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ORIGINAL ARTICLE

Repaglinide plus single-dose insulin glargine: a safe regimen for low-risk type 2 diabetic patients who insist on fasting in Ramadan

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Abstract Aim of this prospective study is to evaluate the effect of repaglinide t.i.d. (three times a day) plus single-dose insulin glargine regimen in low-risk type 2 diabetic patients during Ramadan fasting. Participants had been taking the regimen for at least 3 months. Patients with a history of diabetic coma, severe hypoglycemic crisis or repeating attacks of hypoglycemia were excluded. Hypoglycemic unawareness, kidney or liver disease or HbA1c over 8% were also accepted as exclusion criteria. Eleven patients who insisted on this worship and eight non-fasting cases were involved. All were told to make home-glucose-monitorisation weekly and report any hypoglycemic event throughout Ramadan. Fasting blood glucose (FBG), post-prandial blood glucose (PBG) and fructosamine levels, body weights and blood pressures were recorded just before and after Ramadan. Seven patients in each group concluded the follow-up. Any significant change was detected in the parameters in either groups ($P > 0.05$). Glucose control remained unchanged; fructosamine 318.14 ± 65.38 versus 317.28 ± 52.80 mmol/L in fasting group, 290.71 ± 38.48 versus 290 ± 38.56 mmol/L in non-fasting group. None of them exhibited either a major or a minor hypoglycemic event. The results of this pilot study indicated that repaglinide t.i.d. plus single-dose insulin glargine regimen was safe for low-risk type 2 diabetic patients who insisted on fasting during Ramadan.

Keywords Fasting hypoglycemia · Hypoglycemic agents · Insulin analogs

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Introduction

Fasting during Ramadan, the holy month of Islam, is an obligatory duty for healthy adult Muslims. People who fast during Ramadan must abstain from eating, drinking, smoking and taking medications from daybreak to sunset. The EPIDIAR study showed that about 40–50 millions of diabetic patients insisted on fasting during Ramadan, despite of the warnings of their doctors and religious authorities [1, 2]. Insulin glargine is a long-acting insulin analog which mimicks basal insulin secretion without exhibiting serum peaks [3]. Repaglinide is an oral short-acting insulin secretagogue which helps to regulate post-prandial glucose elevation [4]. Repaglinide t.i.d. with single-dose insulin glargine is a safe combination regimen for type 2 diabetic patients [5].

Although glycemic control is thought to be impaired by Ramadan fasting among diabetic population, there is only a few data about the safety and efficacy of antidiabetic medications during this period [2, 6–9]. In literature, till now, there has not been a controlled study which inquires the effects of a combination therapy; an oral hypoglycemic agent with insulin during Ramadan fasting among diabetic subjects.

In this study, we inquired the safety of the combination regimen; premeal repaglinide plus single-dose insulin glargine among low-risk type 2 diabetic patients who insisted on fasting during Ramadan.

Subjects, materials and methods

Patients with type 2 diabetes mellitus, who had been taking repaglinide t.i.d. (three times a day) and single-dose insulin glargine for at least 3 months were called by telephone to learn whether they would fast during Ramadan or not. The possible risks related to prolonged fasting were told each patient. Patients with a history of diabetic ketoacidosis, non-ketotic hyperosmolar coma, severe hypoglycemic crisis or repeating attacks of hypoglycemia were excluded. Hypoglycemic unawareness, presence of kidney or liver disease or detection of HbA1c level over 8% were also accepted as exclusion criteria. Eligible patients who insisted on performing the worship (fasting group $n = 11$) and the ones who declared that they would not fast during Ramadan (non-fasting group $n = 8$) were invited to undergo an evaluation. The study was approved by the Local Ethics Committee and each patient gave written informed consent.

A total of 19 patients (aged between 35 and 65 years) were included. Before Ramadan fasting, physical examination of each patient was performed, body weights and blood pressures were recorded. Insulin glargine and repaglinide doses were noted. Following an overnight fasting, venous blood samples were obtained to determine fasting blood glucose (FBG), post-prandial blood glucose (PBG) and fructosamine levels. Plasma glucose and fructosamine assays were performed with Abbot Aeroset brand equipment by using the spectrophotometric method. The procedures were repeated at the end of the month.

At inclusion, each participant was taking repaglinide three times a day before meals in equal doses with a single injection of insulin glargine at bed-time (10:00–11:00 p.m.). In fasting group, repaglinide dosing was rearranged according to the time when food consumption took place. In order to mimick the eating pattern of the non-fasting group, they were told to eat three big meals a day; one at the termination of fasting, another at midnight and the last at Sahur (pre-dawn meal) when the new fasting day was to begin. No change was performed regarding insulin glargine. Medical treatment regimen left unchanged in non-fasting group, as well as the timing of meals: breakfast, lunch and dinner.

All patients were advised to adhere with their routine exercise status and total calorie intake. The recommended range of carbonhydrate intake was 50–60% of total calories for each participant. They were told to monitorize and record their blood glucose levels at home. They were also strongly warned to note the time and frequency of hypoglycemic episodes all through the month (blood glucose below 60 mg/dL). The findings were evaluated at visits every week. The dose of repaglinide and/or insulin glargine were planned to be rearranged when needed.

SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, IL, USA) was used for the statistical analyses. Data are presented as means ± SD. A value for $P < 0.05$ was considered statistically significant. *Standard descriptive analysis*, *independent samples T test* and *non-parametric-related samples T test* were used where appropriate.

Results

Four patients in fasting group (36.6%) and one patient in non-fasting group (12.5%) were excluded due to unattendance to control visits and/or inadherence to regular fasting.

Seven cases in each group concluded the study. General characteristics of the participants at inclusion are exhibited in Table 1. The groups did not differ regarding gender, weight, systolic and diastolic blood pressure, FBG and PBG levels and fructosamine levels. The patients in non-fasting group were significantly older ($P = 0.028$).

None of the parameters were found to differ significantly at the end of follow-up (Table 2). The doses of repaglinide and insulin glargine remained unchanged in

Table 1 General characteristics of the fasting and non-fasting groups at inclusion

	Fasting group ($n = 7$)	Non-fasting group ($n = 7$)	P
Gender (F/M) (n)	3/4	3/4	0.704
Age (years)	50.14 ± 9.68 (min. 40–max. 60)	60.57 ± 5.38 (min. 52–max. 66)	0.028
Weight (kg)	83.57 ± 10.68	75.64 ± 15.67	0.290
SBP (mmHg)	130.0 ± 14.14	135.71 ± 18.12	0.523
DBP (mmHg)	81.42 ± 10.69	80.0 ± 8.16	0.784
FBG (mg/dL)	140.42 ± 17.55	122.0 ± 24.89	0.136
PBG (mg/dL)	195.57 ± 52.92	163.42 ± 46.12	0.249
Fructosamine (mmol/L)	318.14 ± 65.38	290.71 ± 38.48	0.358

F female, *M* male, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *PBG* post-prandial glucose
Fructosamine (reference interval 205–285 mmol/L)

Table 2 The change in parameters regarding glucose control and body weight in fasting and non-fasting groups during Ramadan

	Fasting group ($n = 7$) before versus after	P	Non-fasting group ($n = 7$) before versus after	P
Weight (kg)	83.57 ± 10.68 versus 83.30 ± 10.64	0.603	75.64 ± 15.67 versus 76.80 ± 16.54	0.170
FPG (mg/dL)	140.42 ± 17.55 versus 146.28 ± 32.43	0.707	122.0 ± 24.89 versus 113.57 ± 19.52	0.424
PBG (mg/dL)	195.57 ± 52.92 versus 170.0 ± 52.08	0.219	163.42 ± 46.12 versus 188.57 ± 84.43	0.276
Fructosamine (mmol/L)	318.14 ± 65.38 versus 317.28 ± 52.80	0.949	290.71 ± 38.48 versus 290.0 ± 38.56	0.948

both fasting and non-fasting groups throughout the study period; repaglinide 6.429 ± 2.699 and 5.571 ± 3.541 mg ($P = 0.620$); insulin glargine 15.43 ± 6.05 and 13.29 ± 5.56 units ($P = 0.503$), respectively.

The participants reported neither a major nor a minor hypoglycemic event. Any dose adjustement was required for the groups.

Discussion

Hyperglycemia and hypoglycemia are major risks associated with fasting in patients with diabetes. The extensive EPIDIAR study showed a 5-fold increase in the incidence of hyperglycemia and 7.5-fold increase in the incidence of hypoglycemia in patients with type 2 diabetes who insisted on fasting during Ramadan [1]. None of our patients in fasting group reported an hypoglycemic event. This finding may be explained by the strict inclusion criteria which enabled our including low-risk patients. Nevertheless, these criteria inevitably reduced the number of eligible patients for the study. Their glycemic control were detected not to worsen as indicated by the unchanged fructosamine levels, as well.

This is the first study which inquires the safety of pre-meal repaglinide plus single-dose insulin glargine among patients with type 2 diabetes mellitus. Our results indicated that this regimen was safe for low-risk type 2 diabetic patients who insisted on fasting during Ramadan.

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