



Original Article

Comparison different oral glucose lowering drugs effects on fasting patients with type II diabetes



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ABSTRACT

Introduction: Type II Diabetes is the most common metabolic diseases in developed and developing countries with no effective treatment options. This study purpose was to compare different regimens of oral anti-diabetic therapy effects on the type II diabetic patients while fasting during Ramadan.**Methods:** In the double-blind clinical trial 90 patients with Type II Diabetes were divided randomly into three groups: 30 patients continued the previous dose of sulfonylurea (Group 1), 30 participants received a dose which was 25% lower than the previous sulfonylurea dose (group 2), and in the last 30 patients, repaglinide was replaced sulfonylurea (Group 3). Glucose, glycosylated hemoglobin (HbA1C), fructosamine, total cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides levels were measured in all participants before and after Ramadan. The weight and BMI were also controlled.**Results:** In all intervention groups a significant decreasing was seen in the body weight, BMI, fructoseamine, total cholesterol, and LDL; and also, a significant increasing was seen in HDL. The hypoglycemia incidence was significantly lower in Group 3 than Group 1. The results in fructosamine reduction and HDL cholesterol increasing were significantly better in Group 3 compared to Group 2 (P<0.05). Significant changes were not seen in total cholesterol, LDL, triglyceride, FBS, and HbA1C levels among the three treatment groups during Ramadan.**Conclusion:** The repaglinide consumption in comparing with sulfonylurea in patients with diabetes during Ramadan can cause fewer hypoglycemia, and better glyemic, and lipid control.

Introduction

Diabetes mellitus, especially type 2 diabetes mellitus (T2DM) is known as one of the most common metabolic diseases in developed and developing countries. It is estimated that more than 366 million people worldwide in 2030 will be

suffering from type2 diabetes (1). Also, it is a prevalence the disease in Iran is from 9.9 to 13.6% (2, 3). The trend of DM prevalence increased with a growth rate of 22.5% for world and 23.4% for Iran (4). But despite studies in various aspects for the treatment of diabetes the disease spread rises up (5-8). On the other hand, more than one billion Muslims

live around the world and the vast majority of them fast in Ramadan month. Although fasting during Ramadan is a religious order and written in the text of the Quran as a religious duty, but the sick muslims are exceptional to fast (9). Approximately 79% of patients with diabetes mellitus fast in Ramadan (10). The Islamic calendar is based on lunar months, and every nine years Ramadan occurs in a different season; when Ramadan occurs in the summer months the fasting period ranges from 11 to 18 hours (11). Every year before Ramadan, many patients with type-2 diabetes who tend to fast, visit doctors to question the safety of fasting. Such patients use different types of glucose-lowering regimens; therefore, depending on these medications various complications may occur while fasting. A higher rate of hypoglycemia is seen in patients who use Sulfonylurea than biguanides (metformin) and other oral drug categories during long fasting sessions (12). In several studies, due to the fear of hypoglycemia during fasting conditions, participants receiving sulfonylurea were evaluated once a day, and their usual drug dose was taken before breaking the fast instead of before breakfast (13-15). In one study, the use of short-acting non-sulfonylurea insulin secretion stimulating drugs such as repaglinide as an alternative for sulfonylurea during Ramadan was associated with improved glycemic control, and reduction of hypoglycemia (15). In contrast, in a smaller study, no significant changes were seen in the levels of fructosamine, HbA1c (glycosylated hemoglobin), and body weight, which was related to sulfonylurea intake during Ramadan; however, there were fewer hypoglycemia incidences that were associated with it (16). Another aspect of health in fasting patients with diabetes is the control of blood sugar; therefore blood glucose controlling drugs must be prescribed with adequate doses in order to maintain HbA1c and fructosamine at acceptable levels. Because of contradictory results (13-16) about hypoglycemic attacks and glycemic index of these drugs we decided to do this trial. Ahvaz is a large city. It is located in southwestern Iran and has the warm weather; where maximum temperatures can reach up to 54 degrees Celsius. These climatic conditions can exacerbate the possible complications of fasting in diabetic patients. Finding the appropriate dosage and drug type to improve clinical status and prevent hypoglycemia in these situations is required. Also, in this study, the effects of three different protocols (drugs) were studied in diabetic patients during Ramadan.

Methods

In this study a method was used which is similar to the Mafauzy's article "Repaglinide versus

glibenclamide treatment of type 2 diabetes during Ramadan Fasting", after samples were calculated 30 patients were allocated in per pharmaceutical group, and overall 90 patients were studied (15). This randomized clinical trial was performed on patients with type 2 diabetes who attended the diabetes Ahvaz Golestan hospital clinic during Ramadan. This study was approved by Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (No.ETH-706). All participants were under treatment with oral blood sugar reducing medication and they showed a tendency to fast. Power of study was 80%. All patients filled in a written consent and trial number is 8813 approved. Inclusion criteria: Patients with type 2 diabetes, who wanted to fast during Ramadan; aged 20 to 65 years; under treatment with a regimen of fixed-dose oral blood sugar lowering medications for at least three months; HbA1C \leq 8.5; inclined to participate in the study and carry out the necessary tests. Exclusion criteria: Pregnant women, nursing mothers, gestational diabetes, evidence of renal failure (serum creatinine \geq 1.5 mg/dl for men, and \geq 1.4 mg/dl for women), the insulin usage (before or during Ramadan), previous congestive heart failure (III or VI), history of severe hypoglycemia during the three months prior to Ramadan or unawareness of hypoglycemia, history of ketoacidosis or hyperosmolar coma three months before Ramadan. One month before Ramadan, 90 patients were enrolled. Patients who were already under therapy with Sulfonylurea alone or in combination with other non-hypoglycemic oral drugs (metformin, glutazone or acarbose) were randomly divided into three groups: Group 1- Patients used the same previous dose of the Sulfonylurea with consumption time changing. The whole morning Sulfonylurea dose (morning and noon doses) was taken before breaking the fast, and in the evening it was taken before dawn. Group 2- The dose of Sulfonylurea was reduced by 25% during Ramadan. Its two-thirds was given in breaking the fast time (Eftar) and its one-third was given just before dawn. According to previous studies, in order to compare doses of the drug, the group 2 was designed with a dose of 25% less than the first group (17). Group 3- Sulfonylurea was replaced by repaglinide. At first repaglinide was used with a 0.5 mg dose before each meal and if there was necessary, it would be increased by 1, 2 and 4 mg before three main meals. Within one month prior to Ramadan, patients were using the proper repaglinide dose. During Ramadan, the total dosage of repaglinide was calculated to each person and instead of three doses before each meal was changed into two doses before dawn and breaking the fast. Other drugs (metformin, glutazone and acarbose) were given without changing the

dosage during Ramadan. All study groups received information on proper diets for fasting, exercise, physical activity, proper use of the glucometer, symptoms of hypoglycemia, and nutritional advice from a dietitian, diabetes nurse and endocrinologist in the month before Ramadan. During Ramadan blood glucose was measured four times each week using the same glucometer by all patients (before dawn, noon, before breaking the fast and two hours after breaking the fast). Also, the patients were advised to check their blood sugar, every time they experienced symptoms of hypoglycemia or other symptoms (for example, feverish conditions). Hypoglycemia is defined as blood glucose under 60 mg/dl. Patients were advised to break the fast if their blood sugar level was ≤ 60 mg/dl, even if there have not been any hypoglycemia symptoms presence. Patients, who experienced symptoms of the hypoglycemia during Ramadan but still they wanted to fast, had an appropriate drug dosage reduction and they continued to be followed in the same study group. Four days before and after Ramadan, blood samples were collected from the three groups (after at least 12 hours fasting). Blood glucose, glycated hemoglobin, serum fructosamine, total cholesterol, LDL, HDL, and triglyceride levels were measured. Weight, height, BMI, and blood pressure of all patients were measured by trained personnel before and after Ramadan. Other information, including age, gender, duration of diabetes, and type and dose of oral drugs were recorded based on a questionnaire.

Biochemical assessments

All tests were performed at the Diabetes Research Center Laboratory. Blood glucose was measured by oxidase glucose method using a kit. Total cholesterol, HDL, and triglyceride levels were measured by the enzymatic method. LDL was measured using the Friedewald formula (if triglycerides were less than 400 mg/ dL) (18). HbA1C measurement was performed using flow meter method in the Nicocard device. The level of fructosamine was measured using a calorimetric test with Diazyme.

Sample size and statistical methods

Data analysis was performed using SPSS version 21, and results were presented by mean and standard deviation. Paired t-test, t-independent, separate ANOVA, and Tukey's test were used to compare group means. The Chi-square test was used to qualitative variables. The significance level was considered equal to 0.05. sample size was calculated from this formula:

$$n = \frac{(Z_{\alpha/2} \times Z_{\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

(S1 = 4.9), (S2 = 4.8), and mean difference was 10 (13).

Results

The fasting average time was 15 hours in a day (in 24 hours), from 5:00 A.M. until 8:00 P.M. 81 out of 90 patients fasted during all 29 days in Ramadan. Menstruation and vacation were the reasons that 6 and 1 patients not to fasting for one week, respectively; two patients did not fast for one day because of hypoglycemia. The mean and standard deviation of clinical and laboratory variables in the three intervention groups before Ramadan are shown in table 1. There was no significant difference between the three groups at the start of the study in these cases. Laboratory and clinical variables of all 90 persons before and after Ramadan are shown in table 2. At the end of Ramadan, a significant reduction was observed in weight (P= 0.009), BMI (P= 0.027), fructosamine (P= 0.001), total cholesterol (P= 0.03), LDL (P= 0.002), and a significant increasing was observed in HDL (P= 0.001) in the subjects of all three intervention group. The three groups clinical and laboratory data before and after Ramadan and their mean difference is shown in table 3. At the end of Ramadan, the mean differences in weight and BMI were significant between group 1 and two other groups (2 and 3) (P<0.0001, and p>0.001, respectively), but were not significant between groups 2 and 3. fructosamine decreased and HDL increased in all three groups at the end of Ramadan. Compared to the other two groups, group 3 showed a greater dropping in fructosamine and increasing in HDL. The fructosamine dropping and HDL increasing was significant in group 3 compared to group 2 (P= 0.045, and P= 0.046, respectively); however, when the same items were compared between groups 3 and 1, the results were not significant. Also, there were no significant differences between groups 1 and 2 in comparison of the fructosamine reduction and increasing in HDL. Differences in mean levels of FBS, HbA1C, total cholesterol, LDL, and triglyceride among three groups before and after Ramadan between different drug groups were not significant (table 3). 19 cases of hypoglycemia (blood glucose below 60 mg/dl) were seen during Ramadan. 10, 7, and 2 cases were seen in groups 1, 2, and 3, respectively. Groups 3 had the lowest and group 1 had the highest rates of hypoglycemia. There was no significant

Table 1: Demographic and Laboratory Data in the Three Intervention Groups before Ramadan

Group	Sulfonylurea without dose	Sulfonylurea with dose	Repaglinide	p-value
Age (year)	55.1± 10	49.6± 9/9	53.3±7	0.068
Male/ Female	9/21	10/20	10/20	0.95
Height (Cm)	158.8± 8.7	160.8 ± 8.8	159.4 ±6.9	0.62
Weight (kg)	75.4± 15.2	74.2± 12.27	70 ± 11	0.42
BMI (kg/m ²)	29.6±5.9	28± 4	27± 3.6	0.12
Duration of DM (year)	5.4±3.29	7±3.93	6.9± 5.05	0.24
FBS (mg/dL)	151.9± 46.8	157.6± 61.1	165.3± 54	0.62
HbA1c (%)	7.35± 1.2	7.84± 1.2	7.59± 1.4	0.37
Fructosamine (µmol/L)	285.4± 103.3	297.7± 149.8	270± 12.4	0.69
TG (mg/dL)	162.9± 63.7	146.5± 67.9	149.8± 69	0.6
Cholesterol (mg/dL)	164.9± 37.6	156.2±27.8	172± 45.2	0.27
LDL (mg/dL)	85.1± 28.5	78.8±23.1	84.3±24.7	0.59
HDL (mg/dL)	47.2± 9.9	49.4± 7.7	52± 10.3	0.15
Systolic BP (mmHg)	126±15.4	119± 13.7	127± 19.7	0.1
Diastolic BP (mmHg)	74± 8.1	75.3± 11.3	77.6± 12.5	0.41
w/h Ratio	0.96± 0.06	0.95±0.07	0.92±0.06	0.053
Previous anti- diabetic medication:	28 (%93.4)	28 (%93.4)	27(90%)	0=0.72
Combination Treatment n (%)				
Sulfonylurea treatment only n (%)	2 (%6.6)	2 (%6.6)	3(10%)	

difference between hypoglycemia cases in groups 1 and 2 (P= 0.39). But a significant difference existed between the cases of hypoglycemia in group 1 and group 3 (P= 0.01). Also there was no significant difference between cases of hypoglycemia in groups 2 and 3 (P= 0.07). Hypoglycemia was not severe in participants; the lowest amount of sugar during hypoglycemia was 54, which was in group 1. Only 2 out of the 19 patients broke their fasting because of hypoglycemia.

Discussion

Repaglinide stimulates release insulin and have a rapid onset and they are relatively short action duration. It is taken along with food or immediately before meals, and it regulates the glucose after meals, mainly by stimulating the endogenous insulin secretion to the food intake response. This drug is well tolerated and it causes fewer instances of hypoglycemia than sulfonylurea (19-21). The results of this study indicate that the risk of hypoglycemia in patients who

used repaglinide using was significantly less than in patients who received full doses of Sulfonylurea. A significant difference was not seen between hypoglycemic events in patients who were receiving repaglinide compared to patients who were taking Sulfonylurea with dose reduction. Also, there was no significant difference between hypoglycemic events in treated patients via sulfonylurea or without a dose reduction. Glycemic control (serum fructosamine reduction) was improved in all three groups Ramadan. This improvement was greater in the repaglinide group, so that fructosamine was significantly lower in patients who had used repaglinide compared to patients who received sulfonylurea with dose reduction; however, there was no significant difference in fructosamine dropping in Sulfonylurea recipients with or without a dose reduction. Also, significant differences in glycemic control (a fructosamine dropping) was not seen in patients who had received a full sulfonylurea dose compared to repaglinide received patients. HbA1C, fasting blood sugar, total cholesterol, LDL, and triglyceride levels did not significantly change during

Ramadan between groups, but HDL in all groups increased. This increasing was significant in patients taking repaglinide compared to patients taking a reduced Sulfonylurea dose; but increased HDL was not significant in patients taking repaglinide compared to patients who were taking the full dose of Sulfonylurea. Also, there was no significant difference between the sulfonylurea usage with or without a dose reduction in terms of the HDL increasing. Blood pressure and waist-to-hip ratio during Ramadan did not significantly change between the three treatments groups, but a significant reduction was seen in difference of mean weight and BMI before and after Ramadan in patients who treated with the full dose of Sulfonylurea compared to the two other groups. Also, the studies found that reduction of the dose of Sulfonylurea dose, due to fear of hypoglycemia in diabetic patients during Ramadan, did not create significant differences in reducing the hypoglycemia risk; in contrast, it leads to less fructosamine reduction and lower increasing in HDL cholesterol in these patients than patients who were receiving repaglinide. The fructosamine level dropping at the end of Ramadan in the repaglinide receiving group was more than the sulfonylurea full dose receiving group, but this decreasing was not statistically significant. However, an advantage that was seen in patients who were using repaglinide compared to patients who were Sulfonylurea during Ramadan, it was a significant reduction the hypoglycemia occurrence. In all patients, fasting causes a significant reduction in weight, BMI, fructosamine, total cholesterol and LDL, and a significant increasing in HDL levels. Bener et al. in an observational study recruiting 1301 Muslim diabetic patients above 18 years' age reported that fasting during Ramadan is significantly associated with decreasing in blood lipid profile, blood pressures, glucose, and HbA1C level among diabetic patients (22). In several studies, similar to our study, changes in blood pressure were not seen at the end of Ramadan (23-25). In Bell Khadir's study on 542 patients with type 2 diabetes, two types of glibenclamide regimes (with 25% dose reduction and without dose reduction) were compared during the month of Ramadan. At the end of Ramadan significant difference were not seen between the groups in serum fructosamine, HbA1C and number of hypoglycemia cases (17). Our study's results on the sulfonylurea effect with or without dose reduction are similar to those of Bell khadir's study. Mafoozi compared the effect of repaglinide with glibenclamide on 235 patients with type 2 diabetes, who were previously treated with sulfonylurea, during fasting in Ramadan. During Ramadan, significant reductions were seen in serum

Table 2: Clinical and Laboratory Variables Before and After Ramadan in the Entire Intervention Group

Variable	Before Ramadan	After Ramadan	P-Valve
Weight (kg)	73.2	72.6	0.009
BMI (Km/m ²)	28.2	28	0.027
FBS(mg/dl)	158.2	149.4	0.07
HbA1C(%)	59/7	7.52	0.38
Fructosamine (µmol/L)	284.5	220.6	0.001
Cholesterol (mg/dL)	164.4	156.8	0.03
TG (mg/dL)	165.7	154.2	0.32
LDL (mg/dL)	82.6	74.4	0.002
HDL (mg/dL)	49.5	52.5	0.001
Sys Blood pressure (mmHg)	124	121	0.17
Dia Blood pressure (mmHg)	75.6	74.8	0.52
w/h Ratio	0.935	0.931	0.9

fructosamine in the repaglinide group; but such an effect was not observed in the glibenclamide group. The difference between groups was not significant in the changes of HbA1C compared to baseline levels. Also, the hypoglycemia occurrence in the repaglinide group was significantly less than the glibenclamide group (15). Our study's results were similar to (15) results. In our study, a fructosamine reduction in the repaglinide group was only significant compared to the Sulfonylurea group with the dose reduction. A larger sample size could help to determine the usefulness of repaglinide in reducing fructosamine and better glycemic control at the end of Ramadan. Of course, changes in fructosamine levels in diabetic patients at the end of the month of Ramadan varied in different studies; some researchers have not reported any changes while others have reported an increasing (24-26). In a study by Surrey 52 diabetic patients were divided into three groups; the first group was only treated with a diet, the second group received Sulfonylurea and the last group received repaglinide. At the end of Ramadan, levels of HDL increased in the group that received repaglinide, and hypoglycemia was only seen in one patient that received Sulfonylurea (16). Our study also showed similar results. Anwar compared the effect of glimepiride to repaglinide in 41 fasting diabetic patients during Ramadan. During Ramadan and one month after it, blood glucose was measured in each group four times per week. In the glimepiride receiving group blood sugar levels were lower compared to the repaglinide receiving group. In the

Table 3: Comparison of clinical laboratory findings in the three groups before and after Ramadan and their Mean Difference

Parameters	Group 1			Group 2			Group 3			P-value Difference
	Before Ramadan	After Ramadan	Difference	Before Ramadan	After Ramadan	Difference	Before Ramadan	After Ramadan	Difference	
	pre± SD	Post± SD	Difference	pre± SD	Post± SD	Difference	pre± SD	Post± SD	Difference	
Waist/hip Ratio	06.96 ± 0.0	0.94 ± 0.07	-0.02± 0.04	0.95± 0.07	0.95± 0.07	-0.005±0.03	0.92± 0.06	0.91± 0.06	-0.005±0.03	0.087
Weight (kg)	2.4± 15.75	73± 15.2	-2.47± 1.4	74.2± 12.2	75±12.5	0.7± 1.5	70± 11	69.8± 11.3	-0.23± 2.4	<0.001
BMI (kg/m ²)	9.6± 5.29	28.5±6	-1.06± 0.8	28±4	28.3± 4.1	0.28± 0.4	27.1± 3.6	27.2± 3.8	%6± 0.9	<0.001
FBS (mg/dL)	8.9±46.151	134.6±20.8	-17.2± 44	157.6± 61.1	146.6± 41.4	-10.9± 48	165.3± 54	166.9±46.8	1.6± 45	0.28
HbA1C (%)	2.35±1.7	7.25± 0.7	-0.1± 0.8	7.84± 1.2	7.78± 0.9	-%6± 0.9	7.59± 1.4	7.52± 1.1	-%6±0.6	0.98
Fructoseamine (µmol/L)	3.4± 103.285	235.5± 113.9	-47.7± 98	297.7± 149.8	260± 39.8	-37.7± 131	270± 112.4	163± 29.4	-107± 105	0.045
Total cholesterol (mg/dL)	6.9± 37.164	147.5± 47.5	-17.4±36	156.23±27.8	158.57±32.9	2.3±26	172± 45.2	164.6±39.7	-7.4±31	0.059
LDL (mg/dL)	5.17± 28.85	71.47±26.8	-13.7±21	78.83± 23.1	74.14± 26.7	-2.07±22	82.82± 25.5	77.23±26.8	-8.52± 27	0.18
HDL (mg/dL)	9.23±9.47	49.57±9.4	2.33± 6.4	49.43± 7.7	51.37± 8.9	1.93± 5.4	52± 10.3	57.07± 10.9	5.07± 3.3	0.046
Triglyceride (mg/dL)	7.9± 63.162	147.9± 92.9	-14.9±86	146.5±67.9	159.3±87	12.7±69	149.8± 69	143.3±60	-6.59±66	0.34
Systolic BP (mmHg)	4.126±15	5.122±11	-4± 19	119± 13.7	121± 13.9	2± 14	127.6±19.7	121.3± 11.6	-6.3± 22	0.22
Diastolic BP (mmHg)	1.74± 8	8.6± 7.72	-1.3± 10	75.3± 11.3	75.6± 11.9	0.3± 11	77.6± 12.5	76.3±8	-1.3±11	0.81

repaglinide receiving group, the changes in blood sugar were better than the morning; and in the glimepiride receiving group that were better in the afternoon. Also, there were not statistically significant differences between the two groups in the hypoglycemia incidence during Ramadan (13). Our results were inconsistent with Anwar’s study, which may be because of several factors. In Anwar’s study, fructosamine was not checked before and after Ramadan and blood glucose measurements four times per week were used as the only criteria for glycemic control in the study groups. Also, the small sample size of Anwar’s study could be the reason for the lack of significant incidence of hypoglycemia in the two studied groups. On the other hand, in Anwar’s study, the changes of blood glucose were not significant one month after Ramadan, and the advantage of glimepiride over repaglinide was not seen, because only two main meals are eaten during the month of Ramadan (dawn and breaking the fast) and a turn of repaglinide (which was used in non-fasting months along with three main meals (breakfast-lunch-dinner) was omitted. Also, race and

diet are also factors that can affect the research results. Also, the geographic areas impact should be considered. While in our study, the total dose of repaglinide before the start of Ramadan was divided into two equal parts, and it was given along with the dawn (Sahar) and breaking the fast (Eftar) meals. Another study by Mustafa C. Shoor did not show a significant difference in changes of the fructosamine changes levels at the end of Ramadan in three groups receiving glimepiride, repaglinide and insulin glargine (26). The drug compared with repaglinide in this study and Anwar’s study was glimepiride, which was only used as a single daily dose and may lead to different results than Sulfonylurea which was used in our study. In our study, severe hypoglycemia was not seen, and in all of the 90 patients, hypoglycemia was only seen in 21% of patients. Hypoglycemia incidences varied in different studies which are partly due to the differences in hypoglycemia detection methods and study designs (10, 12-15). On the other hand, in the various studies, fasting time may be an effective factor of the differences. All of the individual glycogen stores and difference between

physical activity and eating habits can all affect blood sugar levels in Ramadan. Our study limitations were the amount of energy intake and physical activities during fasting were not evaluated. Also, the metabolic syndrome index, including insulin levels, insulin indicators sensitivity, adiponectin, and CRP were not evaluated. Moreover, follow up_tests (for example, a month after Ramadan) were not done to assess the stability of drug efficacy.

Conclusion

The results of this study revealed that the repaglinide usage instead of sulfonylurea without a dose reduction in fasting patients with diabetes during Ramadan, has been accompanied by fewer hypoglycemia incidents; and it compared with reduced Sulfonylurea dose, repaglinide leads to better glycemic and lipid control (a significant dropping in fructosamine and increasing in HDL cholesterol) at the end of Ramadan. Also Sulfonylurea dose reduction, in the diabetic patients during fasting, does not cause significant differences in reducing hypoglycemia risk; and on the other hand, it leads to less fructosamine dropping and less increasing in HDL cholesterol in these patients compared to patients who were receiving repaglinide during Ramadan month. Therefore, in diabetic patients, who wish to fast during Ramadan, changing sulfonylurea to repaglinide in order to reduce hypoglycemia seems logical. In general, fasting caused a significant reduction in weight, BMI, fructosamine, total cholesterol and LDL, and a significant increasing in HDL levels.

Ethical disclosure

Before performing the research, it was explained to the participants. An informed consent was obtained from all participants included in the study.

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Authors' Contributions

All authors contributed equally in planning and carrying out this project.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

- Rathmann W, Giani G. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27 (10): 2568–9. doi: 10.2337/diacare.27.10.2568
- Latifi SM, Karandish M, Shahbazian H, Hardani Pasand L. Incidence of Prediabetes and Type 2 Diabetes among People Aged over 20 Years in Ahvaz: A 5-Year Perspective Study (2009-2014). *J Diabetes Res*. 2016; 2016: 4908647. doi: org/10.1155/2016/4908647.
- Golozar A, Khalili D, Etemadi A, Poustchi H, Azeltabar A, Hosseini F, et al. White rice intake and incidence of type-2 diabetes: analysis of two prospective cohort studies from Iran. *BMC Public Health*. 2017; 17(1): 133. doi: 10.1186/s12889-016-3999-4
- Nasli-Esfahani E, Farzadfar F, Kouhnavard M, Ghodssi-Ghassemabadi R, Khajavi A, Peimani M, et al. Iran diabetes research roadmap (IDRR) study: a preliminary study on diabetes research in the world and Iran. *J Diabetes Metab Disord*. 2017; 16 (1): 9. doi: 10.1186/s40200-017-0291-9
- Hosseini SA, Alipour M, Zakerkish M, Haghizade M H. Effects of Standardized Extract of Ginseng (G115) on Biomarkers of Systemic Low-Grade Inflammation in Patients with Type 2 diabetes: A Double-blind Clinical Trial. *Iranian J Endocrinol Metabol*. 2014; 16(3):175-82.
- Hosseini SA, Alipour M, Zare Javid A, Ashtary Larky D, Shariatifar R. Impact of Short – Term Intake of Cinnamon on Serum Glucose and Lipid Profile in Patients with Type 2 Diabetes Mellitus. *J Appl Environ Biol Sci*. 2014; 4(2):295- 8.
- Ashtary-Larky D, Ghanavati M, Lamuchi-Deli N, Payami SA, Alavi-Rad S, Boustaninejad M, et al. Rapid Weight Loss vs. Slow Weight Loss: Which is More Effective on Body Composition and Metabolic Risk Factors? *Int J Endocrinol Metab*. 2017; 15(3):e13249. doi: 10.5812/ijem.13249
- SA Hosseini, A Ahangarpour, M Ghanavati, M Aria, M Alipour. Review effects of ginseng on improving glycemic status and other related parameters with Type 2 diabetes. *J Clin Exc*. 2015; 4 (Special Issue), 90-107.
- Malik U, Mahmood N, Khan KA, Hameed M, Randhawa FA, Salman S, et al. Glycaemic Control Of Type 2 Diabetic Patients During Ramazan Fasting. *J Ayub Med Coll Abbottabad*. 2017; 29(1):102-6.
- Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet CB, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care*. 2004; 27:2306-2311.

11. Azizi F. Islamic Fasting and health. *Ann Nutr Metabol.* 2010; 56 (4): 273-82. doi: 10.1159/000295848
12. Glimperide in Ramadan (GLIRA) Study Group. The efficacy and Safety of Glimperide in The management of type 2 diabetes in Muslim Patients during Ramadan. *Diabetes Care.* 2005; 28 (2): 421-2. doi: 10.2337/diacare.28.2.421
13. AnwarA, Azmi KN, Hamidon BB, khalid BA. An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus muslim subjects during the month of Ramadan. *Med J Malaysia.* 2006; 61 (1):28-35.
14. Zargar AH, SirajM, Jawa AA,Hasan M, Mahtab H. Maintenance of glycaemic control with the evening administration of a long acting sulphonylurea in male type 2 diabetic patients undertaking the Ramadan fast. *Int J Clin Pract.* 2010; 64(8):1090-4. doi: 10.1111/j.1742-1241.2009.02262.x
15. Mafauzy M. Repaglinide versus glibenclamide treatment of type 2 diabetes during Ramadan fasting. *Diabetes Res Clin Pract.* 2002; 58(1): 45-53.
16. SariR , Balci MK, Akbas SH, AvciB. The effects of diet, sulphonylurea and repaglinide therapy on clinical and metabolic parameters in type 2 diabetic patients during Ramadan. *Endocrine Res.* 2004; 30 (2):169-77.
17. Belkahdir J, El Ghomari H, Klocker N, Mikou A, NasciriM, Sabrim. Muslims with non-insulin dependent diabetes fasting during Ramadan: treatment with glibenclamide. *BMJ.* 1993; 307:292-5. doi: 10.1136/bmj.307.6899.292
18. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem.* 1974;20 (4):470-5.
19. Menecart M, Mondon K, Malherbe C, Constans T. Delayed hypoglycemia induced by repaglinide in a frail elderly adult with diabetes mellitus. *J Am Geriatr Soc.* 2014; 62(12):2460-2. doi:10.1111/jgs.13144
20. Mantovani A, Grani G, Chioma L, Vancieri G, Giordani I, Rendina R, et al. Severe hypoglycemia in patients with known diabetes requiring emergency department care: A report from an Italian multicenter study. *J Clin Transl Endocrinol.* 2016; 5:46-52. doi: 10.1111/jgs.13144
21. Kawamori R, Kaku K, Hanafusa T, Ioriya K, Kageyama S, Hotta N. Clinical study of repaglinide efficacy and safety in type 2 diabetes mellitus patients with blood glucose levels inadequately controlled by sitagliptin. *J Diabetes Investig.* 2016; 7(2):253-9. doi:10.1111/jdi.12384
22. Bener A, Yousafzai MT. Effect of Ramadan fasting on diabetes mellitus: a population-based study in Qatar. *J Egypt Public Health Assoc.* 2014;89 (2):47-52. doi: 10.1097/01.EPX.0000451852.92252.9b
23. M'guil M, Ragala MA, El Guessabi L, Fellat S, Chraïbi A, Chebraoui L, et al. Is Ramadan fasting safe in type 2 diabetic patients in view of the lack of significant effect of fasting on clinical and biochemical parameters, blood pressure, and glycemic control?. *Clinical and experimental hypertension.* 2008; 30(5):339-57.
24. Bouguerra R, Jabrane J, Maatki C, Salem B, Hamzaoui J, El Kadhi A, et al. Ramadan fasting in type 2 diabetes mellitus. *Ann Endocrinol.* 2006; 67(1): 54-9. doi: 10.1016/S0003-4266(06)72541-0
25. Laajam MA. Ramadan fasting and non-insulin-dependent diabetes: effect on metabolic control. *East Afr Med J.* 1990; 67(10): 732-6. PMID:2282897
26. Cesur M, Corapcioglu D, Gursoy A, Gonen S, Ozduman M, Emral R, et al. A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting. *Diabetes Res Clin Pract.* 2007;75(2):141-7.