Glycemic effects of vildagliptin in patients with type 2 diabetes before, during and after the period of fasting in Ramadan

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Abstract

Objective: To study the incidence of hypoglycemia, glycemic control and body weight changes in patients with type 2 diabetes treated with vildagliptin and metformin *versus* another group treated with sulphonylureas and metformin during and after the period of fasting in Ramadan.

Patients and methods: This is a randomized open-label clinical trial that recruited 69 patients previously treated with a combination therapy of metformin and sulphonylurea. Patients in the control group were maintained on their usual metformin and sulphonylurea regimen with dose adjustment for the fasting period. Patients in the study group were given vildagliptin 50 mg twice daily (at Suhur and at Iftar). One group remained on the previous background therapy unchanged and the other group was switched from sulphonylurea to vildagliptin in combination with metformin. Four visits were scheduled, one before the beginning of Ramadan (baseline), a second visit at mid Ramadan, a third at the end of Ramadan and a final visit 1 month after the end of Ramadan. At every visit, patients were assessed for hypoglycemic events and patient education was given on lifestyle needs and hypoglycemia monitoring and management.

Results: The calculated change in hemoglobin A1c from baseline to last visit was similar for both groups. The incidence of hypoglycemia during Ramadan was higher in the control group (26 episodes *versus* 19 episodes in the study group); this result was not statistically significant ($p = 0.334$). However, the number of patients who dropped out from the study because of discomfort due to treatment and fear of hypoglycemia was higher in the control group.

Conclusion: For patients who insist on observing the fast, physicians can allow it only with close follow up and monitoring for hypoglycemic events, and vildagliptin may be a better agent than sulphonylurea.

Keywords: hypoglycemic events, metformin, Ramadan fasting, sulphonylurea, type 2 diabetes, vildagliptin

Introduction

Ramadan is a month of obligatory daily fasting in Islam and is the ninth month of the Islamic calendar. During this month, fasting Muslims refrain from eating, drinking, smoking and use of oral medications from predawn to after sunset; however, there are no restrictions on food or fluid intake between sunset and dawn. Two meals per day are consumed during this month, one after sunset, referred to as Iftar, and the other before dawn, referred to as Suhur. Islam exempts the sick from the holy duty of fasting, especially if

fasting might exacerbate the patient's condition. Patients with diabetes fall under this category because their chronic metabolic disorder might put them at high risk of a series of complications [Al-Arouj *et al.* 2005]. Nevertheless, many patients with diabetes insist on observing the Ramadan fast, which in turn generates a medical challenge for both patients and physicians.

Hypoglycemia can have an adverse effect on the quality of life in patients with diabetes, is a limiting factor in glycemic control, and forms an

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obstacle in compliance to medication and treatment [Amiel *et al.* 2008; Alvarez Guisasola *et al.* 2008]. Skipping meals and a reduction in food intake are the main causes for developing hypoglycemia in such patients during the Ramadan fast [Amiel *et al.* 2008].

Severe hypoglycemia can lead to serious morbidity, provoking major vascular events such as stroke, myocardial infarction, acute cardiac failure and ventricular arrhythmias [Zammit and Frier, 2005].

For patients with diabetes whether to fast or not is a personal decision that should be made after careful consideration of the risks associated with fasting. The issue has to be clearly discussed with the patient's physician. Most physicians advise patients with diabetes not to undertake fasting. However, some do allow their patients to fast provided they closely follow the recommendations of their healthcare providers for a safer fasting.

The EPIDIAR study [Salti *et al.* 2004] reported that 78.7% of patients with type 2 diabetes mellitus fasted for at least 15 days during Ramadan. In 2003, a study by Laarjani and colleagues demonstrated that during Ramadan fasting, a slight decrease in fasting serum glucose may occur in healthy subjects who are normoglycemic [Laarjani *et al.* 2003]. Previous studies have shown that fasting during Ramadan has no adverse effects on glycemic control in patients with type 2 diabetes [Yarahmadi *et al.* 2003]. In addition, some studies have suggested improved glycemic control [Katibi *et al.* 2010]. For patients with type 2 diabetes who fast during Ramadan, acute metabolic complications are found to be the major problem. Some studies reported increased hypoglycemic events [Salti *et al.* 2004; Salman *et al.* 1992], whereas others did not [Mafauzy *et al.* 1990; The Glimepiride in Ramadan Study Group, 2005].

Patients and methods

The study is an interventional, randomized open-label clinical trial. It has been reviewed and approved by the Institutional Review Board at the American University of Beirut. Informed consent was obtained from 69 adult patients with type 2 diabetes who were insulin naïve and did not have a history of ketoacidosis. All patients intended to fast for Ramadan willingly and had been on a combination therapy of metformin and sulphonylurea for at least 6 months. They had body mass

index (BMI) greater than 25 and less than 40 kg/m² and hemoglobin A1c (HbA1c) greater than 6.5%. Patients in the control group were kept on the same long-acting sulphonylurea medication regimen (glimepiride or gliclazide), with dose adjustment for the fasting period. The study group patients were given vildagliptin 50 mg twice daily (at Suhur and at Iftar). Vildagliptin was added to the regimen instead of the sulphonylurea agent. The metformin dose was kept the same for both groups. Of the 69 recruited patients, only 44 concluded the study. Patients were seen at baseline, before the beginning of Ramadan, at mid Ramadan (2 weeks after its beginning), at the end of Ramadan (just after Eid el Fitr) and 1 month after the end of Ramadan. At every visit, the patient provided the results of an eight-point glucose self-monitoring profile and BMI was recorded together with waist and hip circumferences. The eight-point glucose profile was measured before and after Ramadan as follows: fasting, 2 h after breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner, before sleep and next day fasting. During the month of fasting, the eight-point glucose profile was measured as follows: before Suhur, 2 h after Suhur, at 12 noon, at 2 pm, before Iftar, 2 h after Iftar, before sleep and next day before Suhur. The eight-point profile was a useful tool to assess the presence of hypoglycemic episodes and to help with medication dose adjustment if needed.

At every visit, patients were assessed for hypoglycemic episodes and a routine lab work up including fasting blood glucose and HbA1c was carried out. Patient education emphasized lifestyle changes, including diet and exercise, hypoglycemic episode monitoring by self glucose monitoring at home, as well as education on assessing hypoglycemic symptoms and management. Hypoglycemia was defined based on symptoms of hypoglycemia that improved with sugar intake or any value less than 70 mg/dl recorded by self glucose monitoring. Medications were kept at a stable dose throughout the length of the study, except when medically contraindicated (recurrent hypoglycemia or hyperglycemia reaching 250 mg/dl or more). The dose of sulphonylurea was increased or decreased by 1 mg for glimepiride or 30 mg for gliclazide according to fasting glucose readings.

Statistical analysis

The analysis for comparing the change in HbA1c and BMI before and after Ramadan for both

Table 1. Baseline characteristics for study subjects.

	Vildagliptin group	Control group	
Participants (N, % of total)	30 (43.5%)	39 (56.5%)	
Age (mean $\pm$ SD, years)	57.0 $\pm$ 9.6	54.6 $\pm$ 9.2	$p = 0.293$
Baseline HbA1c (mean $\pm$ SD, %)	7.93 $\pm$ 1.48	8.47 $\pm$ 1.71	$p = 0.193$
Baseline BMI (mean $\pm$ SD, kg/m ²)	29.49 $\pm$ 4.66	28.90 $\pm$ 4.49	$p = 0.612$
Duration of diabetes (mean $\pm$ SD, years)	9.8 $\pm$ 9.2	8.4 $\pm$ 6.4	$p = 0.872$

BMI, body mass index; HbA1c, hemoglobin A1c; SD, standard deviation.

groups was carried out using independent samples Student's *t* test given that both variables are normally distributed across the population. The difference in the number of hypoglycemic episodes accruing before and during Ramadan was computed to allow comparison of the occurrence of hypoglycemia for patients on vildagliptin and sulphonylurea under similar clinical conditions. Pearson's χ^2 test was used to compare hypoglycemic events between the two groups. As a secondary outcome, the variables of HbA1c, BMI and hypoglycemic events were compared for the same patients before and at the end of Ramadan. The analysis continued using dependent samples *t* test for HbA1c and BMI, and using Wilcoxon's signed rank test for hypoglycemia (considered a continuous variable with number of occurrences).

Results

The study population included men and women over 35 years old with type 2 diabetes and BMI 25–40 kg/m² who intended to fast for Ramadan willingly and who were insulin naïve with HbA1c greater than 6.5%. All patients had been on combination therapy of metformin and sulphonylurea for at least 6 months. Baseline characteristics for age, duration of diabetes, initial BMI and HbA1c were similar for both groups (Table 1).

The calculated change in HbA1c was similar for both groups. Mean HbA1c levels in the vildagliptin group were higher at baseline than at the end of Ramadan [7.93% $\pm$ 1.47% *versus* 7.10% $\pm$ 0.84%; Figure 1(a)]. Mean HbA1c levels in the sulphonylurea group were also higher at baseline than at the end of Ramadan [8.47% $\pm$ 1.75% *versus* 7.51% $\pm$ 1.16%; Figure 1(a)].

Fasting blood sugar in both groups was found to be higher at baseline than at the end of the study [150.18 $\pm$ 54.31 *versus* 132.43 $\pm$ 25.11 mg/dl in

Figure 1. Hemoglobin A1c (HbA1c) before and after Ramadan in the vildagliptin group *versus* the sulphonylurea group. (b) Fasting blood sugar (FBS) at baseline and at the end of the study in the vildagliptin group *versus* the sulphonylurea group.

the vildagliptin group and 170.85 $\pm$ 64.46 *versus* 139.89 $\pm$ 47.30 mg/dl; Figure 1(b)].

The overall incidence of hypoglycemia during Ramadan was higher in the sulphonylurea group *versus* the study group (26 *versus* 19). This was not statistically significant [$p = 0.334$; Figure 2(a, b)].

Figure 2. (a) Overall incidence of hypoglycemia in the vildagliptin group *versus* the sulphonylurea group during the month of Ramadan. (b) Number of patients experiencing at least one episode of hypoglycemia during Ramadan fasting in the vildagliptin group *versus* the sulphonylurea group. (c) Number of patients breaking the fast in the vildagliptin group *versus* the sulphonylurea group.

The number of patients experiencing at least one episode of hypoglycemia was higher in the sulphonylurea group (eight patients) compared with the vildagliptin group (five patients).

Patients breaking the fast due to discomfort, intolerance to fasting and fear of hypoglycemia were all in the sulphonylurea group (eight patients) and there were no patients in the vildagliptin group breaking the fast [Figure 2(c)]. The dropout rate was around 36% as 25 patients did not complete the study. The main reasons for dropping out were as follows: the patient stopped fasting because of a loss of interest in the study without any medical reason (seven patients: three in the study group and four in the control group); the patient was traveling (five patients: three in the study group and two in the control group); the patient

developed a medical condition that prevented fasting (nephrolithiasis, deep venous thrombosis and thyroidectomy) (three patients: two in the study group and one in the control group; one patient in the control group took a drug that was noncompatible with the protocol (Figure 3).

The BMI in the vildagliptin group was higher at baseline than after Ramadan (29.49 ± 4.66 *versus* 28.83 ± 4.72 kg/m²), whereas in the sulphonylurea group, the BMI was higher after Ramadan (28.90 ± 4.49 at baseline *versus* 29.79 ± 3.87 kg/m² after Ramadan; Figure 4).

Discussion

Vildagliptin is a drug in a new class of oral diabetes medications called dipeptidyl peptidase 4 inhibitors (DPP-4) inhibitors. The drug reduces blood glucose concentrations by enhancing the effects of 'incretins'. These drugs are therefore also known as 'incretin enhancers'. Vildagliptin acts by improving pancreatic islet function, thus enhancing β - and α -cell sensitivity to glucose [Ahrén and Foley, 2008].

A recent observational study by Devendra and colleagues showed that the addition of vildagliptin to metformin therapy during Ramadan in fasting Muslim patients with type 2 diabetes has advantages in terms of reduction in the incidence of hypoglycemia [Devendra *et al.* 2009]. In this study during the month of Ramadan, there was one severe case of hypoglycemia in the group of patients treated with gliclazide and none in the vildagliptin group. There were 12 times more hypoglycemic events in the gliclazide group compared with the vildagliptin group. A 52-week study by Ferrannini and colleagues showed that in patients with diabetes inadequately controlled by metformin, the addition of vildagliptin to their regimen significantly reduced the severity of hypoglycemic events compared with the addition of glimepiride [Ferrannini *et al.* 2009]. Similar data were not reported in our study, in which the incidence of hypoglycemia was lower in the vildagliptin intervention group (by 13.5%: 19 in the vildagliptin group *versus* 26 in the control group) but this was not statistically significant. In our study, the occurrence of hypoglycemia was similar for both groups compared with the study by Devendra and colleagues, which also showed the association of gliclazide and vildagliptin with a decrease in HbA1c and a slight insignificant increase in weight [Devendra *et al.* 2009]. The

Figure 3. Reasons for dropping out of the study in the vildagliptin group *versus* the sulphonylurea group during the month of Ramadan.

Figure 4. Body mass index (BMI) at baseline and at the end of the study in the vildagliptin group *versus* the sulphonylurea group.

increase in hypoglycemic events during the month of Ramadan has been previously reported in the literature [Salti *et al.* 2004; Uysal *et al.* 1998]. Uysal and colleagues reported that 19.5% of patients would have more hypoglycemic episodes during Ramadan [Uysal *et al.* 1998], which is a smaller percentage than that obtained for the vildagliptin and control groups in our study. They did not encounter any episodes of severe hypoglycemia [Uysal *et al.* 1998]. Our study reflected slightly different results as the general trend for all patients was a decrease in HbA1c and a decrease in waist circumference. It is interesting to note that, at baseline and at the end of the study, mean HbA1c was higher in the control group, but this difference was not statistically significant ($p = 0.19$) and thus should not alter the outcome of comparison. This decrease was found for both groups and did not differ between the control and

vildagliptin groups. Thus, this improved glycemic control and decrease in waist circumference is linked to the effects of Ramadan fasting rather than the effects of the DPP-4 inhibitor. Several studies in the literature failed to demonstrate a significant change in HbA1c [Uysal *et al.* 1998; Laajam, 1990; M'guil *et al.* 2008; Sulimani *et al.* 1991; Alberti *et al.* 2008] or weight [Uysal *et al.* 1998; Laajam, 1990; Alberti *et al.* 2008] when comparing patients before and after Ramadan. However, our results were not unique as a study from Saudi Arabia reported improved HbA1c and decreased weight after Ramadan [Khatib and Shafagoj, 2004]. Along this line of thought, some studies have also shown better blood glucose levels during Ramadan [M'guil *et al.* 2008; Khatib and Shafagoj, 2004; Katibi *et al.* 2010].

The American Diabetic Association (ADA) recommends caution in the use of sulphonylureas during Ramadan. This is related to the fact that diabetes medication is the most common cause of hypoglycemia, especially when the goal of treatment is intensive glycemic control and the treatment medication involves an insulin or an insulin secretagogue such as sulphonylurea and when this is associated with irregular eating habits or skipped meals, which is similar to what happens during Ramadan.

In our study, we found a slight benefit of changing the patient's baseline drug regimen to include vildagliptin in addition to metformin instead of sulphonylurea.

Physicians need to respect the decision of their patients with type 2 diabetes who elect to fast during the month of Ramadan. The literature as well as this study did not show adverse outcomes due to severe hypoglycemia, HbA1c and weight parameters [Uysal *et al.* 1998; Laajam *et al.* 1990; M'guil *et al.* 2008; Sulimani *et al.* 1991; Alberti

et al. 2008; Khatib and Shafagoj, 2004]. However, a clear care plan should be designed taking into consideration the changes in sleeping and eating habits during this month, along with the necessary treatment modifications. It is also crucial to educate patients on meal planning, glucose self monitoring and proper dosing and timing of their medications. Indeed, for the entire sample population of patients with type 2 diabetes, there was a trend toward more hypoglycemic episodes during the month of fasting compared with the following nonfasting month. Nevertheless, one of the observed outcomes of this study still shows better glycemic and weight control at the end of Ramadan. These results could be due to the close follow up set out by the study protocol or to the change in eating habits during the fasting month.

Finally, the small sample size and the very high dropout rate were major limitations of our study, especially in view of the very short duration of the study (around 2–4 months). Thus our study results need to be corroborated by larger studies.

Conclusion

The primary outcome of the study showed no significant difference in hypoglycemic events for patients on vildagliptin compared with patients on sulphonylurea during the month of fasting. Only patients in the sulphonylurea group broke the fast because of fear of hypoglycemia. The addition of this DPP-4 inhibitor to the patient's metformin regimen did not affect overall glycemic and weight control. However, there seems to be an improvement in glycemic and weight control after the fasting period for patients in both groups. Ramadan fasting with close monitoring and follow up is possible for patients with type 2 diabetes who want to observe the month of Ramadan. However, physicians should closely monitor their patients during fasting since it is associated with a higher incidence of hypoglycemia.

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Conflict of interest

The authors have no relevant conflict of interest to disclose.

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