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Majid H Alabbood[1], Nassar T Alibrahim[2], Haider A Alidrisi[3], Ali H Alhamza[2], Ammar M Almomin[1], Ibrahim H Hussein[2]

[1]Department of Medicine, Alzahraa College of Medicine, University of Basrah, Iraq
[2]Faiha Specialized Diabetes, Endocrine and Metabolism Center, Basrah, Iraq
[3]Department of Medicine, College of Medicine, University of Basrah, Iraq

A Study of Combined Oral Anti-Diabetic Drugs during Ramadan

ABSTRACT

Background: The safety and efficacy of combination tablets of metformin plus sulfonylurea or plus dipeptidyl peptidase-4 inhibitors have not been studied previously. This study aimed to compare the efficacy and safety of Gliconorm versus Sitavia plus among patients with Type 2 diabetes mellitus who fast Ramadan.

Methods: This was an open-label study conducted from 1 May 2018 till 1 July 2018. People with type 2 diabetes mellitus who were drug-naïve or on metformin only, with HbA1c < 10 % were included. The participants were divided into two groups. The first group was given Gliconorm (glibenclamide 5 mg + metformin 1000 mg), while the second group was given Sitavia plus (sitagliptin 50 mg + metformin 1000 mg) immediately after Iftar. Glycated hemoglobin (HbA1c) was measured before and after Ramadan. Several home recordings of blood glucose were collected. In addition, patients were asked to report any hypoglycemic or severe hyperglycemic episodes.

Results: A total of 34 participants (18 women) (19 in the first group and 15 in the second group) were involved the study. The mean age was 49.6 ± 9.3 years. HbA1c reduced from 8.7 % (72 mmol/mol) to 7.6 % (60 mmol/mol) and from 8.7% (72 mmol/mol) to 7.7 % (61 mmol/mol) in the first and second group, respectively (p < 0.0001). Only one patient in the first group experienced one episode of hypoglycemia and hyperglycemia.

Conclusions: Both medications seem to be safe and effective during Ramadan fasting. (Clin Diabetol 2022, 11; 2: 61–66)

Keywords: Ramadan, sulfonylurea, dipeptidyl peptidase-4 inhibitors, fasting, hypoglycemia

Introduction

Ramadan Fasting is one of the five pillars of Islam. All healthy adult Muslims should fast the month, which includes refraining from eating, drinking and sexual activity from dawn to sunset [1]. Despite the fact that Islamic rules have exempted sick people such as those with diabetes from fasting, many choose to fast [2]. As Ramadan`s timing is based on the lunar calendar, the length of Ramadan`s day differs depending on the season. For instance, in some parts of the world people may fast for 20 hours a day [1]. In our locality, fasting during May–June (the time of our study) lasts about 14 hours. This represents a great challenge for diabetic patients who practice fasting and place them at increased risk of complications. Of these, the most important are hypoglycemia and dehydration during fasting hours and hyperglycemia post Iftar (the main meal after breaking the fast which coincides with sunset) [3]. Therefore, for people with diabetes who wish to fast Ramadan, a relatively safe and effective treatment should be chosen. Many previous studies tested the efficacy and safety of different antidiabetic medications [4–22]. Based on these studies, several guidelines have been published [1, 23]. Most of the current guidelines recommend against

Address for correspondence:
Majid H Alabbood
Department of Medicine
Izahraa College of Medicine
University of Basrah, Iraq
e-mail: majid.alabbood@uobasrah.edu.iq
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the use of second generation sulfonylurea (SU) during Ramadan due to their hypoglycemic potential [1]. On the other hand, dipeptidyl peptidase-4 inhibitors (DPP-4i) are considered generally safe with minimum side effects especially in terms of hypoglycemia [4, 5, 7, 11, 15, 16, 19, 22]. Few studies compared the efficacy and safety of SU versus DPP4i in head-to-head trials [4, 7, 15, 19]. However, to the best of our knowledge no study has been conducted on the use of both families in combination tablet in Ramadan so far.

The combination of two drugs in one tablet might affect the pharmacodynamics and/or pharmacokinetics of drugs. This study aimed to compare the efficacy and safety of Gliconorm (glibenclamide plus metformin) versus Sitavia plus (sitagliptin plus metformin) among diabetic patients who fast Ramadan.

Material and methods

Study design

This was an open-label non-randomized study conducted at Faiha Specialized Diabetes, Endocrine and Metabolism Center, Basra, Iraq from 1 May 2018 till 1 July 2018. People with type 2 diabetes mellitus (T2DM) (age ≥ 18 years) who were drug-naïve or on metformin only, with HbA1c < 10 % and intended to fast Ramadan were included in the study. On the other hand, those with type 1 diabetes mellitus, those on insulin or oral antidiabetic medication except metformin, pregnant women, those with gestational diabetes, history of diabetic ketoacidosis, liver disease, heart failure (New York Heart Association class III or IV), chronic kidney disease (estimated glomerular filtration rate by Cockroft-Gault < 45 mL/min/1.73 m^2), those who do not wish to fast or had a contraindication for the use of DPP4i were excluded from the study. The eligible participants were divided into two groups in a 1:1 ratio. The first group was given a combination tablet of glibenclamide 5 mg + metformin 1000 mg (Gliconorm, Abiogen pharma, Italy), while the second group was given sitagliptin 50 mg + metformin 1000 mg (Sitavia plus, Pioneer pharma, Iraq) immediately after Iftar. The same starting doses of medications were kept during Ramadan without any change. All the participants were given an individualized meal plan by a dietitian based on their basal metabolic rate. Furthermore, they were instructed to continue their usual daily activity and avoid exercise. At the first visit (at least a month before Ramadan), the following data were gathered: age, gender and duration of diabetes in years. Besides that, body weight and body mass index (BMI) were recorded. In addition, glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) were measured. In addition, all the participants were asked to start their designated treatment at the first visit. During the month of Ramadan, the patients were asked to record several self-monitored blood glucose (SMBG) readings before Iftar and 2 hours postprandial by a glucometer (Accu-Check Aviva Plus, Roche Diabetes Care Inc., Basel, Switzerland). Additionally, patients were asked to report any hypoglycemic (SMBG < 70 mg/dL) or severe hyperglycemic (SMBG > 300 mg/dL) episodes as well as the number of days they broke their fast.

Laboratory measurements

Fasting plasma glucose was measured by the hexokinase method (Cobas Integra C111, Roche Diagnostics, Basel, Switzerland). HbA1c was measured by Cation-exchange high-performance liquid chromatography method (Bio-Rad D-10, Bio-Rad Laboratories, CA, USA).

Outcome measures

The primary endpoint of this study was the mean difference in HbA1c before and after Ramadan. While the secondary endpoints included mean change in fasting and random blood glucose, episodes of any hypoglycemia (defined as SMBG < 70 mg/dL), severe hypoglycemia (requiring assistance by another person), severe hyperglycemia (defined as SMBG > 300 mg/dL) and any hospital admission for diabetes-related emergencies. The participants were reassessed after the end of Ramadan within a time window of 10 days where body weight, BMI, HbA1c and FPG were measured again. In addition, all SMBG readings were reviewed and recorded.

Statistical analysis

Descriptive data are presented as the mean ± SD for normally distributed data or, when distribution was skewed, as the median and interquartile range. Changes in the means of HbA1c values, FPG, pre- and post-Iftar glucose, and BMI before and after Ramadan were analyzed by paired Student's *t* test. All data analyses were performed with IBM SPSS for Windows 25.0 (SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered significant.

Ethical considerations

This study was designed and conducted in accordance with the principles stated by the Declaration of Helsinki of 1975, as revised in 2013. The study was reviewed and approved by the Scientific Committee of Basrah Health Directorate on the 15th of April 2018 with the code (APR/203). An informed consent was obtained from all human adult participants. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

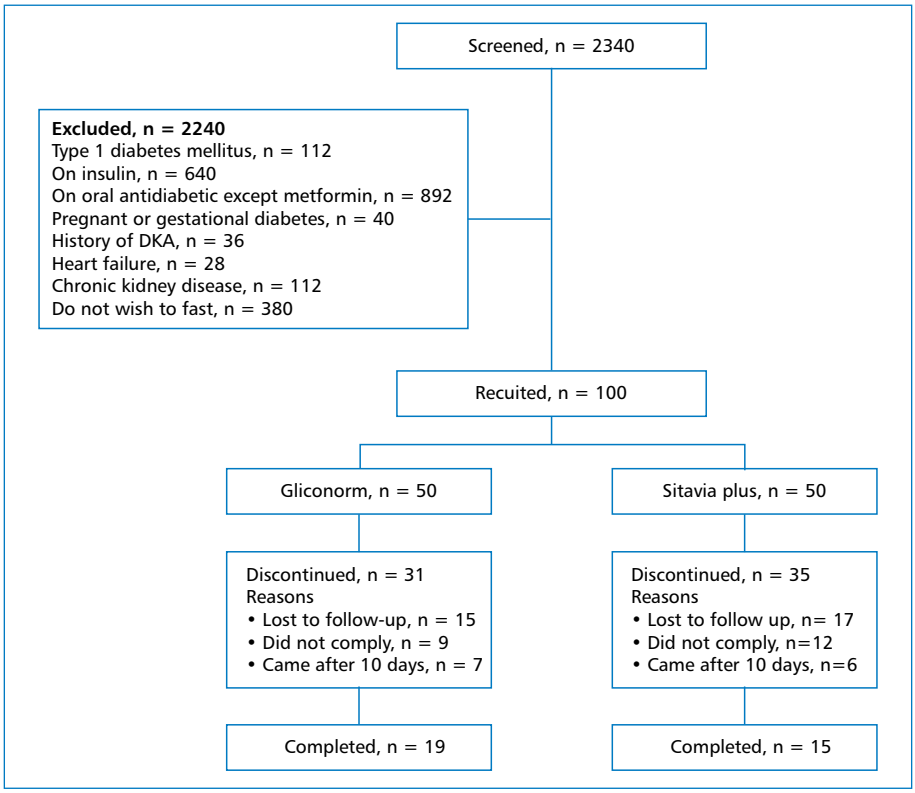

Figure 1. Study Flow Chart

Table 1. Basic Characteristics of the Participants

Variable	Gliconorm	Sitavia plus	Total
Age [years] (mean ± SD)	51 ± 10	47 ± 8	49.6 ± 9.3
Gender [n]			
Males	12	4	16
Females	7	11	18
Duration of diabetes [years] (median ± SE)	3.3 ± 0.7	1.8 ± 0.5	2.9 ± 0.5
BMI [kg/m^2] (mean ± SD)	32.0 ± 1.0	33.0 ± 2.0	32.0 ± 1.0
Entry HbA1c [%] (mean ± SD) [mmol/mol]	8.7 ± 1.4 (72)	8.7 ± 1.4 (72)	8.7 ± 1.4 (72)

BMI — body mass index; HbA1c — glycated hemoglobin

Results

Participants' characteristics

At the screening visit, 100 participants were recruited and divided equally into the two arms. However, ultimately a total of 34 participants (18 women) (19 in the first group and 15 in the second group) completed the study (Fig. 1).

The mean age was 49.6 ± 9.3 years with a mean duration of diabetes of 2.9 ± 0.5 years. The mean BMI was 32.0 ± 1.0 kg/m^2 (Tab. 1).

Glycemic control

There was a significant reduction in HbA1c from 8.7% (72 mmol/mol) to 7.6 % (60 mmol/mol) and from 8.7% (72 mmol/mol) to 7.7 % (61 mmol/mol) in the first and second groups, respectively ($p < 0.0001$), as shown in Figure 2.

A total of 268 SMBG readings were recorded by the participants. The mean fasting and postprandial glucose values were 123 mg/dL and 193 mg/dL in the first group and 130 mg/dl and 177 mg/dL in the second group, respectively (p value between groups 0.4 for fasting and 0.08 for postprandial).

Adverse events

Only one patient in the first group experienced one episode of mild hypoglycemia that did not necessitate breaking the fast and one episode of severe hypergly-

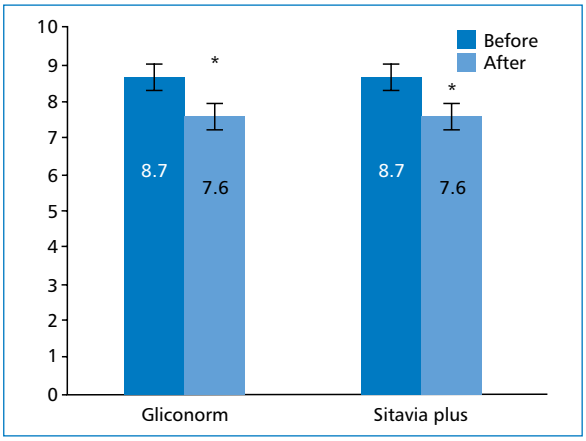

Figure 2. Change in HbA1c in Both Groups Before and After Ramadan. *P value < 0.0001

cemia. None of the participants reported admission to hospital for diabetes-related complications. There was no change in BMI in both groups at the end of Ramadan. All the participants fasted the whole month.

Discussion

This study evaluated the efficacy and safety of combination therapy (SU + metformin versus DPP4i + metformin) in Muslim patients with T2DM during Ramadan. This study shows a significant reduction in HbA1c before and after Ramadan in both arms. However, there was no significant difference in the efficacy of both tested drugs (Gliconorm and Sitavia plus) in reducing HbA1c. In terms of glycemic control, the results of previous studies on glibenclamide are contradictory. One study documented a reduction in HbA1c by 0.9% [19]; two studies revealed no change in HbA1c [5, 18] and a single study showed an increment from baseline by 0.4% [10]. Similarly, previous studies on DPP4i showed either no change in HbA1c [11, 15], or a minimal reduction by 0.2% and 0.4% [5, 16]. Our study is the first one that documented the larger and significant reduction in HbA1c in people who used glibenclamide and sitagliptin in combination with metformin. This might be explained by two factors: First, we used a combination tablet that might have changed the pharmacodynamics and/or the pharmacokinetics of the drug and patient compliance with the therapy. Second, the majority of the participants in our study were newly diagnosed as is evident by the short mean duration of diabetes (2.9 ± 0.5 years). We observed a nonsignificant difference in the means of both fasting and postprandial glucose in both groups. However, we have not compared the changes in the mean fasting and postprandial glucose readings in the same group before and after Ramadan. Only one participant in the Gliconorm arm reported a single episode of mild hypoglycemia and a single episode of severe hyperglycemia. However, these 2 episodes passed uneventfully and the index participant completed his fast safely. Several observational and randomized controlled trials (RCTs) showed that the use of second generation SUs such as glibenclamide during Ramadan carries a high risk of hypoglycemia with an incidence ranging from 8–25% [4, 5, 7, 10, 18]. Nevertheless, none of these studies except one done by Belkhadir *et al.* compared the incidence of hypoglycemia before and after Ramadan [10]. Therefore, the hypoglycemia incidence might be related to the drug itself rather than to its use in Ramadan. Belkhadir *et al.* conducted a RCT on glibenclamide and found a lower rate of hypoglycemic events unexpectedly during Ramadan. The same study has documented the lower ever reported incidence of hypoglycemia in the glibenclamide group [10]. This might be explained by the fact that the baseline HbA1c in that study was high (13.7%), which makes severe hypoglycemia very unlikely.

The rate of hypoglycemic episodes in Belkhadir study was 10/183 which is similar to our study (1/19) [10]. Given the small sample size in our study, we may have underestimated the rate of hypoglycemia among Gliconorm arm. There is a wide variation in the reported incidence of hypoglycemia among patients using DPP4i in previous studies ranging from 0–34.2% [4, 5, 7, 11, 13, 15, 16, 19, 22]. The highest hypoglycemia rate was documented by Halimi *et al.*'s study which was an observational study. The low baseline HbA1c and the prolong fasting hours (16 hours) might explain the high reported rate in that study [13]. Given the observational design of their study, the possibility of over-reporting should be considered. None of the participants in our study reported hypoglycemia in the Sitavia plus arm. This is in line with two other studies where the rate was zero as well [15, 22]. However, the small sample size in our study might underpower it to detect the real rate of hypoglycemia.

Ramadan fasting represents a great challenge for people with T2DM due to two potential complications. First, severe hypoglycemia mainly during the last two hours of daytime especially if the patient is using anti-diabetic drug with hypoglycemic potential. Second, severe hyperglycemia immediately after breaking the fast by Iftar meal as this meal is usually rich in carbohydrates and considered to be like a feast rather than a meal [24]. Therefore, people with T2DM need a safe and effective medication during Ramadan. A safe medication usually means it has low hypoglycemia risk and effective medication means it reduces HbA1c

effectively during the month of Ramadan. According to our results, both studied medications demonstrated safety and effectiveness.

In our study, we have not demonstrated any significant change in body weight and consequently in BMI which is in line with other studies [10, 13, 15, 16, 25]. In contrast, other studies demonstrated a statistically significant weight loss in DPP4i more than in SU [5, 19, 22]. Only one study showed an increment in body weight from baseline in both DPP4i and SU groups and it was statistically significant in the latter [11]. Generally, previous observations in non-fasting times have demonstrated a weight neutral effect of DPP4i and weight gain effect of SU. During Ramadan, the total calorie intake is generally reduced (fasting people are consuming two meals only). This might explain the weight neutral phenomena of both treatment groups that we have observed in our study. Besides that, the addition of metformin might have minimized the weight gaining effect of SU.

In this study, patients in the Gliconorm arm were older than those in the Sitavia plus arm (51 years and 47 years, respectively. However, this difference was not large enough to affect the results. Furthermore, a previous study has shown there is no effect for age difference on glycemic control of patients [26].

Males predominated in the Gliconorm arm while in the Sitavia plus arm, females were the most predominant. The effect of gender on glycemic control is a matter of debate. Some studies demonstrated an effect with females have worse control [27]. On the other hand, other studies demonstrated no difference [28]. There are several limitations to this study that warrants consideration. First, the small sample size might have underpowered the ability of the study to estimate the secondary endpoints (incidence of hypoglycemic and hyperglycemic episodes during Ramadan). Second, it has been conducted in a single center. Third, the high dropout rate which is mainly attributed to failure of majority of the participants to show up at the follow-up visit within the pre-specified time limit after Ramadan (10 days). This time window was set as such to minimize the effect of excessive consumption of carbohydrates that usually follows Ramadan fasting during Eid Festival. Finally, given the short period of fasting (a month), the use of fructosamine might have been more robust indicator of glycemic control than HbA1c. However, most of the previous studies that were conducted during Ramadan utilized the latter as a surrogate of glycemic control. On the other hand, there are strength points that deserve to be mentioned. First, the prospective design of the study has allowed a systematic and detailed follow up and outcome definition. Second, the participants were instructed to report and record blood sugar at the time of hypoglycemia and several times after breaking the fast by two hours to study hyperglycemia. Finally, to limit the confounding effect of dietary intake and exercise, all the participants were asked to follow an individualized meal plan and to avoid exercise during Ramadan.

Conclusions

It seems that the use of both drugs, Gliconorm and Sitavia plus, is effective and safe during the month of Ramadan. Proper patient education plays a major role in minimizing the anticipated side effects of most medications during fasting. The use of combination tablets during Ramadan has a promising beneficial outcome in terms of improved patient compliance and convenience as well as minimizing side effects. Larger RCTs are required to build a robust conclusion on the safety and efficacy of combination tablets during Ramadan fasting.

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Conflict of interest

None declared.

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