

# An Open Label Comparative Study of Glimpiride Versus Repaglinide in Type 2 Diabetes Mellitus Muslim Subjects During the Month of Ramadan

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## Summary

This study was conducted to compare the treatment efficacy between a prandial glucose regulator, repaglinide and a new sulphonylurea, glimepiride in Muslim Type 2 diabetic patients who practice Ramadan fasting. Forty-one patients, previously treated with a sulphonylurea or metformin, were divided to receive either repaglinide (n=20, preprandially three-times daily) or glimepiride (n=21, preprandially once daily) 3 months before the month of Ramadan. During Ramadan, patients modified their eating pattern to two meals daily, and the triple doses of repaglinide were redistributed to two preprandial doses. Four point blood glucose monitoring were performed weekly during the month of Ramadan and the subsequent month. Measurements of the 4-point blood glucose were significantly lower in the glimepiride group compared to the repaglinide group both during and after Ramadan. The glycaemic excursion was better in the morning for the repaglinide group and better in the afternoon and evening for the glimepiride group during the Ramadan period. There was no statistically significant difference in the incidence of hypoglycaemia between the two groups during and after Ramadan. There was no difference in the glycaemic excursion post-Ramadan. The longer duration of action of glimepiride may offer an advantage over repaglinide during the 13.5 hours of fast in Ramadan for diabetic patients.

**Key Words:** Median blood glucose, Ramadan, Glycaemic excursion, Hyperglycaemic range

## Introduction

Muslims observing the fast are required to abstain not only from eating and drinking, but also from consuming oral medications and intravenous nutritional fluids. In Malaysia this is about 13 hours a day. The month of Ramadan has 28 to 30 days. Islam recommends that fasting Muslims eat a meal before dawn, called pre-dawn meal "*sabur*."

Glimepiride (Amaryl®) is an oral anti diabetic agent indicated for type 2 diabetes mellitus when diet, physical exercise and weight reduction alone is not adequate. Glimepiride can be administered as a monotherapy once a day or in combination with

insulin. It is the most potent lowest dose of the sulphonylureas (SU) and has a long duration of action with a half-life of five hours. It is metabolized in the liver to inactive products. Glimepiride works by making the available insulin more effective by its effects on muscle and fat cells and on the liver. Glimepiride decreases blood glucose concentrations, mainly by stimulating insulin release from pancreatic beta cells. This effect is based predominantly on an improved responsiveness of the pancreatic beta cells to physiological glucose stimulus<sup>1,2</sup>.

Repaglinide (NovoNorm®) on the other hand is an insulin secretagogue with a rapid onset and relatively short duration of action<sup>3,4,5</sup> developed for the role of

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prandial glucose regulation (PGR). The PGR principle is to provide insulin when needed by stimulating endogenous insulin secretion in response to food intake. Repaglinide is designed to be taken with each main meal, if and when eaten, to prevent excessive postprandial glucose excursion. The anti-diabetic efficacy of PGR with repaglinide has been demonstrated in placebo-controlled studies<sup>6,7,8</sup>, in which markers of glycaemic control were significantly improved compared with placebo. Temporal improvements in glycaemic control have also been shown in comparative trials with other oral anti-diabetic agents: repaglinide provides a level of glycaemic control at least equivalent to that obtained with SUs<sup>9,11,12</sup> or metformin<sup>13</sup>, and superior to troglitazone<sup>14</sup>. Meal-associated treatment with repaglinide is well tolerated irrespective of the number of meals consumed in a day<sup>15</sup>. Furthermore, in well-controlled Type 2 diabetic patients who miss or delay a meal, the risk of hypoglycaemia is reduced compared with longer-acting SUs (e.g. glibenclamide)<sup>16</sup>.

The purpose of this study was to compare glycaemic control in Muslim Type 2 diabetic patients treated with a post prandial agent (repaglinide) or a long acting SU (glimepiride) during Ramadan. Presently, there is no study comparing the pattern of blood glucose control using either a short acting SU (repaglinide) or a long acting SU (glimepiride).

## Materials and Methods

Forty-one Muslim subjects who fulfilled the WHO criteria for type 2 diabetes mellitus were recruited from the Endocrine Clinic of our institution, 3 months before Ramadan. Prior to enrolment into the study, the patients were on SU either alone or in combination with metformin. Informed consent was obtained prior to commencement of any trial-related activities. The trial was a 5-month open-label, parallel-group comparison between repaglinide and glimepiride treatment, involving 41 patients. After screening at visit 1 to assess eligibility, the patients were randomized block (4x4) into either repaglinide or glimepiride. The study drug was titrated monthly over a 3-month period before Ramadan (visit 1) to reach the optimal dose of 4 mg tid for repaglinide and 6mg daily for glimepiride. The patients visited the clinic every month for assessment and dosage adjustment. In the repaglinide group, the initial starting dose was 1 mg with each main meal and the dosage was increased by 1 mg at the next clinic visit if the fasting blood glucose was above

8 mmol/L until reach the maximum dose of 4 mg tid was reached. When a meal was omitted the dose was not taken.

Glimepiride doses of 1mg were administered once-daily in the morning. Daily doses of more than 1 mg and up to 2mg, were given in two separate doses, with the second dose being taken before the evening meal. The maximum dose was 6 mg daily. One week before Ramadan, blood investigations were carried out (visit 2). The monthly titration period was followed by a 4-week maintenance period during the month of Ramadan), Clinic visit 3 fell during the third week of Ramadan.

During Ramadan, the patients consumed two main meals instead of three meals per day: one pre-dawn and another after sunset. Occasionally a late snack might be taken before retiring to bed. A four point blood glucose measurement using a glucometer was performed by the patient weekly during Ramadan (pre-dawn, 12noon, before 'break of fast' and 10 pm). At the investigator's discretion, the total daily dose of repaglinide (based on three-meal dosing before Ramadan) were re-distributed to two doses, while that of glimepiride remained unchanged and was taken at the breaking of fast. After Ramadan, the patients resumed the appropriate drug dosage for three-meal dosing until the last visit (one month after Ramadan-visit 4). A four point blood glucose measurement was performed by the patient weekly during this period before seeing the doctor at visit 4. Written informed consent was obtained from all patients before they received the study medication. The trial was approved by the ethics and research committee of the Faculty of Medicine, National University of Malaysia.

## Efficacy Assessments

"Glycaemic excursion" is defined as the changes of blood glucose from one point to the next point in time. The patients were requested to record the blood glucose level during any symptomatic hypoglycaemic episodes. A four-point blood glucose measurement was performed by the patient weekly during Ramadan [pre-dawn, 12 noon, 'before break of fast' and 10 pm (bedtime)]. Another 4-point blood glucose readings were taken weekly for a month after Ramadan. The performance of each home blood glucose kit was checked and data in patients' diaries were transferred to record forms during each subsequent clinic visit.

HbA1c was analysed centrally at the chemical pathology lab, National University Hospital Malaysia.

### Safety Assessments

The investigators recorded all adverse events experienced by patients throughout the study. Hypoglycaemic episodes were recorded as those with a blood glucose measurement of <3.1 mmol/L, in accordance with the definition of the American Diabetic Association.

### Statistical Analysis

The power of the study was 80% and sample size was based on calculation from Gelon E: Clinical trials in Career record: Enviroment Health Prospect 32:31,1979. The difference in median blood glucose was 0.5;  $\alpha=0.05$ , power  $(1-\beta) = 0.80$  (2 sided test). Data was analysed using the Statistical Package for Social Sciences computer program (SPSS version 11.0). P values of less than 0.05 were considered statistically significant. Adjustment for baseline levels was made to reduce inter-patient variation in the comparison of the two treatments. Blood glucose changes were tested by chi square method.

### Results

The data from 41 patients receiving either repaglinide (20 patients) or glimepiride (21 patients) were analysed. Thirty-eight patients completed the trial in accordance with the protocol. The reasons for discontinuation of the study were non-compliance with protocol (2 patients), and inability to fast during Ramadan due to an illness (1 patient). These three patients were in the repaglinide group. Demographic data for the patients at 3 months prior to Ramadan are presented in Table I. The dosage of repaglinide during the study was optimized with a median dose of 2 mg tid (minimum; 0.5 mg tid; maximum 4 mg tid) compared to a median dose of glimepiride of 3 mg daily dose (minimum; 1 mg od; maximum 6mg od). As for the patients who completed the trial, 58.8 percent reached the optimal dose level in the repaglinide group (6 mg daily) and 57.1 percent reached the optimal dose level during the titration in the glimepiride group (3 mg daily).

### Glycaemic control during Ramadan

Four- point blood glucose were done weekly for four weeks during Ramadan. The median of these blood glucose results are shown in Figure 1.

The median predawn blood glucose level was 9.2(4.0-13.3) mmol/L in the repaglinide group compared to 6.0(3.0-11.7) mmol/L in the glimepiride group ( $p<0.001$ ). The median 12 noon blood glucose level was 8.3(5.1-14.6) mmol/L in the repaglinide group

compared to 6.9(3.3-12.8) mmol/L in the glimepiride group ( $p=0.003$ ). The median 'before break of fast' blood glucose was 7.0(4.5-11.7) mmol/L in the repaglinide group compared to 4.9(3.4-8.6) mmol/L in the glimepiride group ( $p<0.001$ ). The median bedtime blood glucose was 9.5(4.9-14.6) mmol/L in the repaglinide group compared to lower median blood glucose level of 7.7(3.0-15.1) mmol/L in the glimepiride group ( $p<0.001$ ).

### Glucose excursions during Ramadan

During Ramadan there was a change of median blood glucose profile in both groups glycaemic excursions (Figure 2).

From 'pre-dawn' till '12 noon' the median blood glucose level in the repaglinide group reduced from 9.2 (4.0-13.2) mmol/L to 8.3 (5.1-14.6) mmol/L. In contrast, the median blood glucose profile in the glimepiride group showed increment trend from pre dawn to 12 noon, 6.0(3.0-11.7) mmol/L to 6.9(3.3-12.8) mmol/L ( $p<0.001$ ).

From '12 noon' to 'pre-break of fast' there was reduction in blood glucose level in both groups, from 8.3 (5.1-14.6) mmol/L to 7.0 (4.5-11.7) mmol/L in the repaglinide group compared to 6.9 (3.3-12.8) mmol/L to 4.9 (3.4-8.6) mmol/L in the glimepiride group ( $p<0.001$ ).

For 'pre-break of fast' to 'bedtime', there was an increment of median blood sugar from 7.0(4.5-11.7) mmol/L to 9.5(4.9-14.6) mmol/L in the repaglinide group and from 4.9(3.4-8.6) mmol/L to 7.7 (3.0-15.1) mmol/L in the glimepiride group. However, the difference between the two groups was not statistically significant ( $p=0.16$ ).

There was a reduction in the 'bedtime' to 'pre-dawn' median blood sugar there was a reduction in both group, from 9.5(4.9-14.6) mmol/L to 9.2 (4.0-13.2) mmol/L in repaglinide group compared to 7.7 (3.0-15.1) mmol/L to 6.0(3.0-11.7) mmol/L in the glimepiride group ( $p=0.04$ ).

### Glycaemic control post-Ramadan

The repaglinide group showed higher median fasting blood glucose level of 9.1(3.8-12.4) mmol/L, compared to that of 7.2 (4.2-13.3) mmol/L in the glimepiride group ( $p=0.03$ ) Figure 3. The median pre-lunch blood glucose was 9.0 (5.4-15.4) mmol/L in the repaglinide group compared to that of 6.6 (3.0-15.7) mmol/L in the glimepiride group ( $p=0.004$ ). The median pre-dinner

blood glucose, it was 8.1 (4.4-15.5) mmol/L in the repaglinide group compared to 6.5 (3.9-15.1) mmol/L in the glimepiride group (p=0.001). The median 'bedtime' blood glucose was 9.6 (3.8-16.0) mmol/L in the repaglinide group compared to 8.4(5.3-15.8) mmol/L in the glimepiride group (p=0.03).

**The glycaemic excursions post-Ramadan**

The post Ramadan glycaemic excursions are shown in (Figure 4). From fasting to pre lunch there was a slight reduction in the median blood glucose level in the repaglinide group from 9.1(3.8-12.4) mmol/L to 9.0(5.4-15.5 mmol/L compared to 7.2(4.2-13.3) mmol/L to that of 6.6(3-15.7) mmol/L in the glimepiride group (p=0.2). There was also slight reduction in the median pre lunch to pre dinner blood glucose level in both groups, from 9.0 (5.4-15.4) mmol/L to 8.1(4.4-15.5) mmol/L in the repaglinide group and from 6.6(3.0-15.7) mmol/L to 6.5 (3.9-15.1)mmol/L in the glimepiride group.(p=0.1). There was an increase in the median pre

dinner to bedtime blood glucose in both groups, from 8.1(4.4-15.5) mmol/L to 9.6 (3.8-16.0) mmol/L in the repaglinide group and from 6.5 (3.9-15.1)mmol/L to 8.4 (5.3-15.8) mmol/L in the glimepiride group (p=0.9).

There was reduction in the median bedtime to fasting blood glucose in both groups, from 9.6 (3.8-16.0) mmol/L to 9.1 (3.8-12.4) mmol/L in the repaglinide group and from 8.4 (5.3-15.8) mmol/L to 7.2 (4.2-13.2) mmol/L in the glimepiride group (p=0.3). None of the glycaemic excursion was statistically significant between the two groups after Ramadan.

**Incidence of hypoglycaemia**

During the entire study, 18 hypoglycaemic events were recorded: 6 events by repaglinide-treated patients and 12 events by glimepiride-treated patients. There was no statistically significant difference in the incidence of hypoglycaemia between the two groups during and after Ramadan (Table II).

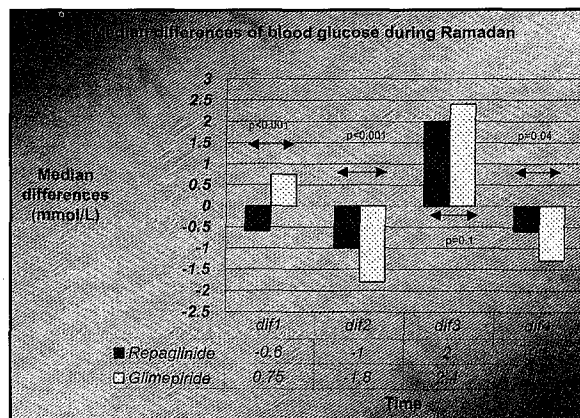
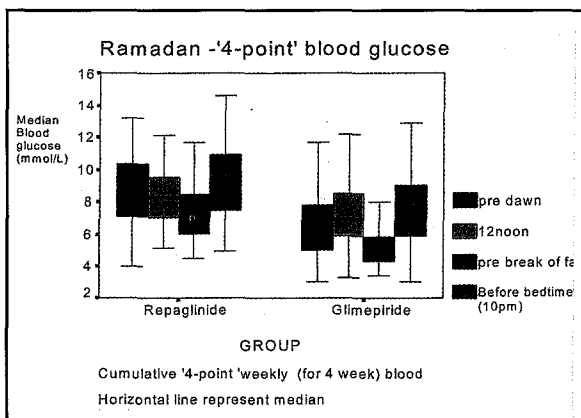
**Table I: Patient demographics 3 months prior to Ramadan**

Group	Repaglinide	Glimepiride	p value
Number of subjects	17	21	
<b>Age(years)</b>			
Median (min-max)	5 (38-65)	49 (30-74)	P=0.56
<b>Gender(%)</b>			
Female	9 (52.9)	13 (61.9)	P=0.64
Male	8 (47.1)	8 (38.1)	
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			
Median (range)	26.5 (21.3-32.5)	26.9 (22.0-33.4)	P=0.72
<b>HbA1c(%)</b>			
Median (range)	7.6 (6.3-10.2)	7.5 (5.0-13.8)	P=0.39
<b>Fasting plasma glucose(mmol/l)</b>			
Median(min-max)	8.2(5.9-13.9)	7.5 (5.6-13.3)	P=0.95
<b>Previous anti-diabetic medication.</b>			
Combination treatment (%)	11 (64.7%)	15 (71.4%)	P=0.72
<b>sulphonylura treatment only (%)</b>	6 (35.3%)	6 (28.6%)	
<b>Duration of diagnosed diabetes (years)</b>			
Median(range)	7 (2-20)	4 (2-18)	P=0.23

All variables were assessed at visit 1 and values are expressed as median (range).

**Table II: Incidence of hypoglycemia during treatment**

GROUP	Repaglinide(N=17)	Glimepiride(N=21)
<b>Hypoglycaemic event</b>		
Overall recorded	68	84
<b>Pre-Ramadan</b>		
BG>3.1(symptom of hypoglycemia)	2(2.9%)	3(3.5%)
BG<3.1	Not recorded	Not recorded
<b>Ramadan</b>		
BG>3.1(symptom of hypoglycemia)	2(2.9%)	3(3.5%)
BG<3.1	0(0%)*	2(2.3)*
<b>Post-Ramadan</b>		
BG>3.1(symptom of hypoglycemia)	2(2.9%)	1(1.1%)
BG<3.1	0(0%)*	3(3.5%)*

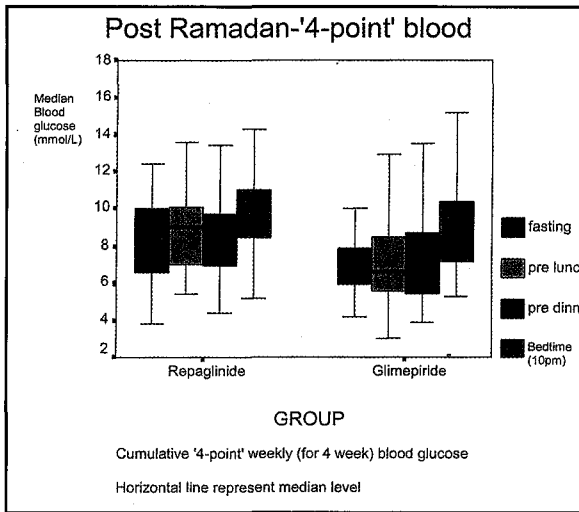


Differences in median blood glucose levels were statistically significant for predawn, 12 noon, before break of fast and 10pm values with p value of 0.001, 0.003, 0.001 and 0.001 respectively. The two main meals were taken at dawn and at 'break of fast'.

Median differences of blood glucose mmol/l. (-) minus dif1= median difference('12 pm'-pre dawn'), dif2= median difference ('pre break of fast'-12 pm'), dif3=median difference ('before sleep'- 'pre break of fast'), dif4= median difference( pre dawn- before sleep). dif1, dif 2 and dif4 were statistically significant.

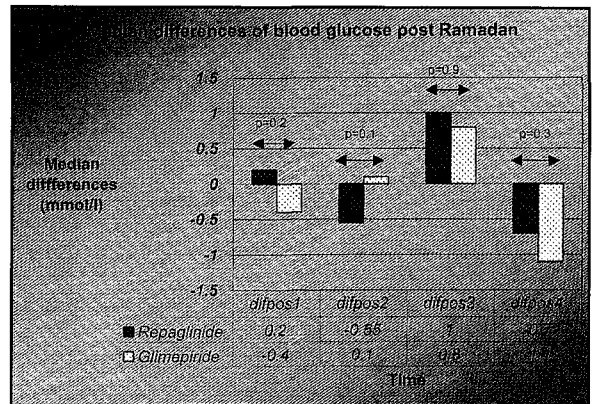
**Fig. 1: Four-point Glucose Profile During Ramadan**

**Fig. 2: Median differences of blood glucose during Ramadan**



There were statistically significant differences in the median in fasting, pre-lunch, pre-dinner and bedtime (10pm) blood glucose level between the two treatment group with p value of 0.03, 0.004, 0.001 and 0.03 respectively.

**Fig. 3: Box plot of '4-point' blood glucose profiles post Ramadan.**



Median differences of blood glucose mmol/l . (-)minus difpos1= median difference (pre-lunch-fasting), difpos2= median difference (pre dinner-pre-lunch), difpos3= median difference (before sleep- pre-dinner), difpos4= median difference (fasting- before sleep).

There were not statistically significant with p value of 0.2, 0.1, 0.9 and 0.9 in difpos1, difpos2, difpos3 and difpos4 respectively.

**Fig. 4: Median differences of blood glucose post Ramadan**

### Discussion

This trial compared repaglinide with glimepiride in Muslim subjects with Type 2 diabetes during the month of Ramadan. The patients had borderline glycaemic control at baseline (HbA1c of 7.5% versus 7.6% respectively). The majority had long standing of diabetes and all had been taking SU or SU combined with metformin before trial entry.

The median blood glucose level for the repaglinide group was significantly higher than the of the glimepiride group. This could be explained by the short duration of action of repaglinide. Another possible explanation is the fact that subjects were taking two meals a day during Ramadan and thus were deprived of the benefit of an extra dose of repaglinide. A reduction of up to 30% of the dose would put this medication which is normally taken thrice daily at a disadvantage.

During Ramadan, there was a reduction of median blood glucose from pre-dawn to 12 noon in the repaglinide group. This could be explained by the post

prandial effect of the drug and its short duration of action. The rapid and relevant increase in insulin secretion after repaglinide administration blunted the sharp rise in glucose that follows a pre-dawn meal as indicated by the 1- to 4-h post-meal decreases in blood glucose excursions. On the other hand, glimepiride group showed increased blood glucose levels, which can be explained by the slower on set of action of the drug and also by the fact that the pre-break of fast level is at the tail end of the action of glimepiride. However, from 12pm to pre-break of fast there was marked reduction of median blood glucose level in glimepiride group as compared to the repaglinide group. This can be explained by the long duration of action of glimepiride. Surprisingly, the reduction of median blood glucose still occurred in the repaglinide group despite the longer duration of fast-a period without food or treatment. From break of fast to bedtime, there was marked increment in blood glucose levels in both groups. Although it was more in the glimepiride group, it was not statistically significant. This can be perhaps explained by the large carbohydrate intake in both groups of patients. From bedtime to predawn, there was marked decrement of median differences of

blood glucose in both groups. It was seen more in the glimepiride group and this was statistically significant. This can be explained by reduced action of repaglinide as it is a short acting agent and its action had tapered off. The glycaemic excursion was better in the morning for the repaglinide group and better in the afternoon and evening for the glimepiride group. These features were also most likely due to the differences in the duration of action of the two drugs.

During the post-Ramadan period, the median blood glucose level for the glimepiride group was significantly lower than the repaglinide group. Therefore, glimepiride is possibly a better anti-diabetic agent to be used as monotherapy post-Ramadan due to its long duration of action. The glycaemic excursions post Ramadan were not statistically significant between the two treatment groups, when compared to during Ramadan. Therefore, the benefit of glimepiride over

repaglinide during the month of Ramadan diminished once the subjects stopped fasting. The subjects were taking 3 times a day meals and with it 3 doses of repaglinide instead of 2 during Ramadan.

In conclusion, Muslims with type 2 diabetes mellitus treated with glimepiride showed a trend towards better glycaemic control than patients treated with repaglinide during Ramadan. Contrary to common belief, there have been no reports of severe hypoglycemia in patients on OHA therapy during Ramadan<sup>17,18,19</sup>. Nevertheless, the decision to prescribe anti-diabetic medication during Ramadan should be individualised.

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