycemia and optimize treatment regimens safely.

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