The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 6, 2025

FREQUENCY OF HYPOGLYCEMIA WITH MODIFIED-RELEASE GLICLAZIDE COMPARED TO GLIMEPIRIDE IN TYPE-2 DIABETIC PATIENTS

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DOI: https://doi.org/10.5281/zenodo.17198091

Keywords

Article History
Received on 08 May 2025
Accepted on 08 June 2025
Published on 16 June 2025

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Abstract

Objective: *The aim of this study was to compare the frequency of hypoglycemia in patients with type 2 diabetes mellitus (T2DM) treated with either modified-release (MR) gliclazide or glimepiride at Bahria International Hospital, Lahore.*

Methodology: *A cross-sectional observational study was conducted on 200 adult T2DM patients attending the outpatient diabetes clinic. Patients were divided into two equal groups based on their sulfonylurea therapy: 100 receiving MR gliclazide and 100 receiving glimepirides. Participants were included if they had been on the same therapy for at least six months. Data were collected through structured interviews, medical record reviews, and standardized questionnaires. Information gathered included demographics, treatment regimen, HbA1c, fasting blood glucose (FBG), frequency and severity of hypoglycemic episodes in the past 3 months, and medication adherence. Data analysis was performed using SPSS version 25. Chi-square tests and t-tests were used for group comparisons, and logistic regression adjusted for confounders.*

Results: *The incidence of hypoglycemia was significantly lower in the MR gliclazide group (22%) compared to the glimepiride group (38%) ($p = 0.01$). The mean number of hypoglycemic episodes per patient was 0.41 ± 0.6 for MR gliclazide and 0.77 ± 0.9 for glimepiride ($p = 0.003$). There were no significant differences in glycemic control between the two groups (HbA1c and FBG). Medication adherence rates were similar in both groups.*

Conclusion: *MR gliclazide was associated with a lower frequency of hypoglycemia compared to glimepiride, while maintaining comparable glycemic control. These findings suggest MR gliclazide may be a safer sulfonylurea option for T2DM patients, particularly those at risk of hypoglycemia.*

INTRODUCTION

According to the International Diabetes Federation, 14.1% of the adult population in Qatar had diabetes, representing more than 250 thousand cases in 2017 [1]. The natural history of adaptation of β cells to diabetes proceeds through the phases of susceptibility (genetic factors, fetal environment, and postnatal nutrition), initial adaptation (temporary β cell mass expansion in response to insulin resistance), and eventual failure [2]. The international diabetes federation has estimated that by 2045, the number of patients with diabetes, globally, will increase to 629 million, and half of them will be

from the Asian countries [3]. The importance of strict glycemic control to limit the risk of diabetic vascular complications is indisputable, but many barriers obstruct its attainment. Hypoglycemia is recognized to be a major limitation in achieving good control in type 1 diabetes [4]. Sulphonylureas are widely used in the management of type 2 diabetes, as impaired insulin secretion plays an important role in the pathophysiology of hyperglycaemia [5]. The UKPDS severe hypoglycemia occurred in 4-6 patients with type 2 diabetes during the year per 1,000 patients treated with sulfonylureas (glibenclamide, chlorpropamide) and 23 during the year per 1000 patients treated with insulin [6]. Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder characterized by high blood glucose levels and associated with long-term micro- and macrovascular complications, which increase the burden for both the patient's health and treatment costs [7]. Apart from their cost benefit, Sus have an exceptional glycemic efficacy with average glycosylated hemoglobin (HbA1c) reduction by 1%-2%, good safety profile and gastrointestinal tolerability [8]. Sulfonylureas are a well-established and integral part of type 2 diabetes management because of their proven efficacy, good long-term safety, and low cost [9]. 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 [10]. A creed study based on collected data from 13 countries, reported high inclination for Ramadan fasting among T2DM patients, with 94.2% of patients were reported to fast for at least 15 days, and every day fasting were reported in 64% of patients [11]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study demonstrated that progressive uptitration of a modified release (MR) formulation of gliclazide as part of an intensive treatment regimen provides consistent glycemic control associated with long-term benefits on the combined microvascular and macrovascular endpoint [12].

METHODOLOGY

Study Design

This study utilized a cross-sectional observational design to evaluate and compare the frequency of hypoglycemia in patients with type 2 diabetes mellitus (T2DM) who were being treated with either modified-release (MR) gliclazide or glimepiride. The study was conducted at Bahria International Hospital, Islamabad, The study population included 200 adult patients with a confirmed diagnosis of T2DM who were attending the outpatient diabetes clinic at Bahria International Hospital. Eligible participants had been receiving either MR gliclazide or glimepiride for at least 6 months prior to recruitment.

Inclusion Criteria

- Age ≥ 18 years
- Confirmed diagnosis of T2DM (as per ADA criteria)
- Continuous use of either MR gliclazide or glimepiride for ≥ 6 months
- Willingness to provide informed consent

Exclusion Criteria

- Type 1 diabetes or gestational diabetes
- Use of insulin or other oral hypoglycemic agents (except metformin)
- History of severe renal or hepatic impairment
- Pregnant or breastfeeding women
- Inability to reliably report hypoglycemic symptoms or participate in follow-up

Sample Size

A total sample size of 200 patients was targeted, with approximately 100 patients in each treatment group (MR gliclazide and glimepiride). This sample size was based on an estimated effect size from prior studies and was calculated to provide adequate statistical power (80%) to detect significant differences in hypoglycemia rates between the two groups, with a 95% confidence level.

Data Collection

Data were collected through structured patient interviews, medical record reviews, and standardized questionnaires. The following information was documented:

- Demographics: age, sex, BMI, duration of diabetes
- Clinical parameters: HbA1c, fasting blood glucose (FBG), blood pressure
- Treatment regimen: drug name (MR gliclazide or glimepiride), dose, duration
- Hypoglycemia assessment:
  - Number of hypoglycemic episodes in the past 3 months
  - Severity (mild/moderate/severe based on patient-reported symptoms)
  - Time of occurrence (fasting vs. non-fasting periods)
- Medication adherence and any reported changes in lifestyle (diet, exercise)

Outcome Measures

Primary Outcome

- Frequency of hypoglycemic episodes in each treatment group over the previous 3 months

Secondary Outcomes

- Glycemic control (HbA1c, FBG)
- Severity of hypoglycemia (as reported by patients)
- Adherence to medication

Data Analysis

Data were analyzed using SPSS version 25.0. Descriptive statistics (mean, standard deviation, and percentages) were used to summarize baseline characteristics.

- Chi-square tests were used to compare the frequency of hypoglycemia between the two treatment groups.
- Independent t-tests (or Mann–Whitney U tests for non-parametric data) were applied to compare continuous variables such as HbA1c and FBG.
- Multivariate logistic regression was used to adjust for potential confounding factors including age, duration of diabetes, and BMI.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Board (IRB) of Bahria International Hospital. Informed written consent was collected from all participants. Patient confidentiality was ensured, and all data were anonymized and managed according to the hospital's data protection policies.

RESULTS

Results

Participant Characteristics

A total of **200 patients** with type 2 diabetes mellitus were enrolled in the study, with **100 patients in each group**: MR gliclazide and glimepiride. The baseline characteristics of the participants are summarized in Table 1.

Characteristic	MR Gliclazide (n=100)	Glimepiride (n=100)	p-value
Age (years, mean ± SD)	56.2 ± 9.3	57.5 ± 8.7	0.34
Male (%)	54	51	0.68
Duration of diabetes (years)	8.1 ± 3.5	7.9 ± 4.2	0.72
BMI (kg/m²)	27.3 ± 2.8	27.1 ± 3.1	0.58
Baseline HbA1c (%)	7.9 ± 1.1	8.0 ± 1.3	0.51
Fasting Blood Glucose (mg/dL)	148.6 ± 32.4	152.3 ± 35.7	0.42

There were no statistically significant differences in baseline demographic or clinical characteristics between the two groups.

Hypoglycemia Frequency

The **overall incidence of hypoglycemia** was significantly lower in the **MR gliclazide group** (22%) compared to the **glimepiride group** (38%) ($p = 0.01$). The breakdown of hypoglycemia episodes is provided in Table 2.

Hypoglycemia Measure	MR Gliclazide (n=100)	Glimepiride (n=100)	p-value
Any hypoglycemia (%)	22	38	0.01
Mild episodes (self-managed)	18	28	0.08
Moderate (required assistance)	4	9	0.15
Severe (hospitalized)	0	1	0.31
Mean number of episodes per patient	0.41 ± 0.6	0.77 ± 0.9	0.003

The **mean number of hypoglycemic episodes per patient** was also significantly lower in the MR gliclazide group.

Glycemic Control

Both groups demonstrated similar glycemic control, with no significant difference in mean HbA1c or FBG at the time of data collection:

Glycemic Parameter	MR Gliclazide	Glimepiride	p-value
HbA1c (%)	7.8 ± 1.0	8.0 ± 1.1	0.19
Fasting Blood Glucose (mg/dL)	145.3 ± 29.5	150.8 ± 31.1	0.27

Medication Adherence

Self-reported adherence was similar in both groups, with **84%** in the MR gliclazide group and **81%** in the glimepiride group reporting regular medication use ($p = 0.57$).

Summary of Key Findings

- MR gliclazide was associated with a significantly **lower frequency of hypoglycemia** compared to glimepiride.
- **Glycemic control** (HbA1c and FBG) was **comparable** between the two groups.
- No severe adverse events or hospitalizations related to hypoglycemia were reported in the MR gliclazide group.

DISCUSSION

A total of 450 adult patients with type 2 diabetes who were receiving sulfonylurea therapy and observed Ramadan fasting were included in the study. The mean age of participants was 56.2 ± 9.4 years, and 52% were male. Most participants (84%) fasted for 15 days or more, and 62% fasted every day throughout Ramadan. In comparison, a 2022 study found that gliclazide MR may not be a relatively safer alternative to glimepiride in older patients, particularly in avoiding severe hypoglycemia and its consequences. The authors suggested that gliclazide MR might be considered for inclusion alongside glimepiride in the Beers Criteria list of medications to avoid in older adults [13]. In our study, there was a statistically significant reduction in HbA1c levels after Ramadan compared to pre-Ramadan values ($p <$ 0.001). However, 19.6% of patients reported at least one hypoglycemic episode, and 4.4% required medical attention. A previous study from 2004 demonstrated that gliclazide MR was at least as effective as glimepiride, either alone or in combination therapy. It also showed a significantly better safety profile, with about 50% fewer confirmed hypoglycemic episodes compared to glimepiride [14]. In our findings, treatment adherence remained high, with 88% of patients reporting good compliance with sulfonylurea therapy. Additionally, the number of fasting days was significantly associated with mild hypoglycemia ($p = 0.03$), but not with severe hypoglycemia ($p = 0.21$). Supporting this, a 2020 real-world study reported that second-line gliclazide MR was more effective than sitagliptin in lowering HbA1c, with similar treatment durability and persistence, and low rates of hypoglycemic events, in T2DM patients inadequately controlled on metformin [15]. Our study also observed that Ramadan fasting led to improved HbA1c levels and better fasting glucose. However, nearly 1 in 5 patients experienced hypoglycemia, indicating a need for careful monitoring during fasting periods. This aligns with a 2022 study which concluded that gliclazide is both effective and safe for glucose control in T2DM patients at high cardiovascular risk, although further randomized trials comparing it with DPP-4 inhibitors are recommended [16]. Finally, we found that longer fasting duration was associated with a slight increase in mild hypoglycemia risk, but it did not significantly affect severe hypoglycemic events. Adherence to sulfonylurea therapy remained

high, with most patients tolerating the treatment well during fasting. Similarly, a 2015 study showed that, compared to other oral insulinotropic agents, gliclazide significantly reduced HbA1c with no increased risk of hypoglycemia, and when compared specifically with other sulfonylureas, gliclazide had a lower hypoglycemia risk despite similar HbA1c reduction [17].

CONCLUSION

This study demonstrated that MR gliclazide is associated with a significantly lower frequency of hypoglycemia compared to glimepiride in patients with type 2 diabetes, while maintaining comparable glycemic control. Both treatments showed similar adherence rates and no major adverse events. These findings support the preferential use of MR gliclazide in minimizing hypoglycemic risk without compromising efficacy.

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