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Real-world evidence on the effectiveness and safety of gliclazide extended-release treatment in Indian patients with type 2 diabetes undergoing Ramadan fast: an analysis from the global DIA-RAMADAN study

Abstract

Background. Glycaemic imbalance, especially hypoglycaemia, is one of the greatest risks for patients with type 2 diabetes mellitus (T2DM) during Ramadan fasting. This paper outlines the efficacy and safety of gliclazide extended-release (XR) in Indian patients with T2DM enrolled in the global DIA-RAMADAN study.

Methods. Adults (aged ≥ 18 years) with T2DM who chose to fast during Ramadan and received a gliclazide-based regimen once daily for 90 days before Ramadan were included in the study. Baseline and end-of-study visits were conducted 6–8 weeks before and 4–6 weeks after Ramadan, respectively. The primary outcome was the incidence of ≥ 1 symptomatic hypoglycaemic event (HE). Changes in glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG), and body weight were secondary outcomes.

Results. Among 246 Indian patients enrolled in the study, most (78.9%, n = 194) were at moderate/low risk as per the International Diabetes Federation and Diabetes and Ramadan guidelines. Most patients (69.1%) received gliclazide XR as monotherapy, and the rest received gliclazide XR with metformin or other antidiabetic therapy. Significant reductions in HbA_{1c} (−0.5 ± 0.8%, P < 0.001) and FPG (−21.8 ± 59.4 mg/dL, P < 0.001) levels were observed but the slight reduction in body weight was not statistically significant (−0.3 ± 3.7 kg, P = 0.614) in patients post-Ramadan. Overall, no HE was reported in Indian patients with T2DM during Ramadan fasting.

Conclusion. Overall, the effectiveness and safety of gliclazide XR in Indian patients were consistent with that observed in the global cohort. Gliclazide XR significantly reduced HbA1c with no incidence of hypoglycaemic events in Indian patients with type 2 diabetes undergoing Ramadan fast, suggesting that gliclazide

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XR may be used without dose modification at Iftar to maintain optimal glycaemic control during Ramadan.
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Key words: gliclazide, glycated haemoglobin, hypoglycaemia, Ramadan, type 2 diabetes mellitus

Introduction

Diabetes mellitus is one of the most common diseases globally with a rapidly increasing prevalence with an estimated 51% rise by 2045 resulting in almost 700 million people living with diabetes [1]. India is projected to be the diabetes capital of the world with approximately 134 million people with diabetes by this date [1, 2]. Type 2 diabetes mellitus (T2DM) accounts for around 90% of all diabetes cases [1].

Fasting and feasting are integral parts of many religions and cultures in India [2]. Ramadan is one of the five pillars of Islam, and fasting during Ramadan is observed by over 1 billion Muslims worldwide [2–4]. A multicentre epidemiology survey of diabetes and Ramadan (EPIDAR) in 12,243 Muslims worldwide, including India, revealed that 78.7% of patients with T2DM fast for at least 15 days during Ramadan [4]. The CREED (a multi-country retrospective observational study of the management and outcomes of patients with diabetes during Ramadan) study of 13 countries reported that 94.2% of patients with T2DM fast for at least 15 days, and 63.6% fast every day during the holy month of Ramadan [5, 6]. Within the Muslim community, there is an intense desire to participate in fasting, even among those who are eligible for an exemption due to medical conditions [2, 3, 5] People observe the fast (without food or water) during daylight that can last up to 20 hours depending on their location in the world [3]. The onset of Ramadan causes a sudden shift in mealtimes, sleep patterns, physical activity, and meal sizes [2–4]. One of the major complications associated with diabetic fasting is hypoglycaemia [2–5]. The EPIDAR study showed that incidence of severe hyperglycaemia increased 5-fold and the risk of hospitalization due to hypoglycaemia increased 7.5-fold in patients with T2DM during Ramadan fasting [4, 7]. Therefore, glycaemic control during fasting is a challenge as patients with T2DM refrain from food, drink, and medications between dawn and dusk. Both fasting and antihyperglycemic therapy could increase the risk of severe hypoglycaemia in patients with T2DM.

The International Diabetes Federation (IDF), and Diabetes and Ramadan (DAR) guidelines have provided the necessary guidance for managing T2DM during Ramadan [3]. Treatments that stabilize blood glucose levels with the lowest risk of hypoglycaemia during fasting are highly recommended [2, 3]. Sulfonylureas (SUs) are recommended for treating T2DM owing to their wide clinical experience and lower therapy costs [8]. They are also widely used to control blood glucose in patients with T2DM in India [2, 9–12] Although concerns have been raised regarding the use of SUs during Ramadan due to increased risk (~13–20%) of hypoglycaemia [3], this risk is lower during fasting with newer generation SUs like gliclazide extended-release (XR) [8, 13–15].

Indians have distinct dietary habits and consume diets predominantly consisting of carbohydrates providing up to 64.1% of total energy thus, predisposing Indian Muslims to a higher risk of hypoglycaemia during Ramadan [2, 16]. Additionally, the safety and efficacy of gliclazide XR treatment in Indian patients with T2DM during Ramadan have not yet been demonstrated in a real-world setting. Recently, the DIA-RAMADAN study was conducted in nine countries, including India, and reported the efficacy and safety of gliclazide XR in patients with T2DM during Ramadan fasting [17]. Herein is presented the efficacy and safety data of gliclazide XR in the Indian subgroup of patients who participated in the DIA-RAMADAN study.

Material and methods

Ethics

This study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from local institutional review boards, ethics committees, and regulatory authorities. Written informed consent was obtained from all patients before the commencement of the study. The trial was registered at ClinicalTrials.gov (NCT04132934).

Study design

Hassanein et al. [17] have recently published the detailed methodology of the DIA-RAMADAN study. In brief, DIA-RAMADAN was an international, real-world, prospective, observational study conducted during the holy month of Ramadan in 2019 at 64 clinical centres from nine Asian and Middle-Eastern countries including India. Owing to its observational nature, T2DM was managed per the local standard clinical practice. Patient visits were scheduled as per recommendations of the IDF-DAR guidelines, i.e., one visit pre- and another visit post-Ramadan.

Patient population

Data from Indian patients (aged ≥ 18 years) with T2DM (controlled or sub-optimally controlled) defined according to American Diabetes Association guidelines

were included. Patients with fasting plasma glucose (FPG) levels ≥ 126 mg/dL, 2-hour blood glucose level ≥ 200 mg/dL in an oral glucose tolerance test, or with glycated haemoglobin (HbA1c) level ≥ 6.5%, body mass index (BMI) ≥ 25–≤ 45 kg/m^2 and treated with gliclazide XR (monotherapy or in combination with antidiabetic therapy except for insulin) at least 90 days before their pre-Ramadan visit, were included in the study. Patients were included if they were familiar with self-monitoring of blood glucose levels and intended to fast during Ramadan. Patients were excluded if they needed insulin therapy, had a severe liver or renal failure, HbA1c level ≥ 9%, were contraindicated for gliclazide XR treatment according to the summary of product characteristics, or were on miconazole treatment. Pregnant or breast-feeding women or patients with a former history of severe or repeated hypoglycaemic events (HEs) without a triggering factor within the year before study initiation were excluded. Only data from Indian patients were included.

Study procedure

There were two visits in the study: the first pre-Ramadan visit was planned 6–8 weeks before Ramadan when the patient eligibility was assessed, and baseline information was collected. The second visit was planned 4–6 weeks after Ramadan. In addition, Ramadan-focused education was provided to patients per IDF-DAR guidelines at the first visit. They were also provided with a diary to record any changes in the treatment regimen, details of any symptoms indicating hypoglycaemia, or other adverse events (AEs) throughout the study.

Study treatment

Management of T2DM in patients was in accordance with standard clinical practice at each participating centre. Gliclazide XR 60 mg tablets were orally administered once daily at breakfast before Ramadan, and patients were advised to adjust the timing for Iftar (post-sunset meal) during the Ramadan period, based on recommendations of the current IDF-DAR guideline [3] at the physician's discretion. Post-Ramadan, gliclazide XR was continued per the pre-Ramadan timings. The global study was conducted with a gliclazide MR formulation that allows progressive drug release in a once-daily dose regimen, which is available as Gliclazide XR in India.

Data collection and endpoints

Data concerning patients' age, gender, height, body weight, blood pressure, heart rate, HbA1c, FPG, history of alcohol and tobacco consumption, occupation, physical activity, IDF-DAR risk classification, T2DM disease and treatment history, relevant medical/surgical history, concomitant treatments, nutritional habits outside Ramadan, and fasting during previous and current Ramadan were recorded. Adherence to gliclazide XR treatment, concomitant medications, and data on safety (AEs and HEs) were also documented. All the data, including records of the patient's paper diary, were collected by investigators using an electronic case report form and kept confidential.

The primary endpoint of the study was the proportion of patients with more than one symptomatic HE (either suggestive or confirmed by a measured glucose concentration of ≤ 3.9 mmol/L or ≤ 70 mg/dL). Changes in HbA1c and FPG levels, change in body weight between pre-Ramadan baseline visit and post-Ramadan visit, and proportion of patients with at least one confirmed HE (asymptomatic or symptomatic) during Ramadan were the secondary endpoints. The proportion of patients with at least one severe or any other type of HE was also considered. Study-specific definitions of HEs are described in Table 1. Other AEs were also recorded during the study.

Statistical analysis

Continuous and quantitative variables were summarized using descriptive statistics and compared using paired t-test or Wilcoxon signed-rank test as applicable at type I error (alpha) of 5%. Categorical data were presented as frequency count (n) and percentage (%) and were compared using the χ^2 test or Fisher's exact test. Analyses were performed using SAS® software, version 9.4 (SAS Institute, North Carolina, USA).

Results

Patients' baseline characteristics and IDF-DAR risk categorization

A total of 1214 patients from nine countries were included. Of these, 640 (52.7%) were from the Asia Pacific region with 255 from India. However, 9 out of 255 patients were excluded as they met one or more exclusion criteria, were noncompliant to inclusion criteria, or withdrew informed consent. A total of 237 (96.3%) patients completed the study, whereas 9 (3.7%) did not due to nonmedical reasons. Patients and physicians were given the option for an unscheduled visit depending on the patient's need or physician's preference; 4 (1.6%) patients had unscheduled visits of which 3 were 'regular visits' and 1 for a reason other than AE or HE.

Patient characteristics at pre-Ramadan visit are summarized in Table 2. Among 246 patients analysed, 112 (45.5%) were women. The mean age of patients

Table 1. Definition of hypoglycaemic events

Types of HE	Definition	Typical hypoglycaemia symptoms
Asymptomatic HE	Absence of typical hypoglycaemia symptoms with measured glucose concentration < 70 mg/dL	Sweating, pallor, tremor, intense hunger, pounding heart, visual disturbance, drowsiness, weakness, dizziness, difficulty in concentrating, difficulty in speaking or writing, incoordination, unexplained behaviour or mood change, confusion, nausea, or headache
Confirmed symptomatic HE	Presence of typical symptoms of hypoglycaemia with glucose concentration ≤ 72 mg/dL	
Suggestive HE	Presence of typical hypoglycaemic symptoms without a measured glucose concentration or with measured glucose concentration > 72 mg/dL	
Severe hypoglycaemia	Symptoms of severe cognitive impairment and requiring third-party assistance for recovery with a measured glucose concentration < 70 mg/dL	–

HE: hypoglycaemic event

Table 2 Patient characteristics before Ramadan

Characteristics	n = 246
Age, years	53.0 ± 10.6
Gender, female	112 (45.5)
Height, cm	162.6 ± 8.9
Weight, kg	73.4 ± 10.9
Body mass index, kg/m^2	27.8 ± 3.9
Heart rate, bpm	84.9 ± 9.2
Systolic blood pressure, mm Hg	128.8 ± 14.2
Diastolic blood pressure, mm Hg	80.6 ± 8.5
Working status	
Active full-time worker	110 (44.7)
Active part-time worker	22 (8.9)
Non-active worker	40 (16.3)
Student	1 (0.4)
Retired	15 (6.1)
Other (housewife)	58 (23.6)
Physical activity	
Sedentary	96 (39.0)
Moderate	145 (58.9)
Intermediate	5 (2.0)
Intensive	0 (0.0)
Duration of T2DM, years	5.8 ± 6.6
HbA1c, %	7.3 ± 0.8
FPG, mg/dL	142.7 ± 53.0
Dose of gliclazide XR, mg	70.2 ± 24.6
Dose of metformin, mg	1023.9 ± 436.3

Table 2 (cont.). Patient characteristics before Ramadan

Characteristics	n = 246
IDF-DAR risk categories	
Category 1: Very high risk	0 (0.0)
Category 2: High risk	52 (21.1)
Category 3: Moderate/low risk	194 (78.9)
Medical history*	
Established cardiovascular disease	1 (0.4)
Arterial hypertension	57 (23.2)
Dyslipidaemia	46 (18.7)
Cardiovascular therapies*	
Statin or ezetimibe	53 (21.5)
ACEi or ARB	35 (14.2)
Beta-blocker	5 (2.0)
Antiplatelet agents	5 (2.0)
Calcium channel blockers	11 (4.5)
Diuretics	10 (4.1)
Nutritional habits outside Ramadan	
Number of meals consumed per day	2.6±0.6
Number of snacks consumed per day	1.4±0.9
Fasting during previous Ramadan	
Fasting during previous Ramadan	243 (98.8)
During the whole previous Ramadan	230 (93.5)
Not during the whole previous Ramadan	13 (5.3)
If not, reason: nonmedical reason	13 (5.3)
Type of antidiabetic treatments at baseline	
Gliclazide XR alone	170 (69.1)
Gliclazide XR + metformin	54 (22.0)

Table 2 (cont.). Patient characteristics before Ramadan

Characteristics	n = 246
Gliclazide XR + SGLT2i with or without metformin	2 (0.8)
Gliclazide XR + DPP4i with or without metformin	17 (6.9)
Gliclazide XR + TZD with or without metformin	2 (0.8)
Gliclazide XR + SGLT2i + other	1 (0.4)
Gliclazide XR + Other	1 (0.4)
Number of antidiabetic drugs at baseline	
One	170 (69.1)
Two	59 (24.0)
≥ Three	17 (6.9)
Duration of treatment, months	
Gliclazide alone	17.1±49.5
Gliclazide + metformin	43.5±75.7
Gliclazide + DPP4i	6.7±3.6

Data are presented as mean ± SD or n (%). *Number of patients with at least one relevant medical history/concomitant treatment. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; DPP4i: dipeptidyl peptidase 4 inhibitor; FPG: fasting plasma glucose; HbA1c: glycated haemoglobin; SGLT2i: sodium-glucose cotransporter 2 inhibitor; T2DM: type 2 diabetes mellitus; TZD: thiazolidinedione; XR: extended-release

Table 3: Nutritional habit, meals, and fasting during Ramadan

Parameters	Patients, n = 246
Nutritional habits during Ramadan	
The average number of meals consumed per day	2.2 ± 0.4
The average number of snacks consumed per day	0.8 ± 0.7
Change of size of a meal during Ramadan	103 (41.9)
Meals larger during Ramadan period	64 (26.0)
Meals smaller during the Ramadan period	39 (15.9)
Change of type of meal during Ramadan	134 (54.5)
More carbohydrate in a meal	66 (26.8%)
More protein in a meal	77 (31.3%)
More fat in a meal	108 (43.9%)
Fasting during Ramadan	
Number of days fasted during Ramadan	29.1 ± 1.7
Number of hours/day fasted during Ramadan	13.9 ± 1.9
Patients who broke the fast during Ramadan	183 (74.4)
Patients who broke the fast for more than 3 consecutive days	6 (2.4)

Data are presented as mean ± SD or n (%)

was 53 ± 10.6 years; duration of T2DM, 5.8 ± 6.6 years; and BMI, 27.8 ± 3.9 kg/m^2. Baseline HbA_{1c} and FPG levels were 7.3 ± 0.8% and 142.7 ± 53.0 mg/dL, respectively. Risk categorization of patients as per IDF-DAR guidelines showed that most (78.9%) patients had moderate/low risk and 21.1% were at high risk. No Indian patients belonged to the very high-risk category. However, 105 (42.7%) patients were advised not to fast during Ramadan by physicians. Of 243 (98.8%) patients who had undergone fasting during previous Ramadan, 230 (93.5%) fasted for the whole month of previous Ramadan and 13 (5.3%) broke their fast early in the month due to non-medical reasons in previous Ramadan. The average number of meals and snacks consumed by patients outside Ramadan was 2.6 ± 0.6 and 1.4 ± 0.9 per day, respectively. A large proportion of patients (69.1%) were on monotherapy at baseline. The mean daily dose of gliclazide XR 60 mg was 70.2 ± 24.6 mg and no dose modification was done during the study.

Nutritional habits and fasting during Ramadan

Approximately 134 (54.5%) patients changed their meal type, and 103 (41.9%) changed their meal size [either larger (26%) or smaller (15.9%)] during Ramadan compared to pre-Ramadan (Table 3). Patients consumed more carbohydrates (26.8%), fats (43.9%) and proteins (31.3%) during their Ramadan meals. However, the average number of meals and snacks consumed by patients was reduced to 2.2 ± 0.4 and 0.8 ± 0.7 per day during Ramadan, respectively. On average, Indian patients fasted for 29.1 ± 1.7 days, 13.9 ± 1.9 hours per day during Ramadan (Table 3). A total of 183 (74.4%) patients broke their fast during Ramadan, and 6 (2.4%) broke the fast for three consecutive days due to nonmedical (n = 1) or other (n = 5) reasons.

Exposure and adherence to gliclazide XR treatment

Gliclazide XR treatment was observed for a mean duration of 63.1 ± 20.2, 29.0 ± 0.2, and 30.8 ± 10.4 days before, during, and after Ramadan, respectively (Table 4). During Ramadan, 172 (69.9%) patients received 60 mg of gliclazide XR once daily, 40 (16.3%) received 120 mg, 19 (7.7%) received 90 mg, and 15 (6.1%) received 30 mg. A total of 240 (97.6%) patients received gliclazide XR as per the prescription, and 4 (1.6%) patients skipped their medication for around 1.8 ± 0.5 intakes due to nonmedical reasons (n = 3) or AEs other than hypoglycaemia (n = 1). Higher adherence

Table 4. Exposure and adherence to gliclazide XR

Exposure to gliclazide XR	Patients, n = 246
Duration of gliclazide XR treatment	
Pre-Ramadan, days	63.1 ± 20.2
During Ramadan, days	29.0 ± 0.2
Post Ramadan, days	30.8 ± 10.4
Mean dose of glicliazide XR, mg	
Pre-Ramadan, days	70.2 ± 24.6
During Ramadan, days	70.1 ± 24.6
Post-Ramadan, days	70.2 ± 24.7
Dose of gliclazide XR received by patients during Ramadan, *n* (%)	
120 mg	40 (16.3)
90 mg	19 (7.7)
60 mg	172 (69.9)
30 mg	15 (6.1)
Gliclazide XR treatment took according to the prescription	240 (97.6)
Gliclazide XR skipped by patients	4 (1.6)
If yes, the number of intakes skipped	1.8 ± 0.5
If yes, reason:	
AE (other than hypoglycemia)	1
Nonmedical reason	3
Adherence to treatment	
Number of patients, n	240
Adherence, %	99.9 ± 0.8
Missing data, n	6

Data are presented as mean ± SD or n (%). AE: adverse event; XR: extended-release

(99.9 ± 0.8%) to gliclazide XR was reported during Ramadan, no changes were made in the mean dose of gliclazide XR, and none discontinued the treatment during Ramadan.

Hypoglycaemic events

No HEs were reported during the study following treatment with gliclazide XR in Indian patients.

Change in HbA1c, FPG, and body weight

Changes in HbA1c and FPG levels and body weight were calculated from pre-Ramadan to post-Ramadan visits. Mean HbA1c reduced from baseline (7.3 ± 0.8% to 6.9 ± 0.8% (mean reduction, −0.5 ± 0.8%, P < 0.001) post-Ramadan (Fig. 1A), and proportion of patients with HbA1c < 7.5% was 48.4% at baseline that increased to 69.5% after Ramadan (Fig. 1B). However, reductions in HbA1c levels were consistent across various age groups (< 50 years, −0.4 [0.8]; ≥ 50 to < 65 years, −0.5 [0.8], ≥ 65 years −0.6 [1.0], P < 0.05 for all comparisons). Similar significant reductions in FPG levels (142.9 ± 54 to 121.1 ± 29.7 mg/dL; mean difference, −21.8 ± 59.4 mg/dL, P < 0.001) were observed (Fig. 1C) however, mean change in body weight was not significant (−0.3 ± 3.7 kg, P = 0.614) from baseline to post-Ramadan (Fig. 1D).

Adverse events

No major AEs or serious AEs were reported. During Ramadan, one gastroenteritis was reported in 2 patients (n = 2, 0.8%), and one urinary tract infection was reported in one patient (n = 1, 0.4%), but no AEs were related to gliclazide XR treatment.

Discussion

This subgroup analysis of Indian patients who were enrolled in this international, real-world, prospective, observational DIA-RAMADAN study showed that most demographic and clinical characteristics of patients were similar to those of the global DIA-RAMADAN cohort. Indian patients observed the Ramadan fast safely without experiencing any HEs with negligible dropouts (3.7%) due to nonmedical reasons.

There is a higher risk of developing hypoglycaemia with SU treatment compared with other oral antidiabetic drugs, and this led to reservations concerning their use in patients observing the Ramadan fast. However, it is important to note that this risk differs among the available SUs due to different receptor binding affinities and duration of action. Studies have shown that gliclazide was associated with a lower risk of hypoglycaemia in patients with T2DM who fast during Ramadan [8, 13–15, 18–20]. In an observational study comparing HEs in patients receiving vildagliptin versus SUs in India during Ramadan, the incidence of HEs was 4.8% in those receiving glipizide or glibenclamide but not for those receiving gliclazide or glimepiride [21]. A meta-analysis of three randomized trials in patients who received a dipeptidyl peptidase 4 inhibitor or gliclazide during Ramadan fasting reported a similarly lower risk for incidence of symptomatic hypoglycaemia [22]. The STEADFAST study conducted in 557 patients fasting during Ramadan at 69 sites across 16 countries including the Middle East, Europe, and Asia reported similar rates of HEs in patients using gliclazide and vildagliptin [15]. A systematic review assessing efficacy and safety of hypoglycaemic agents in patients with T2DM during Ramadan fast also reported gliclazide as a safer option than other SUs [23]. Lower incidence of HEs in patients using gliclazide XR might be due to its

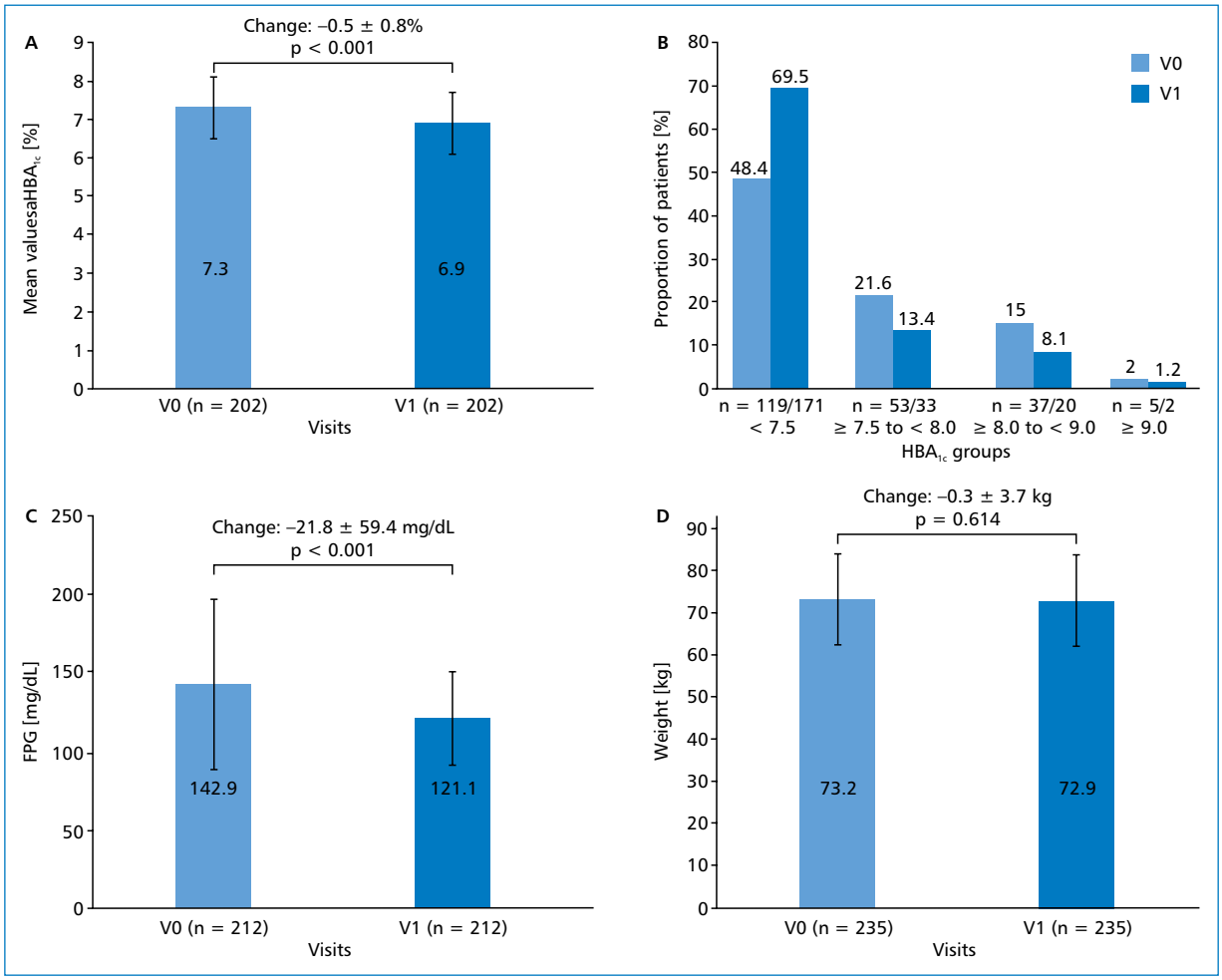

Figure 1. A: HbA1c levels pre-Ramadan baseline visit (V0) and post-Ramadan visit (V1); **B:** Proportion of patients within stratified HbA1c levels at the pre-Ramadan baseline visit (V0) and post-Ramadan visit (V1); **C:** Fasting plasma glucose (FPG) levels pre-Ramadan baseline visit (V0) and post-Ramadan visit (V1); **D:** Patient body weight at the pre-Ramadan baseline visit (V0) and post-Ramadan visit (V1)

selective and reversible binding to SU receptors of the pancreatic β-cells [24, 25]. Various guidelines on managing T2DM during Ramadan suggest adjusting the dose and/or timing of SU intake to reduce the risk of complications [3, 26]. A multicentre observational study reported that switching dosage time from morning to evening for patients on gliclazide XR monotherapy during Ramadan could reduce the incidence of HEs [19]. Following the guidelines and previous studies, patients were advised to take gliclazide XR dose at Iftar that resulted in a very low incidence of HEs in the global DIA-RAMADAN cohort (2.2%) with no HEs reported in the Indian cohort.

Secondary outcomes assessed were changes in HbA_{1c}, FPG, and body weight between pre-and post-Ramadan: gliclazide XR significantly reduced HbA_{1c} and FPG levels of the patients during fasting, with a slight but no significant change in body weight. Previously, a multicentre observational study reported a negligible non-significant rise in HbA_{1c} levels (0.01%, P = 0.958), decrease in body weight (−0.03 kg), and reduction in mean FPG levels (−20 mg/dL) after treatment with SU in Indian patients with T2DM who elected to fast during Ramadan [21]. Similarly, the STEADFAST study also reported similar changes in HbA1c levels with vildagliptin (0.05 ± 0.04%) and gliclazide (−0.03 ± 0.04%) (P = 0.165), and mean reduction in weight (−1.1 ± 0.2 kg) with both medications (P = = 0.987) from pre- to post-Ramadan visits [15]. Overall, changes in HbA_{1c} and FPG levels, and body weight in the Indian cohort were similar to those in the global DIA-RAMADAN cohort indicating that patients using gliclazide XR could consistently maintain glycaemic control and body weight without risk of hypoglycaemia during Ramadan fasting.

In contrast to the 40.7% of the global DIA-RAMADAN population, > 70% of the Indian patients broke their fast during Ramadan. Of these, 2.4% of them

broke their fast for more than three consecutive days due to nonmedical reasons, which was lower than 5.1% in the global population [17].

According to the IDF-DAR risk assessment at the pre-Ramadan visit, no Indian patients were at very high risk of developing hypoglycaemia, but 47 (3.9%) patients from the global cohort were. However, about 43% of Indian patients were advised not to fast, and this proportion was also higher than that in the global population (24.5%) [17]. Patients from the Indian cohort changed their meal size (41.9%) and type (54.5%) and incorporated more carbohydrates (26.8%), protein (31.3%) or fats (43.9%) in their meals during Ramadan than pre-Ramadan period. Whereas, about 32% in the global DIA-RAMADAN study changed their meal type during Ramadan and 15.9% incorporated more carbohydrates in their meals during Ramadan [17]. Overall, the results of the Indian subgroup analyses were found to be similar to those obtained from the global DIA-RAMADAN population. In this study, most patients were on gliclazide XR alone and did not require dose adjustments during or post-Ramadan and showed high treatment adherence. This suggests that patients can be safely treated with gliclazide XR without dose adjustments during Ramadan fasting.

Limitations of the study are similar to those reported in the global study mainly due to the observational nature of the study [17]. This study provided robust real-world evidence for managing T2DM as per the standard clinical practice during Ramadan in India.

Conclusion

Overall, the effectiveness and safety of gliclazide XR in Indian patients was similar to the global DIA-RAMADAN cohort. Gliclazide XR significantly reduced HbA1c with no incidence of hypoglycaemic events in Indian patients with type 2 diabetes undergoing Ramadan fast, suggesting the use without dose modification, at Iftar, to maintain optimal glycaemic control during Ramadan.

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Conflicting interest

Authors declare no conflict of interest.

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REFERENCES:

1. 1. Federation ID. IDF Diabetes Atlas Eighth Edition. International Diabetes Federation Brussels, Belgium; 2019.
2. Saboo B, Joshi S, Shah SN, et al. Management of Diabetes during Fasting and Feasting in India. J Assoc Physicians India. 2019; 67: 70–77.
3. Hassanein M, Al-Arouj M, Hamdy O, et al. International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance. Diabetes and Ramadan: Practical guidelines. Diabetes Res Clin Pract. 2017; 126: 303–316, doi: 10.1016/j.diabres.2017.03.003, indexed in Pubmed: 28347497.
4. Ibrahim S, Benard E, Detournay B, et al. A Population-Based Study of Diabetes and Its Characteristics During the Fasting Month of Ramadan in 13 Countries. Diabetes Care. 2004; 27(10): 2306–2311, doi: 10.2337/diacare.27.10.2306.
5. Jabbar A, Hassanein M, Beshyah SA, et al. CREED study: Hypoglycaemia during Ramadan in individuals with Type 2 diabetes mellitus from three continents. Diabetes Res Clin Pract. 2017; 132: 19–26, doi: 10.1016/j.diabres.2017.07.014, indexed in Pubmed: 28783529.
6. Babineaux SM, Toaima D, Boye KS, et al. Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan in 2010 (CREED). Diabet Med. 2015; 32(6): 819–828, doi: 10.1111/dme.12685, indexed in Pubmed: 25581456.
7. Ahmad J, Pathan MdF, Jaleel MA, et al. Diabetic emergencies including hypoglycemia during Ramadan. Indian J Endocrinol Metab. 2012; 16(4): 512–515, doi: 10.4103/2230-8210.97996, indexed in Pubmed: 22837906.
8. Al Sifri S, Basiounny A, Echtay A, et al. 2010 Ramadan Study Group. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. Int J Clin Pract. 2011; 65(11): 1132–1140, doi: 10.1111/j.1742-1241.2011.02797.x, indexed in Pubmed: 21951832.
9. Sadikot S, Jothydev K, Zargar AH, et al. Clinical practice points for diabetes management during RAMADAN fast. Diabetes Metab Syndr. 2017; 11 Suppl 2: S811–S819, doi: 10.1016/j.dsx.2017.06.003, indexed in Pubmed: 28629656.
10. Khunti K, Hassanein M, Lee MK, et al. Role of Gliclazide MR in the Management of Type 2 Diabetes: Report of a Symposium on Real-World Evidence and New Perspectives. Diabetes Ther. 2020; 11(Suppl 2): 33–48, doi: 10.1007/s13300-020-00833-x, indexed in Pubmed: 32440835.
11. Kalra S, Aamir AH, Raza A, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015; 19(5): 577–596, doi: 10.4103/2230-8210.163171, indexed in Pubmed: 26425465.
12. World Health O. Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus. Geneva: World Health Organization; 2018.
13. Aravind SR, Al Tayeb K, Ismail SB, et al. 2009 Ramadan Study Group. Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: a five-country observational study. Curr Med Res Opin. 2011; 27(6): 1237–1242, doi: 10.1185/03007995.2011.578245, indexed in Pubmed: 21506631.
14. Aravind SR, Ismail SB, Balamurugan R, et al. Hypoglycemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized,

pragmatic study. Curr Med Res Opin. 2012; 28(8): 1289–1296, doi: 10.1185/03007995.2012.707119, indexed in Pubmed: 22738801.
15. Hassanein M, Abdallah K, Schweizer A. A double-blind, randomized trial, including frequent patient-physician contacts and Ramadan-focused advice, assessing vildagliptin and gliclazide in patients with type 2 diabetes fasting during Ramadan: the STEADFAST study. Vasc Health Risk Manag. 2014; 10: 319–326, doi: 10.2147/VHRM.S64038, indexed in Pubmed: 24920915.
16. Joshi SR. Glycemic Variability and Ambulatory Glucose Profile in Indian Diabetics. J Assoc Physicians India. 2016; 64(4): 11–14, indexed in Pubmed: 27734635.
17. Hassanein M, Al Sifri S, Shaikh S, et al. DIA-RAMADAN study investigators. A real-world study in patients with type 2 diabetes mellitus treated with gliclazide modified-release during fasting: DIA-RAMADAN. Diabetes Res Clin Pract. 2020; 163: 108154, doi: 10.1016/j.diabres.2020.108154, indexed in Pubmed: 32330510.
18. Brady EM, Davies MJ, Gray LJ, et al. A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial. Diabetes Obes Metab. 2014; 16(6): 527–536, doi: 10.1111/dom.12249, indexed in Pubmed: 24373063.
19. Zargar AH, Siraj M, Jawa AA, et al. Maintenance of glycaemic control with the evening administration of a long acting sulphonylurea in male type 2 diabetic patients undertaking the Ramadan fast. Int J Clin Pract. 2010; 64(8): 1090–1094, doi: 10.1111/j.1742-1241.2009.02262.x, indexed in Pubmed: 20455956.
20. Sari R, Balci MK, Akbas SH, et al. The effects of diet, sulfonylurea, and Repaglinide therapy on clinical and metabolic parameters in type 2 diabetic patients during Ramadan. Endocr Res. 2004; 30(2): 169–177, doi: 10.1081/erc-200027375, indexed in Pubmed: 15473127.
21. Shete A, Shaikh A, Nayeem KJ, et al. Vildagliptin vs sulfonylurea in Indian Muslim diabetes patients fasting during Ramadan. World J Diabetes. 2013; 4(6): 358–364, doi: 10.4239/wjd.v4.i6.358, indexed in Pubmed: 24379927.
22. Mbanya JC, Al-Sifri S, Abdel-Rahim A, et al. Incidence of hypoglycemia in patients with type 2 diabetes treated with gliclazide versus DPP-4 inhibitors during Ramadan: A meta-analytical approach. Diabetes Res Clin Pract. 2015; 109(2): 226–232, doi: 10.1016/j.diabres.2015.04.030, indexed in Pubmed: 26003888.
23. Rashid F, Abdelgadir E. A systematic review on efficacy and safety of the current hypoglycemic agents in patients with diabetes during Ramadan fasting. Diabetes Metab Syndr. 2019; 13(2): 1413–1429, doi: 10.1016/j.dsx.2019.02.005, indexed in Pubmed: 31336501.
24. Colagiuri S, Matthews D, Leiter LA, et al. The place of gliclazide MR in the evolving type 2 diabetes landscape: A comparison with other sulfonylureas and newer oral antihyperglycemic agents. Diabetes Res Clin Pract. 2018; 143: 1–14, doi: 10.1016/j.diabres.2018.05.028, indexed in Pubmed: 29802958.
25. Seino S, Takahashi H, Takahashi T, et al. Treating diabetes today: a matter of selectivity of sulphonylureas. Diabetes Obes Metab. 2012; 14 Suppl 1: 9–13, doi: 10.1111/j.1463-1326.2011.01507.x, indexed in Pubmed: 22118705.
26. Ibrahim M, Davies MJ, Ahmad E, et al. Recommendations for management of diabetes during Ramadan: update 2020, applying the principles of the ADA/EASD consensus. BMJ Open Diabetes Res Care. 2020; 8(1), doi: 10.1136/bmjdrc-2020-001248, indexed in Pubmed: 32366501.