A Real-World Study in Patients with Type 2 Diabetes Treated with Gliclazide Modified Release during Fasting in Gulf Cooperation Council Countries: An Analysis from the International DIA-RAMADAN Study

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Keywords
Fasting · Gliclazide modified release · Gulf Cooperation Council countries · Ramadan · Type 2 diabetes mellitus

Abstract
Introduction: The safety and effectiveness of gliclazide modified release (MR) in patients with type 2 diabetes mellitus (T2DM) who fasted during Ramadan were previously published. Here, we carried out a regional analysis among patients living in Gulf Cooperation Council (GCC) countries. Patients and Methods: DIA-RAMADAN was a real-world, observational, international, noncomparative study conducted in nine countries that included >1200 T2DM adults receiving gliclazide MR for at least 90 days before inclusion. The study comprised 2 visits: at inclusion, 6–8 weeks before the start of Ramadan (V0) and 4–6 weeks after the end of Ramadan (V1). The primary endpoint was the proportion of patients reporting ≥1 symptomatic hypoglycemic event as collected using a patient diary. Changes in HbA\textsubscript{1c}, fasting plasma glucose (FPG), and weight were also analyzed. This manuscript represents data collected in GCC countries (Kuwait, Saudi Arabia, and United Arab Emirates). Results: Data from 161 patients were analyzed: mean (SD) age 56.8 (10.6) years, 30.4% women, body mass index 29.1 (3.7) kg/m\textsuperscript{2}, T2DM disease duration 6.7 (3.3) years, baseline HbA\textsubscript{1c} 7.9% (0.8). The proportions of patients reporting ≥1 symptomatic hypoglycemic event or confirmed hypoglycemia during Ramadan were 4.3% and 0.6%, respectively. No cases of severe hypoglycemia were reported. Significant reductions in main variables were observed before the start of Ramadan (V0) and 4–6 weeks after the end of Ramadan (V1): HbA\textsubscript{1c} (from 7.9 [0.8] to 7.6 [0.7]; \textit{p} < 0.001), FPG (from 143.5 [24.3] to 137.9 [25.2] mg/dL; \textit{p} = 0.031), and weight (from 79.0 [73.0–86.0] to 78.0 [72.0–85.0] kg; \textit{p} = 0.018). Conclusions: These real-world data indicate that patients with T2DM treated with gliclazide MR during Ramadan in the selected GCC countries have a low risk of hypoglycemia and maintain glycemic control and weight while fasting.

Introduction
Diabetes mellitus (DM) is an international health care problem [1]. The current prevalence of DM in countries such as Bahrain, Saudi Arabia, Kuwait, Oman, Qatar, and United Arab Emirates (UAE) ranges from 8 to 27% [2–5].

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At this moment, there are more than 1 billion Muslims around the world, mainly located in the Asia-Pacific region, Sub-Saharan Africa, and the Middle East/North Africa [6, 7]. However, the number of patients with DM, particularly type 2 DM (T2DM), is expected to increase dramatically in the coming years. This increase will be especially marked in the Middle East [1].

Ramadan fasting is one of the five pillars of Islam. During Ramadan, Muslims fast from sunrise (Sahur) to sunset (Iftar) throughout the ninth lunar month of the Islamic calendar and are required to abstain from food and fluids, including oral and most of injectable drugs [6, 8]. Although patients with some chronic conditions may be exempt from fasting, the majority of patients with T2DM choose to fast [9, 10]. Patients with T2DM who fast during Ramadan are at risk of developing complications, including hyperglycemia and hypoglycemia due to fasting, changes in dietary patterns, and dosage modifications of antidiabetic medications [11, 12]. Indeed, hypoglycemia is by far the most common concern for T2DM patients during Ramadan fasting [7, 13]. Unfortunately, currently available information about Ramadan fasting and diabetes is limited and is mainly derived from observational studies of limited sample size, underscoring the need for advice [14] that goes beyond current recommendations for managing patients with T2DM during Ramadan [11, 12, 15, 16].

Sulfonylureas increase insulin secretion by pancreatic beta cells. Although first-generation sulfonylureas have been associated with hypoglycemia during fasting, second-generation sulfonylureas appear to be safer. In this context, gliclazide modified release (MR) has been designed to release gliclazide progressively, allowing for a once-daily dosing regimen and a reduction in the risk of hypoglycemia [17–20]. In fact, International Diabetes Federation (IDF) and Diabetes and Ramadan (DAR) International Alliance Ramadan 2021 guidelines classify gliclazide MR as a “low-risk” treatment option during Ramadan and recommend that, when sulfonylureas are taken, gliclazide and glimepiride should be used instead of glibenclamide [16]. Despite these recommendations, recent consensus about the management of patients with T2DM during Ramadan suggests that consideration should be given to substituting, stopping, or reducing the dose of sulfonylureas in these patients during the Ramadan period [12].

Until recently, the safety and effectiveness of gliclazide MR treatment during Ramadan fasting had not been well established in a real-world setting. However, the DIA-RAMADAN study (NCT04132934), which recruited 1,244 patients with T2DM in nine Asian and Middle Eastern countries, showed that treating this population with gliclazide MR during Ramadan, taken at Iftar without dose modification, has a low risk of hypoglycemia and maintains glycemic control and weight while fasting [21]. These results oppose recommendations put forward by some authors [12]. However, as different regions of the world exhibit disparities in culture and nutritional habits, it is important to ascertain whether the results of the International DIA-RAMADAN study can be extended to other areas. In the current study, we present an analysis of data from the DIA-RAMADAN study pertaining to Kuwait, Saudi Arabia, and UAE.

Methods

Study Design

The design and details of the DIA-RAMADAN study have been published previously [21]. Briefly, DIA-RAMADAN was a real-world, observational, noncomparative, and international study that included patients aged ≥18 years with T2DM defined according to American Diabetes Association (ADA) guidelines, with controlled or sub-optimally controlled T2DM (glycosylated hemoglobin [HbA1c] <9%), who were treated with breakable gliclazide MR 60 mg for at least 90 days prior to study enrollment, either as monotherapy or in combination with any other antidiabetic drugs except insulin, and with experience in blood glucose self-monitoring; had a body mass index (BMI) between 25 and 45 kg/m², and were willing to fast during Ramadan. All patients provided informed written consent before participating in the study. Excluded were patients requiring treatment with insulin; those with severe liver or renal disease; HbA1c ≥9%; any contraindication to gliclazide treatment; pregnancy or breast-feeding; or previous severe or repeated hypoglycemia without a triggering factor within the year prior to study start. The study was approved by the corresponding Ethics Committees. The trial was registered at ClinicalTrials.gov (NCT04132934).

Two patient visits were planned according to the IDF-DAR guidelines [22]: the first visit (V0) was 6–8 weeks prior to Ramadan, and the second visit (V1: end of study) was 4–6 weeks after Ramadan. During the first visit (V0), informed patient consent was obtained and patient demographics (age, gender, working status), physical examination (BMI, weight, blood pressure), lifestyle habits, physical activity levels (sedentary, moderate, intermediate, intensive), IDF-DAR risk classification (very high, high, moderate/low risk), medical history, antidiabetic and concomitant treatments, and HbA1c and fasting plasma glucose (FPG) levels were recorded. Recommendations about gliclazide intake during Ramadan according to IDF-DAR guidelines were provided (i.e., gliclazide MR should be taken orally once daily at breakfast until the beginning of Ramadan; during Ramadan, gliclazide MR should be administered at Iftar, the post-sunset meal; after Ramadan, gliclazide MR should be taken as previously). Investigators were instructed to continue management and treatment of participants according to their usual practice and guidelines. Patients used a diary to record any treatment changes, details about symptoms.
Table 1. Baseline characteristics according to the region origin

| Biodemographic data | International overall population (n = 1,214) | KUW/KSA/UAE (n = 161) |
|---------------------|---------------------------------------------|-----------------------|
| Mean age (SD), years | 54.1 (10.5)                                 | 56.8 (10.6)           |
| Age-groups, n (%)   |                                             |                       |
| <50 years           | 408 (33.6)                                  | 41 (25.5)             |
| ≥50–65 years        | 637 (52.5)                                  | 81 (50.3)             |
| >65 years           | 169 (13.9)                                  | 39 (24.2)             |
| Female, n (%)       | 549 (45.2)                                  | 49 (30.4)             |
| Patients advised to not fast, n (%) | 297 (24.5) | 100 (62.1) |
| Working status, n (%) |                                             |                       |
| Active full-time worker | 424 (34.9) | 62 (38.5) |
| Active part-time worker | 143 (11.8) | 26 (16.1) |
| Nonactive worker    | 200 (16.5)                                  | 8 (5.0)               |
| Student             | 3 (0.2)                                     | 0                     |
| Retired             | 206 (17.0)                                  | 53 (32.9)             |
| Other               | 221 (18.2)                                  | 12 (7.5)              |
| Missing data        | 17 (1.4)                                    | 0                     |
| Physical examination |                                             |                       |
| BMI (SD), kg/m²     | 28.4 (4.3)                                  | 29.1 (3.7)            |
| Weight (SD), kg     | 76.5 (14.1)                                 | 79.0 (73.0–86.0)*     |
| Diabetes            |                                             |                       |
| Mean HbA1c (SD), %  | 7.5 (0.9)                                   | 7.9 (0.8)             |
| Mean FPG, mg/dL     | 140.3 (41.1)                                | 143.5 (24.3)          |
| Mean disease duration (SD), years | 5.4 (5.7) | 6.7 (3.3) |
| IDF-DAR risk category, n (%) |                             |                       |
| Category 1: very high risk | 47 (3.9)  | 44 (27.3) |
| Category 2: high risk | 155 (12.8)                                 | 41 (25.5)             |
| Category 3: moderate/low risk | 993 (81.8) | 76 (47.2) |
| Missing data        | 19 (1.6)                                    | 0                     |
| Diabetic nephropathy, n (%) | 9 (0.7)  | 4 (2.5)   |
| Diabetic retinopathy, n (%) | 9 (0.7)  | 2 (1.2)   |
| Diabetic neuropathy, n (%) | 85 (7.0)  | 28 (17.4) |
| Cardiovascular risk factors/vascular disease |                             |                       |
| Arterial hypertension, n (%) | 435 (35.8) | 35 (21.7) |
| Dyslipidemia, n (%)  | 350 (28.8)                                  | 40 (24.8)             |
| Physical activity, n (%) |                                             |                       |
| Sedentary           | 427 (35.2)                                  | 71 (44.1)             |
| Moderate            | 669 (55.1)                                  | 81 (50.3)             |
| Intermediate        | 90 (7.4)                                    | 9 (5.6)               |
| Intensive           | 9 (0.7)                                     | 0                     |
| Missing data        | 19 (1.6)                                    | 0                     |
| Vascular disorders, n (%) | 437 (36.0)  | 35 (21.7) |
| Antidiabetic treatments |                                             |                       |
| Number of antidiabetic drugs, n (%) |                             |                       |
| 1                   | 495 (40.8)                                  | 35 (21.7)             |
| 2                   | 362 (29.8)                                  | 12 (7.5)              |
| ≥3                  | 357 (29.4)                                  | 114 (70.8)            |
| Mean dose of gliclazide MR (SD), mg | 74.0 (26.8)  | 98.8 (23.6) |
| Dose groups for gliclazide MR, n (%) |                             |                       |
| 30 mg               | 61 (5.0)                                    | 0                     |
| 60 mg               | 798 (65.7)                                  | 33 (20.5)             |
| 90 mg               | 84 (7.0)                                    | 48 (29.8)             |
| 120 mg              | 271 (22.3)                                  | 80 (49.7)             |
suggesting hypoglycemia, and any adverse events. Data were recorded in a specific electronic case report form by the investigator. During the second visit (V1), data about physical examination, treatment changes and adherence to gliclazide MR treatment, nutritional habits and fasting pattern during Ramadan, laboratory values (performed 1 month after Ramadan), adverse events, and hypoglycemic episodes were collected.

In the international DIA-RAMADAN study, a total of 1,214 patients were included in the final analysis set. Of these, 161 (13.3%) came from the Gulf Cooperation Council (GCC) country region: 14 (8.7%) from Kuwait, 130 (80.7%) from Saudi Arabia, and 17 (10.6%) from UAE; 157 (97.5%) patients completed the study (4 patients discontinued the study prematurely, 2 due to an adverse event, and 2 because of nonmedical reasons).

Outcome Measures
The primary endpoint of the study was the proportion of patients with at least one symptomatic hypoglycemic event (HE), either suggestive or confirmed. The proportion of patients with ≥1 confirmed hypoglycemic event (asymptomatic or symptomatic), ≥1 hypoglycemic event of any type, and ≥1 severe hypoglycemic event was also determined. A confirmed asymptomatic hypoglycemic event was defined as the absence of typical symptoms of hypoglycemia, but with a measured glucose concentration ≤70 mg/dL (≤3.9 mmol/L). Confirmed symptomatic hypoglycemic events were defined as the presence of typical symptoms of hypoglycemia and a measured glucose concentration ≤72 mg/dL (≤4.0 mmol/L). Suggestive hypoglycemic events were defined as the presence of typical hypoglycemic symptoms, but without a measured glucose concentration or a measurement >72 mg/dL (>4.0 mmol/L). Severe hypoglycemia was defined as symptoms of severe cognitive impairment that required third-party assistance for recovery. Changes in HbA1c, FPG, and BMI during the follow-up period were also investigated. All reported adverse events, their severity, and possible causal relationship with the study drug were recorded by the patient’s physician. Adverse events that occurred during the study were coded according to MedDRA version 19.0.

Statistical Analysis
Absolute and relative frequency distributions are reported for qualitative variables. Measures of central tendency and dispersion (mean/median, standard deviation/interquartile range, according to normality) are reported for quantitative variables. The statistical tests associated with paired quantitative data were the paired \( t \) test or the Wilcoxon signed-rank test in case of strong violation of normality (skewness and kurtosis not in [−1.5; 1.5]). Thus, the paired Student’s \( T \) test was used to analyze differences in HbA1c, FPG, and BMI during the study. A ranked sign test was used to analyze changes in weight between baseline and study end. The threshold for statistical significance was defined as \( p \) value of <0.05. Analyses were carried out using SAS software version 9.4 or higher (SAS Institute, Cary, NC, USA).

Results
The main baseline characteristics of patients included in the GCC country region are presented in Table 1. Mean (standard deviation) age was 56.8 (10.6) years, 30.4% of patients were women, BMI was 29.1 (3.7) kg/m², mean T2DM disease duration was 6.7 (3.3) years, and mean HbA1c was 7.9 (0.8) %. More than half of the patients (54.6%) were considered as active workers (either full- or part-time), most patients (94.4%) reported none or moderate physical activity, approximately half of the subjects (47.2%) were moderate to low risk according to IDF-DAR guidelines, and 62.1% of patients had been advised not to fast by their treating physicians. With regard to antidiabetic treatments, 70.8% of patients were taking 3 or more drugs; 7.5% were taking 2 antidiabetic drugs; and 21.7% were taking gliclazide MR as monotherapy. When combined, gliclazide MR use was at 28.0% combined with a dipeptidyl peptidase 4 inhibitor ± others, at 21.1% with a glucagon-like peptide-1 receptor ag-
onist ± others, and at 11.2% with a sodium-glucose cotransporter 2 inhibitor ± others (Fig. 1). The most frequently prescribed dose of gliclazide MR was 120 mg (49.7%), followed by 90 mg (29.8%).

Regarding nutritional habits and fasting during Ramadan in the GCC country region (Table 2), the mean number of fasting days was 29.7 (0.7), and the number of fasting hours 15.7 (0.7) per day (vs. 28.7 days and 14.7 h, respec-
### Table 3. Hypoglycemic events in patients receiving gliclazide MR treatment

| Patients with ≥1 symptomatic HE (confirmed or suggestive), n (%) | Pre-Ramadan | During Ramadan | Post-Ramadan |
|---|---|---|---|
| International overall population (n = 1,214) | KUW/KSA/UAE (n = 161) | International overall population (n = 1,212) | KUW/KSA/UAE (n = 161) | International overall population (n = 1,208) | KUW/KSA/UAE (n = 160) |
| Patients with ≥1 symptomatic HE (confirmed or suggestive), n (%) | 2 (0.2) | 0 | 27 (2.2) | 7 (4.3) | 4 (0.3) | 0 |
| Patients with ≥1 confirmed HE (asymptomatic or symptomatic), n (%) | 2 (0.2) | 0 | 19 (1.6) | 1 (0.6) | 1 (<0.1) | 0 |
| Patients with ≥1 HE of any type, n (%) | 2 (0.2) | 0 | 28 (2.3) | 7 (4.3) | 4 (0.3) | 0 |
| Patients with ≥1 severe HE, n (%) | 0 | 0 | 0 | 0 | 0 | 0 |

HE, hypoglycemic event; MR, modified release. Data relating to the primary endpoint are highlighted in bold.

### Table 4. Evolution of glycemic and physical examination parameters during the study period

| International overall population | KUW/KSA/UAE |
|---|---|
| | pre-Ramadan | post-Ramadan | change | p value | pre-Ramadan | post-Ramadan | change | p value |
| HbA1c (SD), % | 7.5 | 7.2 | −0.3 (0.8) | <0.001 | 7.9 (0.8) | 7.6 (0.7) | −0.3 (0.8) | <0.001 |
| FPG (SD), mg/dL | 140.3 | 130.2 | −9.7 (43.6) | <0.001 | 143.5 (24.3) | 137.9 (25.2) | −5.7 (29.9) | 0.031 |
| Weight (SD), kg | 76.5 | 76.1 | −0.5 (3.9) | <0.001 | 79.0 (73.0–86.0)* | 78.0 (72.0–85.0)* | −0.7 (−1.0 to 1.0) | 0.018 |

SD, standard deviation; KUW/KSA/UAE, Kuwait/Saudi Arabia/United Arab Emirates. *Median (interquartile range).
tively, in the international overall population). A total of 20 (12.4%) patients changed the type of meal compared to the pre-Ramadan period (85.0% reported eating more carbohydrates during Ramadan, 50.0% more proteins, and 35.0% more fats). While 75.8% of patients broke their fast during Ramadan, only 1.2% broke the fast for more than three consecutive days. In the international overall study population, 30.9% of patients changed the type of meal compared to the pre-Ramadan period, and 5.1% broke their fast for three consecutive days (3 out of 62 due to hypoglycemia).

The mean study observation period was 89.3 (13.5) days with an average of 26.3 days pre-Ramadan, 29 fasting days during Ramadan, and 33.8 days post-Ramadan. No patient definitively discontinued gliclazide MR treatment, and no gliclazide MR dose modifications were observed during the study (mean dose 98.8 [23.6] mg).

The proportion of patients reporting at least one symptomatic hypoglycemic event or confirmed hypoglycemia during Ramadan in the GCC country region was 4.3% (vs. 2.2% in the international overall study population) and 0.6% (vs. 1.6%), respectively. No cases of severe hypoglycemia were reported before, during, and after Ramadan in the GCC country region (Table 3).

Few adverse events (other than hypoglycemia) were reported in the GCC country region. Two (1.2%) serious adverse events were reported during the entire study (1 during Ramadan and 1 during post-Ramadan period), and no drug-related adverse events were observed (vs. 0.9% SAEs and 0% drug-related AEs in the international overall study population, respectively).

The evolution of glycemic and physical examination parameters between pre- and post-Ramadan visits is presented in Table 4 and Figure 2. Significant reductions during the study in HbA1c (−0.3 [0.8] %; p value <0.001), FPG (−5.7 [29.9] mg/dL; p value = 0.031), and body weight (−0.7 [−1.0 to 1.0] kg; p value = 0.018) were observed in the GCC country region.

**Discussion**

In this sub-analysis of the DIA-RAMADAN study, we report data from the GCC (Kuwait, Saudi Arabia, and the UAE) countries involved in the international study. Although there were relevant differences in the clinical profile of patients from this region compared with that of the international overall study population (patients from the GCC countries were older and had a higher IDF-DAR risk, and more patients were taking gliclazide MR 120 mg, as well as gliclazide in combination with other antidiabetic drugs) [21], the main results were consistent, regardless of geographic origin, including a low risk of hypoglycemia with gliclazide MR during Ramadan fasting with no severe hypoglycemic cases, as well as significant and comparable reductions in HbA1c, FPG, and body weight.

In the GCC country region (13% of the international overall study population), mean HbA1c was 7.9% and approximately 71% of patients were taking 3 or more antidiabetic drugs. Previous studies have shown that sulfonylureas are commonly used as first-line therapy in the

![Fig. 2. Evolution of HbA1c, FPG, and weight during the study period. FPG, fasting plasma glucose.](image-url)
management of T2DM in GCC countries [23]. Our data suggest that, compared with the international overall study population, glycemic control might be poorer in the GCC region, thus requiring more intensive antidiabetic treatment, with gliclazide MR at higher doses and more frequently in combination with other antidiabetic drugs. However, it is likely that with a population more comparable for age, weight, and physical activity, similar glycemic control and drug therapy prescription would have been observed. In fact, physicians are aware that they can increase the dose of gliclazide MR before intensifying with another oral antidiabetic drug. Of note, previous studies have shown increasing rates of obesity and sedentary lifestyle in the GCC countries in recent years. As a result, more efforts are warranted to reduce obesity in this region, through improvements in diet and physical activity that would translate into increased glycemic control [24, 25].

Regarding nutritional habits and fasting during Ramadan in the GCC country region, whereas three-quarters of patients broke their fast during Ramadan, only around 1% broke the fast for more than three consecutive days (vs. 5% in the international overall study population). However, the low rates of symptomatic hypoglycemia observed in our study strongly suggest the existence of other reasons for breaking fast apart from hypoglycemia (only 1 patient broke fast for more than 3 consecutive days for hypoglycemia and 1 patient for a nonmedical reason). In addition, a number of patients changed their meal type compared with the pre-Ramadan period, particularly by eating more carbohydrates during Ramadan, leading to a lower risk of hypoglycemia, but also by increasing proteins and to a lesser extent fats. This is highly relevant since changes in fasting patterns during Ramadan could be associated with clinical outcomes in T2DM patients [10]. Unfortunately, dietary changes during Ramadan have not been well analyzed in other studies and currently available information is scarce, with substantial disparities between previous studies, likely due to differences in culture and nutritional habits between regions [10, 26, 27].

With regard to antidiabetic treatment, in the international overall study population, the most frequently prescribed dose of gliclazide MR was 60 mg (65.7%), whereas in the GCC country region the most common dose was 120 mg (49.7%), indicating that prior to a further step in treatment intensification, up-titration of gliclazide was performed in usual practice [21]. Different studies have shown that, although prescription patterns have changed somewhat in recent years, oral antidiabetics remain the most common therapy for adults with T2DM who fast during Ramadan [10]. In addition, during this period, the use of oral antidiabetics as monotherapy has decreased markedly and, conversely, the combination of two or more oral antidiabetics has increased [10]. Our study is in line with these reports, as the use of combined therapy was the most common prescription pattern (78% in the GCC country region and 59% in the international overall study population). Of note, prior research has shown a decrease in the proportion of patients taking sulfonylureas, likely due to the higher risk of hypoglycemia associated with first-generation sulfonylureas compared with other oral antidiabetics [10, 17]. However, the use of newer second-generation sulfonylureas with a lower risk of hypoglycemia, such as gliclazide MR, has increased during this time [10, 28]. In addition, evidence from randomized clinical trials has shown that gliclazide MR is an effective glucose-lowering agent with a very low risk of severe hypoglycemia and with no differences in the risk of mortality or cardiovascular events compared with other classes of glucose-lowering therapies [8, 28]. Although real-world studies have confirmed these results in clinical practice [28], the DIA-RAMADAN study has recently shown that the benefits of using gliclazide MR can also be extended to T2DM patients who fast during Ramadan [21]. Similarly, other studies have reported a lower risk of hypoglycemia with gliclazide MR compared with other sulfonylureas during Ramadan [19, 29]. This could be related to differences in the pharmacokinetic and pharmacodynamic properties of gliclazide MR compared with other sulfonylureas [30]. Our data showed that, in the GCC country region, no patient definitively withdrew gliclazide MR treatment during the study, no dose modification was required during Ramadan, and medication adherence was high. This relates to the low incidence of adverse events associated with gliclazide MR. In fact, rates of symptomatic and confirmed hypoglycemia were low, no cases of severe hypoglycemia were reported, and no drug-related adverse events occurred. Although it has been reported that dose adjustment of sulfonylureas could reduce the risk of hypoglycemia among patients who fast during Ramadan [31], our data showed that this was not necessary with gliclazide MR, in line with new IDF-DAR guidelines classifying gliclazide MR as a "low-risk" antidiabetic drug during Ramadan [16].

Finally, our study showed that, in the GCC country region, treatment with gliclazide MR was associated with significant reductions in HbA1c, FPG, and body weight throughout the study. Of note, these reductions were comparable to those reported in the international overall
study population [21]. Similarly, the STEADFAST study also showed decreases in HbA1c and body weight after Ramadan with gliclazide and metformin [32]. These beneficial effects are comparable to those obtained with newer oral hypoglycemic agents, including DPP4 inhibitors, GLP1 receptor agonists, and SGLT2 inhibitors [33]. Although the main target during Ramadan should be to maintain glycemic control without an increased risk of side effects, our data suggest that gliclazide MR could provide added value in the management of T2DM patients.

The study has limitations. As this was an observational and noncomparative study, no direct comparisons can be made with other oral antidiabetics regarding the effects of gliclazide MR on metabolic and physical examination parameters. In particular, given the known specificities of gliclazide compared to older generation sulfonylureas, further studies would need to be carried out to compare the effectiveness and safety of different agents in this class [28, 34]. However, this real-world evidence study showed usual daily clinical practice in the region, which was not changed during Ramadan. On the other hand, because current treatment with gliclazide MR for at least 90 days prior to enrollment was an inclusion criterion, it is likely that the drug was already well tolerated in these patients. Although the sample size of our study was limited, it should be noted that our results are derived from a cohort that has not been well characterized previously (i.e., T2DM patients from GCC countries who are receiving gliclazide MR as baseline antidiabetic therapy). Consequently, our data provide original and relevant information about this population taking gliclazide MR (as monotherapy or in combination) as part of their antidiabetic treatment.

**Conclusion**

In T2DM patients from selected GCC countries, treatment with gliclazide MR alone or in combination during Ramadan, up to a dose of 120 mg, was effective and safe, no dose modifications were required during Ramadan, and medication adherence was high. Rates of hypoglycemia and side effects were low, no cases of severe hypoglycemia or drug-related adverse events were reported, and significant reductions in HbA1c, FPG, and body weight were observed throughout the study. These data suggest that gliclazide MR may be used without dose modification at Iftar to maintain optimal glycemic control during Ramadan and support the use of gliclazide MR during Ramadan in the GCC country region.

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**Statement of Ethics**

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the corresponding Ethics Committees. The trial was registered at ClinicalTrials.gov (NCT04132934). The study was approved by Dubai Scientific Research Ethics Committee (UAE, DSREC-12/2018_14), Dasman Institute Ethics Committee (Kuwait, RA/054/2019), and Institutional Review Board King Fahad Medical City (Saudi Arabia, IRB00010471, FWA00018774). All patients provided informed written consent to participate in the study.

**Conflict of Interest Statement**

Thamer Alessa has received research grants from Servier; advisory board fees from Sanofi-Aventis, AstraZeneca, Novo Nordisk, Ely Lilly, and Novartis; and honoraria from Sanofi-Aventis, AstraZeneca, Servier, Novo Nordisk, Ely Lilly, and Novartis. Mohamed Hassanein has received speaker fees and/or advisory board fees from Servier, Sanofi-Aventis, AstraZeneca, Novo Nordisk, Ely Lilly, BI, and Novartis, and AstraZeneca, Abbott, and LifeScan. Saud Al Sifri has received speaker fees and/or advisory board fees from Servier, Sanofi-Aventis, AstraZeneca, Novo Nordisk, Ely Lilly, BI, and Novartis, and AstraZeneca, Abbott, and Pfizer. Ashraf Shaaban has received speaker fees and/or advisory board fees from Servier, Sanofi-Aventis, AstraZeneca, Novo Nordisk, Ely Lilly, BI, and Novartis, and AstraZeneca, Abbott, and Pfizer.

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**Author Contributions**

All named authors contributed to the conception, conduct, and data analysis of the study and were involved in drafting, further development, and revision of the manuscript and approval of its final version.

**Data Availability Statement**

The data that support the findings of this study are not publicly available because they have been hosted in hospital sites where the study was carried out but are available from the corresponding author upon reasonable request.
Gliclazide MR in Fasting T2DM Patients

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