



Impact of Microvascular Complications on Glycemic Outcomes in People with Type 2 Diabetes Observing Ramadan Fasting

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Abstract

Background Fasting during Ramadan may increase the risk of hypoglycemia and hyperglycemia in people with type 2 diabetes mellitus (T2D). This study investigated whether the presence of microvascular complications increases the risk of such events during Ramadan fasting.

Materials and Methods This cross-sectional analysis analyzed data on demographics, neuropathy, nephropathy, retinopathy, and fasting-related glycemic events from the 2020 and 2022 Diabetes and Ramadan Global Surveys of adults with T2D.

Results Of 12,529 individuals, 10,707 (85.5%) fasted during Ramadan. Of those, 15.5% experienced hypoglycemia and 15.1% hyperglycemia, with 9.2 and 3.4% breaking their fast due to each, respectively, and 1.8 and 0.9% experienced severe hypo- and hyperglycemia requiring medical intervention, respectively. Having ≥ 1 microvascular complication more than doubled the odds of daytime hypoglycemia (odds ratio [OR] = 2.16–2.31, $p \leq 0.0001$) and hyperglycemia (OR = 2.00–2.43; all $p \leq 0.0001$). The odds of breaking the fast due to hypoglycemia (OR = 2.25, 2.84, and 3.13) or hyperglycemia (OR = 2.09, 2.71, and 3.46) increased progressively with the number of microvascular complications (all $p \leq 0.0001$). The odds of severe hypoglycemia requiring medical intervention (OR = 1.47 with 1, 1.82 with 2, and 3.50 with three complications; $p \leq 0.05$ –0.0001) or severe hyperglycemia (OR = 2.94, 3.69, and 6.49, respectively; all $p \leq 0.0001$) during Ramadan fasting also increased with the burden of

Keywords

- diabetic nephropathy
- diabetic neuropathy
- diabetic retinopathy
- hyperglycemia
- hypoglycemia
- microvascular complications
- Ramadan fasting
- risk assessment
- type 2 diabetes

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microvascular complications. Neuropathy was consistently associated with increased odds of all outcomes (all $p \leq 0.0001$) apart from severe hypoglycemia ($p = 0.67$).

Conclusion The presence and overall burden of microvascular complications increase the risk of adverse glycemic events during Ramadan fasting in people with T2D. Pre-Ramadan risk stratification should consider complication burden, especially neuropathy.

Introduction

Fasting during Ramadan for individuals with type 2 diabetes mellitus (T2D) can be challenging, with a higher risk of both hypoglycemia and hyperglycemia due to altered meal patterns, prolonged fasting hours, and adjustments in medication timing. According to the Diabetes and Ramadan (DAR) Global Surveys conducted in 2020 and 2022, approximately 85% of participants with T2D fasted during Ramadan.^{1,2} While more than half completed the entire fasting month, around 15% reported experiencing hypoglycemia or hyperglycemia during fasting.^{1,2}

Microvascular complications may increase the risk of adverse glycemic events during fasting. According to the 2022 DAR survey, the prevalence of reported microvascular complications included diabetic neuropathy (20.7%), retinopathy (14.3%), or nephropathy (10.3%).² Diabetic autonomic neuropathy, in particular, may impair the warning signs of low blood glucose and blunt the counterregulatory responses.³ Nephropathy can reduce the clearance of glucose-lowering medication and increase the risk of hypoglycemia.⁴ While diabetic retinopathy per se does not have a mechanistic link to adverse glycemic events, it frequently coexists with other microvascular complications.⁵

Current guidelines consider individuals with diabetic nephropathy at higher risk during Ramadan and recommend individualized assessment or exemption from fasting.^{6–8} However, there is limited evidence on the impact of other microvascular complications on adverse glycemic outcomes during Ramadan. This study assessed whether the presence and number of reported microvascular complications were associated with the likelihood of fasting during Ramadan, risk of daytime hypoglycemia, hyperglycemia, fasting interruption, and severe glycemic events requiring medical attention.

Materials and Methods

Study Design and Participants

This was a cross-sectional analysis of pooled data from the DAR Global Surveys conducted in 2020 and 2022, which aimed to evaluate the characteristics, care practices, and outcomes of individuals with T2D during Ramadan. The original surveys recruited adult Muslim patients with T2D who attended routine diabetes care in participating centers across multiple countries in Southeast Asia, the Indian Subcontinent, the Gulf region, the Middle East, Turkey, North

Africa, Sub-Saharan Africa, and the United Kingdom. The study received ethics approval from the Dubai Health Authority (DHA: DSREC-04/2002_29).

Eligible participants were interviewed by their attending physicians using a standardized, prevalidated questionnaire. Data collection occurred within 10 weeks after Ramadan in 2020 and 2022. Informed consent was obtained from all participants. As part of the original study protocol, ethical approvals were secured locally in each participating country.

Data Collection

Based on clinical records, data were collected on demographics, diabetes duration, HbA1c, and the presence of neuropathy, nephropathy, and retinopathy. Fasting-related outcomes included self-reported daytime hypoglycemia and hyperglycemia, breaking the fast due to either, and events requiring emergency department visits or hospitalization. Hypoglycemia was based on the reporting of classical symptoms, while hyperglycemia was defined as blood glucose >300 mg/dL. The cumulative burden of microvascular complications was assessed (0, 1, 2, or 3 complications).

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Logistic regression was performed to examine the association between microvascular complications and each of the following outcomes: (1) daytime hypoglycemia, (2) hyperglycemia, (3) breaking the fast due to glycemic events, and (4) severe hypoglycemia or hyperglycemia requiring medical attention. Odds ratios (ORs) and adjusted odds ratios (AORs) were reported with 95% confidence intervals (CIs). Models were adjusted for age, sex, diabetes duration, HbA1c, hypertension, hyperlipidemia, macrovascular disease, diabetic foot problems, and insulin and sulfonylurea therapies. Multiple linear regression analysis was used to assess the association between the number of microvascular complications and the number of days fasted. A two-sided p -value ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics version 30.

Results

Demographics and Clinical Characteristics

A total of 12,529 participants with T2D participated in the survey during Ramadan 2020 and 2022, with 10,707 (85.5%) fasting during Ramadan. Of those who fasted, the mean age

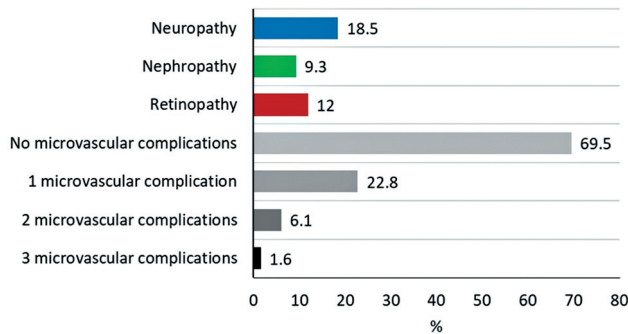


Fig. 1 Prevalence of individual and combined microvascular complications among participants with type 2 diabetes mellitus during Ramadan.

was 54.3 ± 11.4 years, 52.0% were female, the duration of diabetes was 9.4 ± 7.1 years, and their HbA1c was $8.3 \pm 1.8\%$ (67 ± 20 mmol/mol).

Overall, 15.5% of participants reported experiencing daytime hypoglycemia, of whom 9.2% broke their fast due to hypoglycemia, and 1.8% experienced severe hypoglycemia requiring medical attention. Hyperglycemia occurred in 15.1% of participants, of whom 3.4% disrupted their fast due to hyperglycemia, and 0.9% required medical attention for severe hyperglycemia.

The prevalence of neuropathy, nephropathy, and retinopathy was 18.5, 9.3, and 12.0%, respectively ($\rightarrow$ Fig. 1). Additionally, 69.5% had no microvascular complications, 22.8% had one, 6.1% had two, and 1.6% had all three ($\rightarrow$ Fig. 2). Hypertension and hyperlipidemia were present in 47.1 and 41.5% of the cohort, respectively, while macrovascular complications and diabetic foot problems were reported in 5.9 and 2.7%.

Association of Microvascular Complications with Fasting

The odds of fasting were 14% lower in those with one microvascular complication (OR = 0.86, 95% CI: 0.75–0.98, $p = 0.030$), 54% lower in those with two complications (OR = 0.46, 95% CI: 0.37–0.58, $p \leq 0.0001$), and 68% lower in those with three complications (OR = 0.32, 95% CI: 0.24–0.43, $p \leq 0.0001$). With more microvascular complications, participants fasted 0.7 fewer days (95% CI: -0.9 to -0.6 , $p \leq 0.0001$).

Daytime Hypoglycemia

The odds of experiencing daytime hypoglycemia were more than twice as high in individuals with one (116% higher; OR = 2.16, 95% CI: 1.92–2.43, $p \leq 0.0001$), two (131% higher; OR = 2.31, 95% CI: 1.90–2.80, $p \leq 0.0001$), or three (119% higher; OR = 2.19, 95% CI: 1.53–3.14, $p \leq 0.0001$) microvascular complications compared with those with none. However, the increase in risk was not associated with an increasing burden of microvascular complications. When evaluating individual microvascular complications in the adjusted model, neuropathy had the highest association with daytime hypoglycemia (AOR = 1.75, 95% CI: 1.52–2.00, $p \leq 0.0001$), followed by nephropathy (AOR = 1.27, 95% CI: 1.05–1.53, $p \leq 0.01$), while there was no significant association with retinopathy ($p = 0.92$) ($\rightarrow$ Fig. 3 and $\rightarrow$ Table 1).

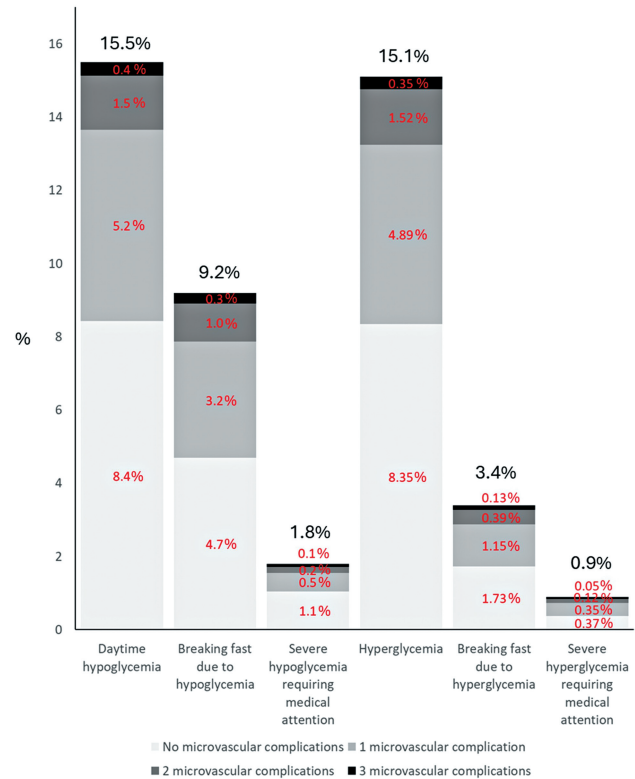


Fig. 2 Prevalence of adverse glycemic events during Ramadans by number of microvascular complications.

Breaking Fast due to Hypoglycemia

The odds of breaking the fast due to hypoglycemia during Ramadan were significantly 125% higher in individuals with one microvascular complication (OR = 2.25, 95% CI: 1.94–2.60, $p \leq 0.0001$), 184% higher with two complications (OR = 2.84, 95% CI: 2.27–3.56, $p \leq 0.0001$), and 213% higher with three complications (OR = 3.13, 95% CI: 2.11–4.65, $p \leq 0.0001$), compared with those with none, with the risk increasing progressively with more complications. In the adjusted model evaluating individual complications, neuropathy showed the highest association with breaking the fast due to hypoglycemia (AOR = 1.64, 95% CI: 1.39–1.93, $p \leq 0.0001$), followed by nephropathy (AOR = 1.37, 95% CI: 1.10–1.70, $p \leq 0.01$), but not with retinopathy ($p = 0.12$) ($\rightarrow$ Fig. 3 and $\rightarrow$ Table 1).

Severe Hypoglycemia

The odds of experiencing severe hypoglycemia requiring medical attention were significantly 47% higher in individuals with one microvascular complication (OR = 1.47, 95% CI: 1.06–2.04, $p \leq 0.05$), 82% higher with two complications (OR = 1.82, 95% CI: 1.10–3.00, $p \leq 0.05$), and 250% higher with three complications (OR = 3.50, 95% CI: 1.75–7.02, $p \leq 0.0001$), compared with those with none. In the adjusted model, only retinopathy remained significantly associated with the outcome (AOR = 1.77, 95% CI: 1.19–2.65, $p \leq 0.01$), while neuropathy ($p = 0.67$) and nephropathy ($p = 0.88$) were not independently associated with severe hypoglycemia requiring medical attention ($\rightarrow$ Fig. 3 and $\rightarrow$ Table 1).

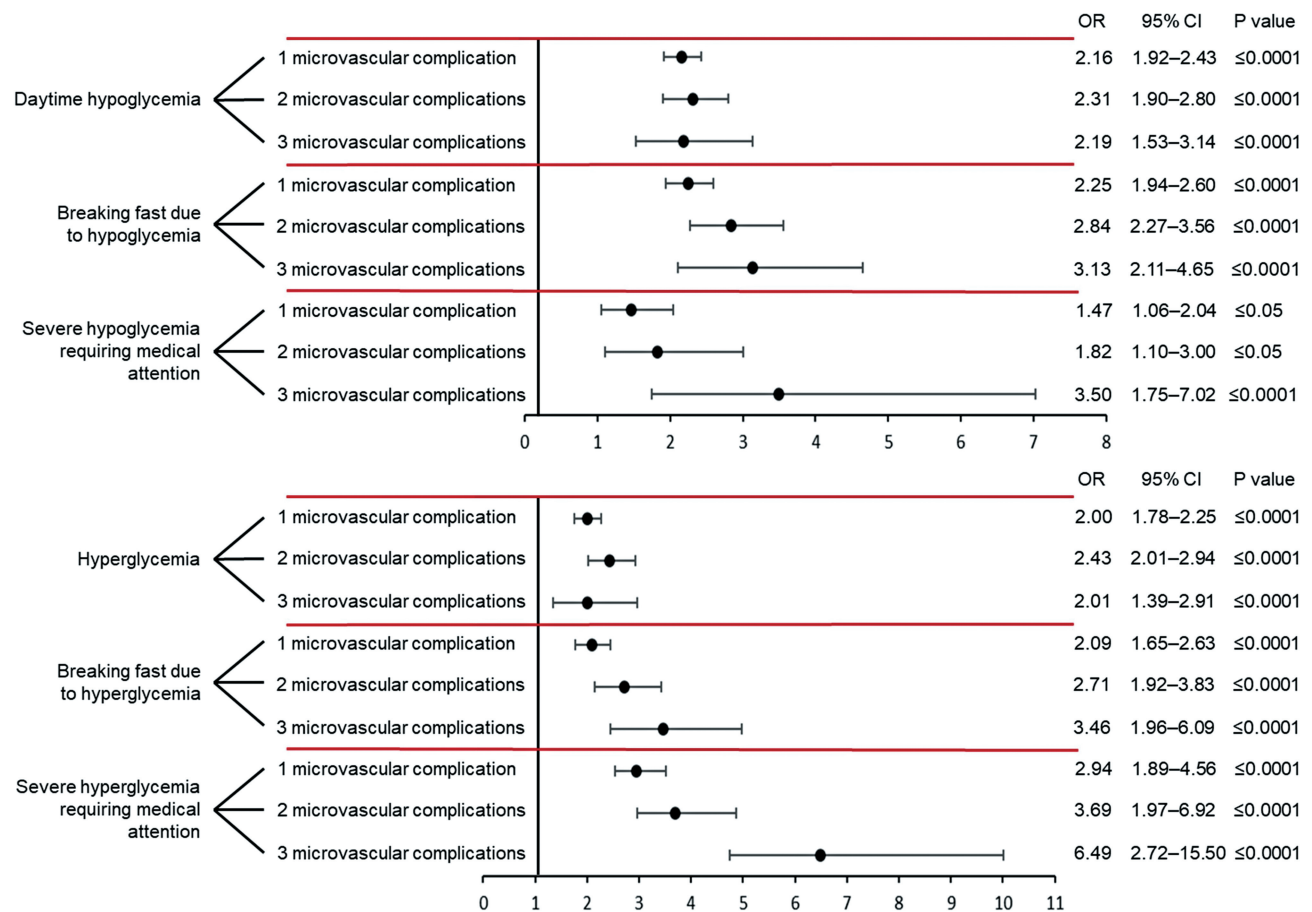


Fig. 3 Association of the burden of microvascular complications with hypo- and hyperglycemia-related outcomes during Ramadan.

Table 1 Association of microvascular complications with hypoglycemia-related outcomes during Ramadan

Outcome	Risk factors	AOR	95% CI	p-Value
Daytime hypoglycemia	Neuropathy	1.75	1.52–2.00	≤0.0001
	Nephropathy	1.27	1.05–1.53	≤0.01
	Retinopathy	0.99	0.83–1.18	0.92
Breaking fast due to hypoglycemia	Neuropathy	1.64	1.39–1.93	≤0.0001
	Nephropathy	1.37	1.10–1.70	≤0.01
	Retinopathy	1.18	0.96–1.44	0.12
Severe hypoglycemia requiring medical attention	Neuropathy	0.92	0.63–1.35	0.67
	Nephropathy	1.04	0.63–1.70	0.88
	Retinopathy	1.77	1.19–2.65	≤0.01

Bold values indicate statistically significant associations ($P < 0.05$).

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

Hyperglycemia

The odds of experiencing hyperglycemia were twofold higher in individuals with one (100% higher; OR=2.00, 95% CI: 1.78–2.25, $p \leq 0.0001$), two (143% higher; OR=2.43, 95% CI: 2.01–2.94, $p \leq 0.0001$), or three (101% higher; OR=2.01, 95% CI: 1.39–2.91, $p \leq 0.0001$) microvascular complications compared with those with none. In the adjusted model, both neuropathy (AOR=1.62, 95% CI: 1.41–1.87, $p \leq 0.0001$) and retinopathy (AOR=1.44, 95%

CI: 1.21–1.71, $p \leq 0.0001$) were significantly associated with increased odds of hyperglycemia, whereas nephropathy was associated with a decreased odds (AOR=0.71, 95% CI: 0.57–0.87, $p \leq 0.01$) (►Fig. 3 and ►Table 2).

Breaking Fast due to Hyperglycemia

The odds of breaking the fast due to hyperglycemia were significantly 109% higher in individuals with one microvascular complication (OR=2.09, 95% CI: 1.65–2.63,

Table 2 Association of microvascular complications with hyperglycemia-related outcomes during Ramadan

Outcome	Risk factors	AOR	95% CI	p-Value
Hyperglycemia	Neuropathy	1.62	1.41–1.87	≤0.0001
	Nephropathy	0.71	0.57–0.87	≤0.01
	Retinopathy	1.44	1.21–1.71	≤0.0001
Breaking fast due to hyperglycemia	Neuropathy	2.22	1.73–2.84	≤0.0001
	Nephropathy	1.09	0.75–1.57	0.65
	Retinopathy	1.10	0.79–1.53	0.57
Severe hyperglycemia requiring medical attention	Neuropathy	2.88	1.84–4.52	≤0.0001
	Nephropathy	1.94	1.10–3.43	≤0.05
	Retinopathy	0.86	0.47–1.57	0.62

Bold values indicate statistically significant associations ($P < 0.05$).

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

$p \leq 0.0001$), 171% higher with two complications (OR = 2.71, 95% CI: 1.92–3.83, $p \leq 0.0001$), and 246% higher with three complications (OR = 3.46, 95% CI: 1.96–6.09, $p \leq 0.0001$), compared with those with none. In the adjusted model, neuropathy remained significantly associated with breaking the fast due to hyperglycemia (AOR = 2.22, 95% CI: 1.73–2.84, $p \leq 0.0001$), while nephropathy ($p = 0.65$) and retinopathy ($p = 0.57$) were not independently associated with breaking the fast due to hyperglycemia (► Fig. 3 and ► Table 2).

Severe Hyperglycemia

The odds of experiencing severe hyperglycemia requiring medical attention were significantly 194% higher in individuals with one microvascular complication (OR = 2.94, 95% CI: 1.89–4.56, $p \leq 0.0001$), 269% higher with two complications (OR = 3.69, 95% CI: 1.97–6.92, $p \leq 0.0001$), and 549% higher with three complications (OR = 6.49, 95% CI: 2.72–15.50, $p \leq 0.0001$), compared with those with none. In the adjusted model, both neuropathy (AOR = 2.88, 95% CI: 1.84–4.52, $p \leq 0.0001$) and nephropathy (AOR = 1.94, 95% CI: 1.10–3.43, $p \leq 0.05$) were independently associated with a significantly higher odds of severe hyperglycemia requiring medical attention, while retinopathy ($p = 0.62$) was not significantly associated with the outcome (► Fig. 3 and ► Table 2).

Discussion

This multicenter study of over 12,500 individuals with T2D is the first large-scale investigation to provide real-world evidence on the impact of microvascular complications on clinical outcomes and glycemic events during Ramadan fasting. Current fasting risk calculators account only for nephropathy, not retinopathy or neuropathy, and none assess the cumulative burden of microvascular complications on fasting ability or glycemic safety.⁶ Our findings show that of individuals who fasted during Ramadan, around 15% experienced hypoglycemia or hyperglycemia, with 9.2 and 3.4%, breaking their fast, while severe hypoglycemia and hyperglycemia requiring medical intervention occurred in 1.8 and 0.9%, respectively. The odds of daytime hypoglycemia

and hyperglycemia more than doubled with one or more microvascular complications, and the odds of breaking the fast increased progressively with the number of microvascular complications, for hypoglycemia and hyperglycemia. The odds of severe hypoglycemia and hyperglycemia also increased progressively with the number of microvascular complications. Neuropathy was consistently and most highly associated with all adverse glycemic outcomes, except severe hypoglycemia. These findings highlight the need to assess each individual microvascular complication, especially the cumulative burden of microvascular complications, when risk stratifying the ability of patients with T2D to fast.

Overall, our study found that 30.5% of participants had at least one microvascular complication with neuropathy (18.5%) being the most prevalent, followed by retinopathy (12.0%) and nephropathy (9.3%), which is consistent with that reported in the global literature (18.8–57.6%).^{9–11} The substantial prevalence and impact of these complications, coupled with the high proportion of individuals who fast (83.6–84.9% in previous DAR surveys),^{1,2} highlight the importance of understanding their impact on fasting safety. The presence of any microvascular complication doubled the odds of experiencing daytime hypoglycemia and hyperglycemia, but their risk did not increase with the cumulative burden of complications. However, fasting disruption or events requiring medical attention increased progressively with the number of complications. This is an important observation as although hypoglycemia reporting in our survey was not confirmed, breaking the fast due to hypoglycemia is a marker that the symptoms were significant for the individual. Indeed, this supports the complication burden concept, in which each additional complication amplifies physiological stress, and increases susceptibility to acute metabolic events.^{9,10} Our study highlights the particular vulnerability of individuals with diabetes and multiple microvascular complications during periods of metabolic stress such as fasting during Ramadan.

The differential impact of each complication on glycemic outcomes provides insights into the pathophysiological mechanisms behind the increased risks during fasting. Neuropathy

showed the highest and most consistent associations across outcomes, particularly with daytime hypoglycemia and severe hyperglycemia requiring medical attention, which aligns with the known effects of autonomic neuropathy on the body's physiological response to falling glucose levels and reduced hypoglycemia awareness.^{3,12,13} Autonomic neuropathy may also contribute to erratic glucose fluctuations due to delayed gastric emptying,¹³ especially following the carbohydrate-rich postfast iftar meal. In this study, nephropathy was associated with both daytime hypoglycemia and breaking the fast, likely due to altered drug metabolism with reduced kidney function.^{4,14} It was inversely associated with nonsevere hyperglycemia, but positively with severe hyperglycemia, possibly reflecting tighter glycemic control in patients with nephropathy, while reduced physiological reserves increase the risk of severe worsening when hyperglycemia occurs.⁴ Retinopathy was associated with hyperglycemia and severe hypoglycemia, possibly reflecting the practical challenges of glucose monitoring and corrective treatment in individuals with visual impairment.⁵

Our findings support a risk stratification approach that considers both the type and overall number of microvascular complications for pre-Ramadan risk stratification and management. The International Diabetes Federation and Diabetes and Ramadan International Alliance (IDF-DAR) guidelines⁶ emphasize the need for individualized care based on complications and other risk factors, suggesting a personalized approach to managing fasting during Ramadan. For individuals with microvascular complications, enhanced glucose monitoring protocols may be warranted due to their elevated risk of both hypoglycemia and hyperglycemia.¹³ Furthermore, careful adjustment in medication dose may be required to reduce the risk of hypoglycemia.^{4,6} Fasting exemptions or medically supervised modified fasting schedules should be considered.^{1,6} The observed impact of microvascular complication burden on glycemic outcomes during Ramadan fasting may extend to other prolonged fasting contexts where medication adjustment may be required, for example, intermittent fasting¹⁵ and Coptic Orthodox Christian fasting during Great Lent.¹⁶

This study has several strengths, including its large and geographically diverse sample, focus on Ramadan-specific outcomes, inclusion of both severe and nonsevere glycemic events and accounting for insulin and sulfonylurea therapy.¹⁷ We acknowledge that the reliance on self-reported data for complications and glycemic events introduces potential for recall bias and misclassification. The presence and severity of each complication was indirectly graded through questions related to frequency, decision to break the fast and need for medical assistance. Grading of the severity of microvascular complications would strengthen future assessments of whether advanced stages confer higher risk.

Conclusion

In conclusion, the presence of multiple microvascular complications increases the risk of adverse glycemic outcomes

and impacts on the ability to fast in individuals with T2D during Ramadan. The risk of severe events and fasting disruption rises with the cumulative number of complications, and individual complications contribute differentially to specific risks. These findings support incorporating microvascular complication assessment into pre-Ramadan evaluations to enhance safety and reduce the risk of acute glycemic events during fasting.

Authors' Contribution

M.H., R.A.M., and G.P. were responsible for the concept of the article and led the project. All authors have written parts of and have reviewed the whole manuscript.

Compliance with Ethical Principles

The study received ethics approval from the Dubai Health Authority (DHA: DSREC-04/2002_29).

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None.

Conflict of Interest

None declared.

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