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Article

The Dawn Phenomenon Exacerbates Post-Breakfast Hyperglycemia in Type 2 Diabetes Mellitus: A Cross-Sectional Continuous Glucose Monitoring Study

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Abstract

Aims/Background: The dawn phenomenon (DP), characterized by spontaneous morning hyperglycemia in type 2 diabetes mellitus (T2DM), may exacerbate post-breakfast glucose excursions. This study investigated the association between DP and postprandial hyperglycemia, referred to as the "extended dawn phenomenon". **Methods**: In this cross-sectional study, 500 T2DM patients (glycated hemoglobin A1c (HbA1c) <7.5%) were recruited from Huadong Hospital, Fudan University between 2021 and 2023. A total of 40 participants were excluded due to incomplete data, resulting in 460 patients for final analysis. All participants underwent continuous glucose monitoring (CGM) and were stratified by the magnitude of DP (δDawn, defined as the difference between fasting glucose and nocturnal nadir glucose, with a threshold of $\geq$1.11 mmol/L). They were then matched by fasting glucose. Glycemic profiles, including peak post-breakfast glucose and time-in-range (TIR; percentage of time within the target glucose range of 3.9–10.0 mmol/L), were compared between groups. Multivariable logistic regression was used to identify determinants of post-breakfast hyperglycemia. **Results**: Despite comparable fasting glucose levels, patients with DP exhibited higher peak post-breakfast glucose (median (interquartile ranges [IQR]): 9.7 [8.2–10.7] *vs* 8.9 [8.0–10.0] mmol/L, $p = 0.02$) and reduced TIR in the overall cohort (94.1% [85.8–100.0] *vs* 100.0% [92.3–100.0], $p < 0.001$), although this difference attenuated after matching ($p = 0.133$). δDawn independently predicted post-breakfast hyperglycemia (odds ratio (OR) = 1.591, 95% confidence interval (CI): 1.283–1.993, $p < 0.001$), along with HbA1c (OR = 2.322, 95% CI: 1.530–3.566, $p < 0.001$), homeostatic model assessment for insulin resistance (HOMA-IR) (OR = 1.308, 95% CI: 1.110–1.548, $p = 0.001$), and homeostasis model assessment of β-cell function (HOMA-β) (OR = 0.990, 95% CI: 0.983–0.997, $p = 0.004$). **Conclusion**: DP contributes to prolonged postprandial hyperglycemia, underscoring its role as a potential therapeutic target for optimizing glycemic control in T2DM.

Keywords: continuous glucose monitoring; type 2 diabetes mellitus; postprandial hyperglycemia

1. Introduction

The dawn phenomenon (DP), initially described in 1981 by Schmidt *et al*. [1], refers to elevated fasting blood glucose levels or spontaneous increases in early-morning insulin requirements. This condition is now recognized as highly prevalent among diabetic populations [2]. Using continuous glucose monitoring (CGM), DP can be assessed by measuring the difference between the nocturnal nadir and fasting glucose levels [2]. The impact of DP is approximately a 0.4% increase in glycated hemoglobin A1c (HbA1c) and a 12.4 mg/dL rise in average 24-hour mean glucose concentrations [3]. Although direct evidence is limited, DP appears to contribute to elevated blood glucose levels that extend into both preprandial and postprandial phases [4,5]. Previous studies have shown that the highest peak glucose values in people with diabetes occur during the post-breakfast period [3,6,7]. In addition, post-breakfast hyperglycemia is a consistent finding in individuals with type 2 diabetes mellitus, regardless of HbA1c level, therapeutic interventions, or β-cell function status [6]. For these reasons, the post-breakfast glucose excursion in individuals with diabetes is regarded as a continuation of DP, also known as the "extended dawn phenomenon" [3,5].

Compared to DP, the "extended dawn phenomenon" may play a more critical role in postprandial glucose regulation due to its prolonged hyperglycemic effects. However, research on the "extended dawn phenomenon" remains scarce, and its underlying mechanisms are poorly characterized. Notably, there is currently limited evidence directly linking DP and post-breakfast hyperglycemia. Addressing this gap, our study hypothesizes that DP is independently associated with post-breakfast hyperglycemia and aims to investigate its potential as a target for glycemic control.

2. Methods

2.1 Study Population

This cross-sectional study enrolled 500 individuals with type 2 diabetes mellitus (T2DM), aged 27–88 years (male-to-female ratio approximately 1.17), from both inpatient endocrinology wards and outpatient metabolic clinics

at Huadong Hospital, Fudan University, during a 24-month recruitment window (2021–2023). The investigation protocol was approved by the Ethics Committee of Huadong Hospital, Fudan University (approval number: 2020K033), ensuring strict adherence to international bioethical principles outlined in the Declaration of Helsinki. All participants provided written informed consent following comprehensive disclosure of the study protocol.

2.2 Selection Criteria

Inclusion criteria were as follows: (a) ability to provide informed consent and willingness to participate; (b) diagnosis of type 2 diabetes mellitus (WHO 1999 criteria) [8]; (c) stable treatment with metformin and diet therapy for at least 3 months; (d) age $\geq$18 years and body mass index (BMI) $\geq$18.5 kg/m^2; and (e) HbA1c $<$7.5%. Exclusion criteria encompassed: (a) acute metabolic decompensation (ketoacidosis/hyperosmolar states); (b) active hypoglycemic episodes; (c) severe heart disease or other major illnesses; (d) severe liver or kidney disease; (e) confirmed or suspected diagnosis of type 1 diabetes mellitus (T1DM); and (f) unverified pharmacological combinations.

2.3 Clinical Investigations and Laboratory Examinations

Anthropometric parameters and venous blood specimens were systematically collected from all participants. Centralized laboratory analyses quantified fasting plasma glucose (FPG), HbA1c (measured by high-performance liquid chromatography), and serum insulin (exclusively for computing homeostatic model assessment (HOMA) indices: homeostatic model assessment for insulin resistance (HOMA-IR) and homeostasis model assessment of β-cell function (HOMA-β)). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Insulin resistance and β-cell function were assessed using validated computational models based on the HOMA2 algorithm (Diabetes Trials Unit, University of Oxford, Oxford, UK) [9]. To minimize circadian and dietary confounders, participants adhered to a fixed meal schedule with standardized time windows: breakfast (07:00–07:30), lunch (11:00–11:30), and dinner (17:00–17:30).

2.4 Continuous Glucose Monitoring Parameters

All subjects underwent 72-hour ambulatory glucose profiling using a blinded CGM system (iPro-2 CGM, Medtronic, MN, USA). To exclude potential artifacts associated with sensor attachment and detachment, CGM-derived data from the initial 48-hour period (days 1–2) were utilized for analysis. Mean glucose concentrations were calculated by averaging all valid measurements across both full monitoring days to ensure data robustness. Glycemic control metrics were computed as follows: time-in-range (TIR) was quantified as the percentage of 24-hour glucose readings maintained between 3.9 and 10.0 mmol/L, consistent with international consensus criteria [10].

2.5 The Dawn Phenomenon and the "Extended Dawn Phenomenon"

The magnitude of DP (δDawn) was calculated as the arithmetic difference between FPG and the nocturnal glucose nadir. A clinically significant threshold was defined as δDawn $\geq$1.11 mmol/L (20 mg/dL), in accordance with established diagnostic criteria [3,11]. Since DP can be quantified by the increment from the nocturnal nadir to fasting glucose [3,11], the magnitude of the extended dawn phenomenon (δExdawn) was defined as the peak post-breakfast glucose minus the fasting glucose level.

2.6 Grouping

Participants were categorized into two groups based on the presence or absence of DP. To isolate the impact of DP on postprandial glucose dynamics, pairwise 1:1 matching between the two groups was conducted using fasting glucose levels as the primary covariate (Fig. 1). Specifically, a propensity score matching algorithm (implemented in SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA)) was applied to match DP patients with non-DP controls, ensuring balanced baseline characteristics for quantifying post-breakfast glucose elevation. Following this process, 102 DP patients and 102 matched non-DP counterparts were retained for further analysis. Adapting an established methodology [3], the influence of DP was assessed by statistically comparing the mean peak postprandial glucose amplitudes between matched pairs.

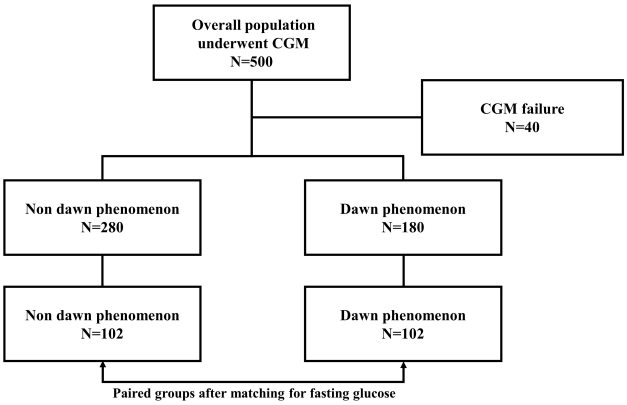

Fig. 1. Experimental workflow demonstrating participant enrollment and group allocation with matched fasting glucose. The figure was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA). CGM, continuous glucose monitoring.

2.7 Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess normality of continuous variables. As most variables were

not normally distributed, continuous data are presented as median values with interquartile ranges (IQR), and between-group comparisons were performed using the non-parametric Wilcoxon rank-sum test. Categorical variables (sex) are reported as the number of male and female participants in each group, and differences in sex distribution were evaluated using Pearson's Chi-squared test with Yates' continuity correction. All statistical analyses employed two-tailed hypothesis tests, with a significance level set at $\alpha = 0.05$.

For comparisons of mean glucose levels between the DP and non-DP groups, a false discovery rate (FDR) correction was applied to account for multiple testing across 11 hypotheses. Adjusted p-values were computed using the formula: FDR-adjusted $p = p$-value $\times$ 11/p-value rank. Bivariate correlations between glycemic variability indices (δDawn, δExdawn, TIR) were quantified using Spearman correlation coefficients. Univariate and multivariable logistic regression models were used to identify determinants of elevated postprandial glucose peaks in the overall cohort and in sex-stratified subgroups (male and female), as detailed in **Supplementary Table 1**. In the multivariable logistic regression models, sex, age, and BMI were included as covariates to control for potential confounding effects. Data visualization was performed using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA) and Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA). Additional statistical analyses were conducted in R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Clinical Characteristics and Glucose Profiles in the Overall Population

After excluding 40 individuals (8.0%) due to incomplete data (Fig. 1), the final cohort comprised 460 participants. The median (interquartile ranges [IQR]) age was 63.0 (58.0–70.0) years, with a BMI of 24.8 (22.7–26.7) kg/m^2 and an HbA1c level of 6.5% (6.1–7.0). Insulin resistance, as measured by HOMA-IR, has a median value of 3.2 (2.4–4.2), while β-cell function (measured by HOMA-β) had a median value of 68.9 (48.0–91.5). Participants exhibited a mean 24-hour glucose level of 7.2 (6.5–8.0) mmol/L, and 39.1% (180/460) displayed DP (δDawn $\geq$1.11 mmol/L). The median δDawn was 0.9 mmol/L (0.3–1.6), while δExdawn had a median value of 2.6 mmol/L (1.6–3.9). Post-breakfast hyperglycemia (>10 mmol/L) was observed in 37.4% (172/460) of participants (Table 1).

3.2 Clinical Characteristics and Glucose Profiles in the Different Groups

A total of 460 participants with valid CGM data were initially stratified into two cohorts based on the presence (N = 180) or absence (N = 280) of DP. Participants with DP had higher HOMA-IR levels [median (interquartile ranges [IQR]): 3.5 (2.5–4.5) *vs* 3.0 (2.3–4.0), $p < 0.001$] and lower HOMA-β levels [59.2 (41.8–75.0) *vs* 77.7 (56.8–103.0), $p < 0.001$] compared to the non-DP group (Table 1). Both groups subsequently underwent secondary 1:1 matching using fasting glucose levels as the primary matching variable. This process resulted in 102 well-matched participants from each group, forming a final balanced cohort of 204 individuals for comparative analysis (Fig. 1). Participants with DP presented lower nocturnal nadir glucose [5.0 (4.5–5.4) mmol/L *vs* 6.3 (5.7–7.0) mmol/L, $p < 0.001$], higher peak post-breakfast glucose [9.7 (8.2–10.7) mmol/L *vs* 8.9 (8.0–10.0) mmol/L, $p = 0.02$], higher peak post-lunch glucose [8.9 (8.1–10.7) mmol/L *vs* 8.2 (7.4–9.8), $p = 0.02$], higher δDawn levels [1.7 (1.4–2.0) mmol/L *vs* 0.5 (0.1–0.7) mmol/L, $p < 0.001$] and higher δExdawn levels [2.8 (2.0–3.7) mmol/L *vs* 2.1 (1.3–3.0) mmol/L, $p < 0.001$] than the non-DP group. The median impact of DP on peak post-breakfast glucose was 0.7 mmol/L (95% confidence interval (CI): 0.55–0.85) between the two paired groups. After adjustment for multiple testing, no significant differences in pre-lunch or pre-dinner glucose levels were observed between the groups (Table 2 and Fig. 2).

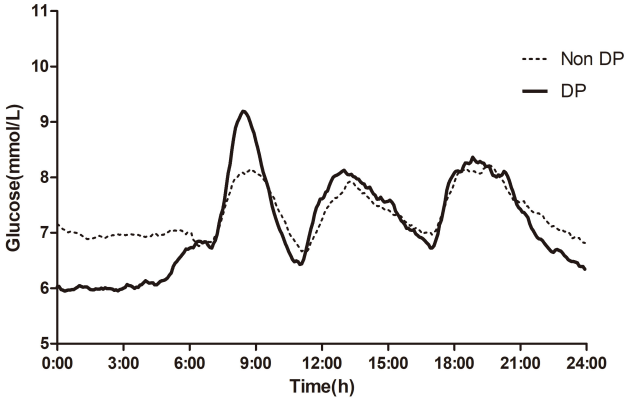

Fig. 2. Mean glucose levels across the whole day. The non-DP and DP groups were shown separately. DP, dawn phenomenon.

3.3 Correlation and Regression Analysis

The correlation analysis showed that δDawn was positively correlated with δExdawn (Spearman's rho = 0.183, $p < 0.01$) and negatively correlated with TIR (rho = –0.281, $p < 0.01$) (Fig. 3). To identify determinants of clinically significant post-breakfast glycemic excursions, a binary index was established as post-breakfast glucose >10 mmol/L, according to the recommended target set by the American Diabetes Association Professional Practice Guidelines [12]. A logistic regression model was constructed incorporating demographic (sex, age), anthropometric (BMI), and metabolic parameters (HbA1c, HOMA-IR, HOMA-β, δDawn) as covariates, with the binary post-breakfast glycemic response as the dependent variable. It is worth noting that other variables were excluded from the

Table 1. Main clinical characteristics of patients in the overall samples.

	Overall	Non-DP	DP	Z/χ^2	*p*-value
Sample size	460	280	180		
Male/female	248/212	136/144	112/68	7.68	0.006
Age (years)	63.0 (58.0–70.0)	63.0 (59.0–70.0)	62.5 (57.0–69.0)	1.11	0.267
BMI (kg/m^2)	24.8 (22.7–26.7)	24.7 (22.7–26.1)	24.9 (22.7–27.7)	–1.75	0.080
HbA1c (%)	6.5 (6.1–7.0)	6.4 (6.1–6.9)	6.6 (6.3–7.0)	–2.56	0.010
HOMA-IR	3.2 (2.4–4.2)	3.0 (2.3–4.0)	3.5 (2.5–4.5)	–3.44	<0.001
HOMA-β	68.9 (48.0–91.5)	77.7 (56.8–103.0)	59.2 (41.8–75.0)	6.13	<0.001
Mean glucose values (mmol/L)					
Nocturnal nadir	5.6 (4.8–6.3)	5.8 (5.3–6.7)	5.0 (4.5–5.9)	8.14	<0.001$^{\#}$
Fasting	6.7 (5.9–7.4)	6.3 (5.6–7.0)	7.2 (6.5–8.0)	–8.33	<0.001$^{\#}$
Peak post-breakfast	9.4 (8.1–10.8)	8.9 (7.8–10.3)	10.0 (8.6–11.4)	–5.72	<0.001$^{\#}$
Pre-lunch	6.8 (5.9–7.9)	6.7 (5.9–7.7)	6.9 (5.9–8.1)	–1.96	0.049$^{\#}$
Peak post-lunch	8.7 (7.5–10.1)	8.1 (7.3–9.5)	9.3 (8.2–10.9)	–6.04	<0.001$^{\#}$
Pre-dinner	6.8 (6.0–8.2)	6.7 (5.9–8.0)	7.1 (6.1–8.4)	–2.29	0.022$^{\#}$
Peak post-dinner	8.9 (7.8–10.3)	8.6 (7.5–9.9)	9.3 (8.2–11.1)	–4.35	<0.001$^{\#}$
24 h mean glucose	7.2 (6.5–8.0)	7.0 (6.3–7.9)	7.4 (6.8–8.0)	–3.61	<0.001$^{\#}$
TIR (%)	98.3 (89.6–100.0)	100.0 (92.3–100.0)	94.1 (85.8–100.0)	4.68	<0.001$^{\#}$
δDawn (mmol/L)	0.9 (0.3–1.6)	0.5 (0.1–0.8)	1.8 (1.4–2.6)	–18.11	<0.001$^{\#}$
δExdawn (mmol/L)	2.6 (1.6–3.9)	2.4 (1.4–3.8)	2.7 (1.8–4.0)	–1.90	0.057

Continuous variables are expressed as median (interquartile ranges), and categorical data (sex) are reported as counts (sample size).

p-value indicates the statistical significance of differences between non-DP and DP groups, calculated using the Wilcoxon rank-sum test for continuous variables and a Pearson's Chi-squared test with Yates' continuity correction for sex. # denotes statistical significance after multiple testing adjustment.

DP, dawn phenomenon; HOMA-IR, homeostatic model assessment for insulin resistance; HbA1c, glycated hemoglobin A1c; HOMA-β, homeostasis model assessment of β-cell function; TIR, time-in-range; δDawn, the magnitude of DP; δExdawn, the magnitude of the extended dawn phenomenon; BMI, body mass index.

model to prevent over-adjustment and statistical robustness. Regression analysis showed that HbA1c [odds ratio (OR) (95% CI): 2.322 (1.530–3.566), $p < 0.001$], HOMA-IR [OR (95% CI): 1.308 (1.110–1.548), $p = 0.001$], HOMA-β [OR (95% CI): 0.990 (0.983–0.997), $p = 0.004$] and δDawn [OR (95% CI): 1.591 (1.283–1.993), $p < 0.001$] were independently associated with increased post-breakfast glucose levels (Table 3). In male and female groups, both HbA1c and δDawn remained significant indicators of post-breakfast glucose excursions in males [HbA1c: OR (95% CI): 1.825 (1.053–3.226), $p = 0.035$; δDawn: OR (95% CI): 1.681 (1.253–2.296)], $p = 0.001$ and females [HbA1c: OR (95% CI): 3.235 (1.694–6.380), $p < 0.001$; δDawn: OR (95% CI): 1.452 (1.058–2.028), $p = 0.024$].

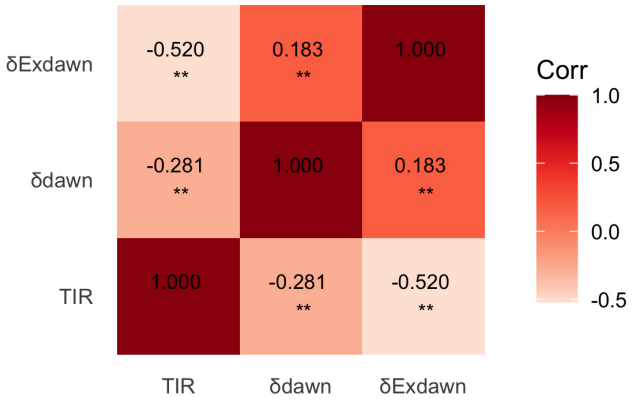

Fig. 3. Heatmap visualizing Spearman correlations among TIR, δDawn, and δExdawn. Coefficients are labeled; significance level **: $p < 0.01$. TIR, time-in-range; δDawn, the magnitude of DP; δExdawn, the magnitude of the extended dawn phenomenon.

4. Discussion

Our findings supported the existence of the "extended dawn phenomenon". First, even when fasting glucose was matched, participants with DP had higher peak post-breakfast glucose and greater δExdawn levels compared to those without DP. Second, glucose increments attributed to DP persisted into the postprandial period (median Δ = 0.7 mmol/L). Third, logistic regression analysis identified δDawn as an independent predictor associated with increased post-breakfast glucose. These results indicate that the impact of DP on blood glucose extends beyond fasting and also affects post-breakfast glucose levels.

Emerging evidence suggests that the mechanisms underlying DP in diabetes are multifactorial, including: (1)

Table 2. Main clinical characteristics of patients of non-DP and DP groups with matched fasting glucose.

	Overall	Non-DP	DP	Z/χ^2	*p*-value
Sample size	204	102	102		
Male/female	104/100	42/60	62/40	7.08	0.008
Age (years)	63.0 (58.0–71.0)	63.0 (59.2–70.8)	61.0 (56.2–70.8)	1.59	0.112
BMI (kg/m^2)	24.8 (22.8–27.1)	24.5 (22.7–26.1)	24.9 (22.9–28.8)	–1.56	0.119
HbA1c (%)	6.4 (6.0–6.8)	6.4 (6.0–6.8)	6.4 (6.1–6.8)	–0.59	0.556
HOMA-IR	3.2 (2.4–4.1)	3.1 (2.6–4.0)	3.3 (2.4–4.3)	–0.44	0.663
HOMA-β	68.0 (50.6–83.2)	69.0 (53.6–81.5)	64.6 (46.7–90.0)	0.41	0.684
Mean glucose values (mmol/L)					
Nocturnal nadir	5.5 (5.0–6.3)	6.3 (5.7–7.0)	5.0 (4.5–5.4)	10.30	<0.001$^{\#}$
Fasting	6.9 (6.1–7.3)	6.9 (6.1–7.3)	6.9 (6.1–7.3)	0.00	1
Peak post-breakfast	9.2 (8.1–10.3)	8.9 (8.0–10.0)	9.7 (8.2–10.7)	–2.60	0.020$^{\#}$
Pre-lunch	6.7 (5.8–7.5)	6.8 (5.9–7.7)	6.6 (5.6–7.4)	2.08	0.070
Peak post-lunch	8.7 (7.8–10.0)	8.2 (7.4–9.8)	8.9 (8.1–10.7)	–2.70	0.020$^{\#}$
Pre-dinner	6.7 (6.0–7.9)	6.7 (6.0–8.1)	6.6 (5.8–7.9)	1.13	0.284
Peak post-dinner	9.1 (8.0–10.7)	8.8 (7.5–10.4)	9.1 (8.2–10.7)	–1.82	0.108
24-hour mean glucose	7.1 (6.5–7.8)	7.2 (6.6–8.0)	7.0 (6.5–7.5)	1.52	0.156
TIR (%)	91.1 (79.9–100.0)	89.6 (79.9–97.7)	93.1 (80.2–100.0)	–1.64	0.133
δDawn (mmol/L)	1.1 (0.5–1.7)	0.5 (0.1–0.7)	1.7 (1.4–2.0)	–12.34	<0.001$^{\#}$
δExdawn (mmol/L)	2.6 (1.4–3.4)	2.1 (1.3–3.0)	2.8 (2.0–3.7)	–3.30	<0.001$^{\#}$

Continuous variables are expressed as median (interquartile ranges), and categorical data (sex) are reported as counts (sample size).

p-value indicates the statistical significance of differences between non-DP and DP groups, calculated using the Wilcoxon rank-sum test for continuous variables and a Pearson's Chi-squared test with Yates' continuity correction for sex. # denotes statistical significance after multiple testing adjustment.

DP, dawn phenomenon; HOMA-IR, homeostatic model assessment for insulin resistance; HbA1c, glycated hemoglobin A1c; HOMA-β, homeostasis model assessment of β-cell function; TIR, time-in-range; δDawn, the magnitude of DP; δExdawn, the magnitude of the extended dawn phenomenon.

progressive β-cell dysfunction [4]; (2) growth hormone-mediated insulin resistance [13]; (3) circadian-driven elevations in insulin-like growth factor binding protein-1 during early morning hours [14]; (4) dyssynchrony of Gamma-Aminobutyric Acid-ergic (GABAergic) neuronal nuclear receptor subfamily 1 group D member 1 (*REV-ERB*α) oscillations, a core circadian regulator [15,16]; and (5) sleep architecture disturbances compounded by circadian rhythm dysregulation [7]. The mechanism of the extended dawn phenomenon may be similar to DP. In our study, both HOMA-IR and HOMA-β were significantly and independently correlated with increased post-breakfast glucose, which indicates that increased insulin resistance and the decreased β-cell function contribute substantially to post-breakfast hyperglycemia. Additionally, a previous study suggested that the administration of growth hormone in the early evening can reduce insulin sensitivity 16 hours later [13], implicating growth hormone in the rise of post-breakfast glucose.

Monnier *et al*. [3], quantified the contribution of DP to chronic hyperglycemia, reporting a 0.4% increase in HbA1c and a 12.4 mg/dL increase in 24-hour mean glucose. Our data corroborate this metabolic burden, showing higher HbA1c (6.6% *vs* 6.4%) and 24-hour mean glucose (7.4 *vs* 7.0 mmol/L) in the DP compared to the non-DP group (Table 1). CGM revealed a dual circadian effect: DP participants exhibited 1.1 mmol/L higher post-breakfast hyperglycemia (10.0 *vs* 8.9 mmol/L) and a 5.9% absolute reduction in TIR (94.1% *vs* 100.0%), equivalent to 89 fewer daily minutes within the target range (3.9–10.0 mmol/L). This aligns with Monnier's hypothesis that morning glucose surges may persist beyond fasting phases; our use of CGM provides higher temporal resolution, directly linking nocturnal glucose increments to postprandial peaks. Notably, while Monnier's cohort focused on HbA1c-driven glucose exposure, our data delineate a metabolic gradient: DP participants demonstrated 16.7% higher insulin resistance (HOMA-IR 3.5 *vs* 3.0) and 23.8% worse β-cell function (HOMA-β 59.2 *vs* 77.7) compared to non-DP controls (Table 1). This dyad drives a cycle in which elevated nocturnal glucose increments (δDawn 1.8 *vs* 0.5 mmol/L) impair morning insulin sensitivity, resulting in a 1.591-fold increased risk of post-breakfast hyperglycemia per 1 mmol/L rise in δDawn (OR = 1.591, 95% CI: 1.283–1.993; Table 3). In fasting glucose-matched cohorts (Table 2), DP participants maintained significantly higher postprandial peaks (peak post-breakfast: 9.7 *vs* 8.9 mmol/L; peak post-lunch: 8.9 *vs* 8.2 mmol/L) despite com-

Table 3. Associated factors of increased post-breakfast glucose by logistic regression analysis.

Variable	OR (95% CI)	*p*-value	Male		Female	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
HbA1c	2.322 (1.530–3.566)	<0.001	1.825 (1.053–3.226)	0.035	3.235 (1.694–6.380)	<0.001
HOMA-IR	1.308 (1.110–1.548)	0.001	1.392 (1.100–1.778)	0.007	1.238 (0.980–1.573)	0.075
HOMA-β	0.990 (0.983–0.997)	0.004	0.988 (0.978–0.997)	0.011	0.992 (0.981–1.002)	0.121
δDawn	1.591 (1.283–1.993)	<0.001	1.681 (1.253–2.296)	0.001	1.452 (1.058–2.028)	0.024
Age	1.010 (0.990–1.030)	0.338	1.011 (0.986–1.038)	0.401	1.012 (0.981–1.045)	0.461
BMI	0.944 (0.881–1.009)	0.095	0.980 (0.884–1.085)	0.694	0.912 (0.825–1.001)	0.060
Sex	1.106 (0.717–1.706)	0.647				

δDawn, the magnitude of DP; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; CI, confidence interval. OR, odds ratio.

parable HbA1c (6.4% *vs* 6.4%). This dissociation suggests that dawn phenomenon-induced hyperglycemia operates through meal-responsive pathways rather than through chronic exposure. The difference in TIR was decreased and not statistically significant in this matched cohort (93.1% *vs* 89.6%), suggesting that normalization of fasting glucose may partially mask the circadian rhythm-driven worsening of TIR. Nevertheless, DP participants exhibited significantly lower TIR compared to non-DP controls (median 94.1% *vs* 100.0%), with δDawn levels 1.3 mmol/L higher in the DP group (1.8 *vs* 0.5 mmol/L; Table 1). These findings indicate a potential dose-response relationship between nocturnal glucose increments and TIR deterioration. The observed 1.591-fold increased risk of post-breakfast hyperglycemia per 1 mmol/L δDawn rise may mechanistically contribute to TIR deterioration, as elevated postprandial glucose directly reduces TIR. Elevated postprandial blood glucose (PPG) is strongly associated with the development and progression of diabetic complications. Extensive evidence demonstrated that poor PPG control constitutes a critical risk factor for both microvascular and macrovascular complications in diabetes [17,18], including diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease. Similarly, suboptimal TIR control has been extensively documented as a significant contributor to these complications in clinical studies [19–24]. These findings highlight the importance of stringent management of both PPG and TIR, particularly in addressing clinical challenges linked to DP.

Notably, our stratified analysis revealed sex-specific differences in glycemic regulation pathways. As demonstrated in Table 3, female participants exhibited a stronger correlation between HbA1c elevation and post-breakfast hyperglycemia (OR = 3.235 *vs* 1.825 in males), whereas male participants showed greater susceptibility to dawn phenomenon-mediated glucose increments (δDawn OR = 1.681 *vs* 1.452 in females). This sexual dimorphism may be attributable to fundamental differences in endocrine physiology. Estrogen has been shown to enhance insulin sensitivity by modulating hepatic gluconeogenesis and peripheral glucose uptake [25]. Specifically, activation of the Estrogen Receptor alpha-Protein Kinase B-Forkhead box protein O1 (ERα-Akt-Foxo1) signaling pathway is a key mechanism by which estrogen controls glucose homeostasis [26], potentially mitigating the impact of nocturnal glucose surges in premenopausal women. Conversely, the fat mass and obesity-associated gene (*FTO*) rs9939609 T/A polymorphism appears to interact synergistically with lifestyle factors, particularly high saturated fat consumption, to promote visceral adipose tissue (VAT) accumulation in adult males, as demonstrated in longitudinal cohort analyses [27]. Increased VAT exacerbates insulin resistance through multiple interrelated mechanisms, aggravating circadian dysregulation of hepatic gluconeogenesis and skeletal muscle glucose uptake. This metabolic derangement ultimately impairs glycemic stability in insulin-resistant individuals, increasing susceptibility to dawn phenomenon-associated postprandial glycemic excursions and reducing TIR. The observed sex disparity in baseline characteristics (Table 1) provides additional context, with the DP group displaying a higher proportion of males (62.2% *vs* 48.6% in the non-DP group). Emerging evidence also suggests that testosterone may augment growth hormone pulsatility [28], potentially mediating DP pathophysiology through this mechanism.

Postprandial hyperglycemia is a hallmark of diabetes in China, with nationwide data indicating that 46.6% of newly diagnosed T2DM patients exhibit isolated postprandial hyperglycemia (50.2% in females *vs* 44.1% in males) [29]. In our cohort of well-controlled patients (HbA1c <7.5%), post-breakfast glucose >10 mmol/L persisted in 37.4%, consistent with previous reports that post-meal variability constitutes the major component of glycemic burden despite controlled fasting levels [30]. DP has emerged as a promising therapeutic target for optimizing glycemic control, given the suboptimal efficacy demonstrated by current therapeutic modalities—including lifestyle interventions (e.g., caloric restriction therapy), conventional pharmacological agents (e.g., insulin sensitizers and secretagogues), and even intensive insulin regimens—across di-

verse treatment algorithms [3,4,31–33]. While basal insulin and pre-breakfast exercise may mitigate the effects of DP [5,34,35], their efficacy requires further validation. Our sex-stratified analyses revealed distinct patterns of glycemic regulation: females exhibited stronger associations between HbA1c and postprandial hyperglycemia (OR = 3.235 *vs* 1.825 in males), whereas males were more susceptible to dawn phenomenon-driven excursions (δDawn OR = 1.681 *vs* 1.452 in females). These differences likely reflect underlying hormonal and body composition profiles (e.g., estrogen-mediated enhancement of insulin sensitivity in females *vs* androgen-driven visceral adiposity in males). Clinically, these findings suggest that prioritizing HbA1c control ($<$6.5%) in females and implementing dawn phenomenon-targeted interventions (e.g., bedtime insulin or exercise) in males may optimize glycemic outcomes. While these findings highlight DP as a potential therapeutic target, the observational design of our study precludes causal inference. Future research should investigate the role of hormonal modulation (e.g., menopausal status, testosterone levels) in glycemic regulation and conduct interventional trials to determine whether mitigating nocturnal glucose surges can improve TIR and postprandial glycemic control.

5. Conclusion

This cross-sectional study demonstrates that DP significantly exacerbates post-breakfast hyperglycemia in individuals with type 2 diabetes mellitus, independent of fasting glucose levels. Key metabolic determinants (e.g., HbA1c, insulin resistance, β-cell dysfunction, δDawn)—independently predicted heightened postprandial glycemic excursions. Notably, sex differences were observed: females exhibited a higher risk associated with elevated HbA1c, while males were more susceptible to δDawn, suggesting divergent therapeutic priorities. Circadian dysregulation underlying the DP prolongs postprandial hyperglycemia and reduces TIR, underscoring the clinical relevance of targeting nocturnal glucose increments to optimize glycemic control.

Key Points

- The dawn phenomenon (DP) significantly exacerbates post-breakfast hyperglycemia in type 2 diabetes mellitus, with affected patients exhibiting 1.1 mmol/L higher glucose peaks and a 5.9% reduction in TIR, independent of fasting glucose levels.
- The magnitude of DP (δDawn; OR = 1.591 per 1 mmol/L), HbA1c, insulin resistance and β-cell dysfunction independently predict postprandial hyperglycemia, highlighting the synergistic roles of nocturnal glucose surges, insulin resistance, and β-cell failure.
- Females demonstrate a stronger association between HbA1c and postprandial hyperglycemia risk (OR = 3.235 *vs* 1.825 in males), whereas males exhibit greater susceptibility to DP-driven excursions (δDawn OR = 1.681 *vs* 1.452 in females), supporting sex-tailored therapeutic approaches.
- Targeting DP with interventions such as bedtime insulin or exercise may optimize glycemic control by reducing postprandial hyperglycemia and improving TIR, thereby lowering the risk of diabetic complications.
- Longitudinal and interventional studies are needed to confirm a causal association between nocturnal glucose suppression and improved TIR, as well as to explore the role of hormonal modulation (e.g., estrogen/testosterone) for precision diabetes management.

Availability of Data and Materials

All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

WT and YH designed the study. WT and JZ acquired the data. WT, CJ and XT interpreted the data. WT drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The investigation protocol received ethical approval from the Ethics Committee of Huadong Hospital, Fudan University (approval number: 2020K033). The study followed the ethical guidelines outlined in the Declaration of Helsinki and the principles of confidentiality. All participants provided written informed consent following comprehensive disclosure of the study protocol.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM51727.

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