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The Efficacy and Safety of Metformin and Glimepiride Combination among Jordanian Patients with Type 2 Diabetes during Ramadan

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ABSTRACT

The Aims of the study: The prevalence of Type 2 diabetes mellitus (T2DM) is increasing worldwide including Islamic countries. Ramadan fasting increases risk of complications from T2DM especially hypoglycemia. The primary objective of the study was to assess glycemic control and incidence of hypoglycemia before, during and after Ramadan. Methods: One hundred adult Jordanian patients with Patients with T2DM who were on dual therapy with metformin and glimepiride and practice Ramadan were recruited. Glycemic control was assessed by HbA1c and fasting blood glucose (FBG), in addition to number of hypoglycemic episodes, before, during and after Ramadan. Results There was a significant decrease in HbA1cand FBG at the end of Ramadan compared to that before Ramadan (10.6±1.9 vs. 9.4±1.7 and 386.4±110) vs. 271.9 ±102.4; respectively). On the other hand, the number of hypoglycemic episodes was significantly less six to eight weeks after Ramadan than that during Ramadan ($p<0.001$), and those during Ramadan were significantly less than those prior to Ramadan. No statistically significant correlation ($p>0.05$) was detected between the number of hypoglycemic episodes and FBG or HbA1c at all visits. However, the percentage of patients with hypoglycemia during Ramadan was higher than that of after Ramadan (86% vs. 41%, $p<0.01$). Conclusion: While Ramadan fasting might be considered efficacious in patients with Patients with T2DM on combination of glimepiride and metformin, patients and/or their caregivers should be educated on the monitoring for signs and symptoms of hypoglycemia.

Keywords Hypoglycemia, Glimepiride, Metformin, Ramadan, Type 2 diabetes.

1. INTRODUCTION

Diabetes mellitus is a widespread chronic progressive disease with a global prevalence that is worryingly growing. In 2013,382 million people suffered from diabetes and the number is estimated to rise to 592 million by 2035[1].Because of the urbanization and socioeconomic developments, a 10% annual increase in the prevalence of diabetes was observed in countries with large Muslim populations[2]. Worldwide, almost 1.6 billion of the world's population follows Islam.

Fasting during the month of Ramadan is essential to Islamic faith. Ramadan is the ninth month of the Islamic lunar calendar. During this month, Adult Muslims are required to abstain from eating, drinking, smoking and taking oral drugs between sunrise and sunset[3].Ramadan can occur any time in the year and lasts for up to 30 days. The duration of fasting can range from a few to more than 20 hours depending on the geographic location and the

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season of the year. Islam exempts people with serious illness from the obligation of fasting, if fasting might adversely affect patient's condition. Although Patients with diabetes fall in this category, many diabetic patients insist to fast the holy month of Ramadan[4]. The population-based Epidemiology of Diabetes and Ramadan study (EPIDIAR) showed that almost 43%of patients with Type 1 diabetes(T1DM) and 79%of patients with Type 2 diabetes (T2DM) from 13 Islamic countries reported fasting for at least15 days during Ramadan[5]. Ramadan Fasting increases the potential complications in patients with T2DM. The EPIDIAR study also showed that fasting increased significantly the risk of severe hyperglycemia by 5-fold and severe hypoglycemia by 7.5-fold in diabetic patients during Ramadan, compared with previous months. Moreover, up to 2% of the fasting Patients with T2DM required hospitalization because they experienced at least one episode of severe hypoglycemia [5], [6]. Therefore, in the context of fasting, healthcare professionals need to be considerate to patients who are eager to fast [7]. If modifications can be made to a patient's treatment regime, they can be counselled about these. Pharmacists plays an important role as they can offer professional advice on the management of medicines and can communicate with the patient's endocrinologist to make any necessary changes to their medicines regime in preparation for Ramadan.[8]

The primary objective of the study was to assess glycemic control before, during and after Ramadan in terms of HbA1c and FBG. The glycemic control between newly diagnosed subjects and subjects already being treated for T2DMat the end of the study was assessed.

The secondary objective of the study was to assess the incidence of hypoglycemic episodes before, during and after Ramadan. The relationship between glycemic control and number of hypoglycemic episodes before and during Ramadan was also evaluated.

Research design and Methods

This was an observational study of Muslim patients with T2DMreceivingdual therapy of metformin and glimepiride during the holy month of Ramadan. Patients who aged 18 years and over, and willing to participate in fasting throughout Ramadan month, were included in the study. Participants attended diabetes clinic in Prince Ali University Hospital and Jordanian Royal Medical Services. The study was carried out From June to September in 2017. All patients participating in the study received an education regarding the management of their diabetes and identification of hypoglycemia events during Ramadan.

Sample size was done by G*power 3.1.10 base on study by Shin *et al.*[9], that is to detect a difference of 1 unit in HbA1c before and after Ramadan, and have 80% power, and 0.05 error, a 89 patients would need to be recruited. Therefore, we recruited 100 patients to account for dropouts.

Accordingly, out of 143 patients approached, a total of 100 Patients with T2DM treated with dual therapy of metformin-glimepiride who practiced Ramadan fasting were included to the study (response rate 70%). Fifty patients were newly diagnosed subjects (diagnosed in the 12 months or less preceding inclusion) and the remaining were subjects already being treated forT2DM.

Patients were requested to attend diabetes clinic in four visits. A screening visit (Visit 0) was at the inclusion of the study (One month before Ramadan). Visit 1 was just at the start of Ramadan (Within the first five days of Ramadan). Visit 2 was at the end of Ramadan (Last five days of Ramadan). Finally visit 3 was between 45-60 days after the end of Ramadan. At every visit, the number of hypoglycemic episodes and a routine laboratory tests including fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) were assessed. Hypoglycemic episodes were defined asymptomatic; based on self-monitoring of blood glucose using a glucometer (defined as ≤70 mg/dL).

During there- and post-Ramadan observation periods, subjects administered the study drugs as usually prescribed. During Ramadan, study drugs were

administered at the time of breaking the fast in the evening. The doses of study drugs were kept stable throughout the length of the study, except when medically contraindicated (recurrent hypoglycemia or hyperglycemia reaching 250 mg/dl or more).

The following patients were not eligible for this study: patients with type 1 diabetes, patients with T2DM treated with insulin or blood glucose-lowering agents other than the study medication, pregnant or breastfeeding women, patients with known hypersensitivity to metformin or glimepiride, and finally patients with diabetic ketoacidosis or/and progressive fatal disease.

Statistical analysis

Mean and standard deviation were used to describe continuous variables, and percentages to describe categorical variables. Repeated-measures ANOVA was used to compare glycemic control at V0, V1, V2 and V3 followed by Tukey's post-hoc analysis. Independent t-test was used to compare glycemic control in patients with short vs. long duration T2DM. Number of hypoglycemic episodes at V0, V1, V2 and V3 was compared using Wilcoxon-Signed Ranks test followed by post-hoc analysis. Percentage of patients with hypoglycemia episodes before, during and after Ramadan was compared using McNamara test between each of the two groups. Spearman correlation was done to assess the relationship between HbA1c, FBG and number of hypoglycemic episodes. All statistical tests were considered significant at p-value less than 0.05. SPSS® statistical software version20 was used to carry on all analyses.

Results:

Baseline characteristics

One hundred patients with T2DM were recruited. Table 1 describes baseline characteristics (demographics) of these patients.

Table 1: Baseline characteristics (demographics) of patients.

	Mean (SD)	Range
Age (year)	57.4 (13.2)	(30-93)
Weight (kg)	77.4 (11.3)	(55-105)
Height (cm)	169.2 (7.1)	(155-190)
BMI (kg/m^2)	26.8 (2.8)	(23-29)
Time since first diagnosis (years)	26.5 (24.4)	(2-120)
With 12 months	50%	
More than 12 months	50%	
Glimepiride daily dose (mg)	5.9 (35)	(2-16)
Gender		
Female (%)	56	
Male (%)	44	

Glycemic control (as measured by HbA1c and FBG)

Repeated-measures ANOVA was used to compare HbA1c and FBG at V0, V1, V2 and V3 as depicted in **table 2**. The mean HbA1c values were statistically significantly different among visits [F (1.7, 167.7) = 106.5, p < 0.0001]. Mean FBG levels were similarly statistically significantly different [F (2.113, 209.231=77.06, p<0.0001]. Post-hoc Bonferroni correction revealed that there was a significant drop in HbA1c after the beginning, during (V0 vs. V1, V2, V3 and V3, V1 vs. V2 and V3; p<0.0001) and after Ramadan (V2 vs. V3, p=0.001). As for FBG levels, there was a

statistically significant decrease after the beginning, during (V0 vs. V1, V2, and V3, V1 vs. V2 and V3; p<0.0001) but **not** after Ramadan (V2 vs. V3, p=1.00).

Table 2: Glycemic control before, during, at the end and after Ramadan. Data are represented as means.

Parameter Mean (SD)	Visit 0	Visit 1	Visit 2	Visit 3
HbA1c (%)	10.2 (1.9)	9.8 (1.8)	9.4 (1.7)*	9.2 (1.5)
FBG (mg/ld.)	386.4 (110)	325.5 (97.8)	271.9 (102.4)*	258.3 (100.5)

*P<0.05 for visit 2 vs. visit 0.

Glycemic control (according to duration of diabetes)

HbA1c and FBG were compared at each time point between patients which were diagnosed within 1 year and those diagnosed for more than one year (Table 3). Although, HbA1c values tend to be higher in those with longer time since diagnosis, no statistically significant differences were detected between both HbA1c and FBG at V3, where FBG was significantly higher in patients with longer duration of disease (after Ramadan).

Table 3: Glycemic control according to duration of diabetes at each time point. Data are represented by means (*p<0.05).

Parameter	Time since diagnosis	
	Within 12 months (n=50)	More than 12 months (n=50)
HbA1c- visit 0	9.9 (1.9)	10.4 (1.9)
FBG- visit 0	391.9 (117.3)	380.9 (103.0)
HbA1c-visit 1	9.6 (1.7)	10.0 (1.8)
FBG (mg/dl)- visit 1	330.5 (107.2)	320.6 (88.1)
HbA1c-visit 2	9.2 (1.7)	9.5 (1.6)
FBG (mg/dl)- visit 2	265.2 (93.2)	278.5 (111.3)
HbA1c-visit 3	9.0 (1.6)	9.4 (1.5)
FBG (mg/dl)- visit 3	238.3 (95.4)	278.3 (102.3)*

Frequency of hypoglycemic episodes

The number of hypoglycemic episodes was significantly less post-Ramadan than that during Ramadan (p<0.001), and those during Ramadan were significantly less than those prior to Ramadan. No statistically significant correlation (p>0.05) was detected between the number of hypoglycemic episodes and FBG or HbA1c at all visits (data now shown).

In addition, the percentage of patients with and without hypoglycemia was compared before, during and after Ramadan (Table 4). Percentage of patients with hypoglycemia was significantly higher before and during Ramadan than those six to eight weeks after it.

Table 4: Number of hypoglycemic episodes before, during, and after Ramadan. Described as median and Inter-quartile range (IQR).

Time point	Median (IQR)	Patients with hypoglycemia (%)
Visit 0	2 (0-4)	71
Visit 1	1 (1-2)	86
Visit 4	0 (0-1)	41*

*P<0.01 for visit 4 vs. visit 1.

Discussion

Fasting is optional during the holy month of Ramadan for diabetic patients. Yet, many Muslims prefer to abstain from food and water for about 12-20 hours in observance of this pillar. This might expose these patient to less glycemic control and higher risk of hypoglycemia when compared to that of non-fasting periods, especially when taking medications that can increase the risk of hypoglycemia , namely insulin and sulfonylureas[10]. The aim of the present study was to compare glycemic control, and hypoglycemia in Patients with T2DM_ who are treated with a combination of metformin and glimepiride_ before, during and 6 to 8 weeks after Ramadan. Our results showed that Ramadan fasting did not affect the efficacy nor safety of the combination from glimepiride and metformin.

Previous literature showed similar findings to our study. M'guil and colleagues (2008) [11] assessed the safety of Ramadan fasting in 120 Moroccan patients (62 females, 58 males) with T2DM who were on diet and/or gliclazide (belongs to sulfonylureas). Our study, however, evaluated the effect of a combination of metformin and a sulfonylurea (glimepiride). Various parameters were measured at four occasions. Prior Ramadan fasting, days 15 and 29 days of fasting and 15 days after Ramadan ends. With regard to diabetes control, only in females, fasting and 2-hr postprandial glucose levels, and insulin-like growth factor (IGF-1) decreased during Ramadan but returned to be close to baseline values after Ramadan was over. The later results resembles our finding as patients had hypoglycemia during Ramadan, but recovered during the post-Ramadan period. Insulin levels exhibited the same later pattern in both males and females. HOMA-IR continued to decrease even when assessed 15 days after fasting. Plasma fructosamine decreased after fasting in males, but plasma C-protein and HbA1c did not change, like our findings

Similarly, Sahin *et al.* (2013) [9], observed 122 patients with T2DM (67.2% females) to evaluate their glycemic control during Ramadan in fasting and non-fasting group. Patients were treated with different antidiabetic regimens. About 66% of patients were treated with mono- or biotherapy of oral antidiabetic drugs (OAD), 7.4 % with a combination of OAD plus eventide, 6.5 % with a combination of insulin plus OAD divided between glandes and metformin or sit gliptin),and 19.7 % with insulin alone. These percentages were similar in both arms of the study. Comparable to our findings, Shin *et al.* showed that there was a tendency of higher frequency of hyperglycemia and hypoglycemia episodes during fasting but this was not statistically significant. However, the frequency of hyperglycemia was associated with reduction of insulin dose. In our study, we did not have insulin, and the dose of both medications was constant throughout the study which gives our results more conformity. Moreover, other parameters of glycemic control including fasting blood glucose (FBG), post-prandial glucose (PPG), fructosamine, HbA1c and fasting insulin did not change significantly in the fasting group. In Turkey, the effects of glimepiride (n=21), repaglinide (n=18), and insulin glargine (n=10) in fasting Patients with T2DM on the

glucose metabolism were compared to non-fasting controls [12]. FBG, PPG, HbA1c, and fructosamine were assessed in before Ramadan, immediately after Ramadan and 1-month after Ramadan. There was no significant change in FBG, PPG, and HbA1c variables in fasting diabetics before Ramadan when compared to those shortly after Ramadan and 1-month after Ramadan. The later matched results from our study. However, PPG was found to be significantly higher in***n on-fasting*** control diabetic sat both time-points after Ramadan. Fructosamine levels increased significantly in both fasting group and non-fasting group 1-month after Ramadan in patients treated with glimepiride or repglinide or glargine. Risk of hypoglycemia did not significantly differ between fasting and non-fasting diabetics in patients treated with three drug therapies [12]. However, the later study did not evaluated the combined effect of metformin and glimepiride. The glimepiride study group (GSG) (2005)[13] evaluated the effect of Ramadan fasting on control of T2DM in 332 patients, form 33 centers in six countries (Algeria, Egypt, Indonesia, Jordan, Lebanon, and Malaysia), controlled on glimepiride ***only***, unlike ours which evaluated a biotherapy with metformin One hundred of patients were newly diagnosed and 232 were already-treated. Patients were assessed at baseline (V0 or inclusion visit), start (V1), during (V2) and 45-75 day after Ramadan (V3). HbA1c values decreased significantly in both newly diagnosed and subjects who were already treated. The mean FBG value at the baseline, simultaneously, decreased. In line with our findings, hypoglycemic events were 25 at V1, 15 at V2 and 8 at V3, especially in the already treated group. GSG concluded that the efficacy and safety of the same median dose of glimepiride (2 mg/day) in Patients with T2DM was not changed during Ramadan fasting, even when the time of administration of glimepiride is changed from the morning to the evening.

In continuum to the work of GSG[13], the significance of our study is that it was first relatively large observational longitudinal study to evaluate the potential effect of Ramadan fasting on glycemic control and hypoglycemia in Jordanian patients with T2DM taking a combination of metformin and glimepiride. The efficacy of this combination was unaltered in our 100 patients. ***However,*** the incidence of ***hypoglycemia was lower after Ramadan*** when compared to that of during and pre-Ramadan time points. But, no symptomatic or server hypoglycemic episodes were reported. Our study is limited by the lack of non-fasting control Patients with T2DM although patients' baseline can serve as their own controls. Future studies should aim to compare fasting patients to non-fasting counterparts. Also, since patients were visiting outpatient clinics, their adherence to lifestyle recommendations and medication could not be accurately assessed.

Conclusion

While Ramadan fasting might be considered efficacious in Patients with T2DM on combination of glimepiride and metformin, patients who insist on fasting and/or their caregivers should be assessed before and during Ramadan, and educated on their dietary plans, physical activities, as well as monitoring for signs and symptoms of hypoglycemia.

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Compliance with ethical standards

Conflict of interest the authors declare that they have no conflict of interest.

Ethical standard Approval for the study was obtained from the ethical committee associated with the Faculty of Medicine at Muta University and Royal Medical Services (Reference number: 20170).

Human rights all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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فعالية ومأمونية استخدام دواء محتوي على الميتفورمين وجليمبيريد في مرضى السكري من النوع 2 في الأردن خلال شهر رمضان

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ملخص

الأهداف: انتشار داء السكري من النوع 2 (T2DM) في جميع أنحاء العالم بما في ذلك البلدان الإسلامية في زيادة مستمرة. يزيد صيام رمضان من خطر حدوث مضاعفات من T2DM وخاصة نقص السكر في الدم. كان الهدف الأساسي من الدراسة هو تقييم التحكم في نسبة السكر في الدم ومعدل حدوث نقص السكر في الدم قبل وأثناء وبعد شهر رمضان. منهجية البحث: تضمنت الدراسة مائة مريض أردني بالغ من مرضى T2DM والذين كانوا يخضعون للعلاج المزدوج بالميتفورمين والجليميبيريد خلال الصيام. تم تقييم التحكم في نسبة السكر في الدم بواسطة HbA1c ونسبة الجلوكوز في الدم (FBG) ، بالإضافة إلى عدد نوبات سكر الدم ، قبل وأثناء وبعد شهر رمضان. النتائج: كان هناك انخفاض ملحوظ في HbA1c و FBG في نهاية شهر رمضان مقارنةً به قبل شهر رمضان (10.6 ± 1.9 مقابل 9.4 ± 1.7 و 386.4 ± 110 مقابل 271.9 ± 102.4, على التوالي). على الجانب الآخر ، كان عدد نوبات نقص السكر في الدم أقل بكثير من ستة إلى ثمانية أسابيع بعد رمضان مقارنة بشهر رمضان ($p<0.001$) ، وكانت تلك خلال شهر رمضان أقل بكثير من تلك التي سبقت رمضان. لم يتم الكشف عن ارتباط ذي دلالة إحصائية ($p>0.05$) بين عدد نوبات سكر الدم و FBG أو HbA1c في جميع الزيارات. ومع ذلك ، كانت نسبة المرضى الذين يعانون من نقص السكر في الدم خلال شهر رمضان أعلى مما كانت عليه بعد رمضان (86٪ مقابل 41٪ ،$p<0.01$). الاستنتاجات: في حين أن صيام رمضان يمكن اعتباره فعالًا في المرضى الذين يعانون من T2DM على مزيج من جليمبيريد والميتفورمين ، يجب تثقيف المرضى و / أو مقدمي الرعاية حول مراقبة علامات وأعراض نقص السكر في الدم.

الكلمات الدالة: نقص السكر فى الدم ، جليمبيريد ، ميتفورمين، رمضان ، السكري من النوع 2.

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