The Influence of Calorie Restriction During The Ramadan Fast on Serum Fructosamine and The Formation of Beta Hydroxybutirate in Type 2 Diabetes Mellitus Patients

Reno Gustaviani R*, Pradana Soewondo**, Gatut Semiardji**, Aru W Sudoyo***

ABSTRACT

Aim: *to determine whether the Ramadan fasting can improve metabolic control evaluated from serum fructosamine and beta hydroxybutirate in patients with Type 2 diabetes mellitus.*

Methods: *this was a prospective one group before and after study (self-controlled study). Twenty four patients from the outpatient clinic of the Metabolic Endocrinology Division of the Department of Internal Medicine, Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo General Hospital who were well under control underwent assessment for serum fructosamine at weeks -1, 4, and 6 (2 weeks after the Ramadan fast) and beta hydroxybutirate formation at week 4.*

Results: *the mean serum fructosamine on weeks -1, 4, and 6 were 334.2 ± 45.7; 303.9 ± 34.5 dan 313.6 ± 45.9 umol/L. The beta hydroxybutirate level was 0.3 mmol/L.*

Conclusion: *the Ramadan fasting in patients with well-controlled and medium-controlled type 2 diabetes mellitus could cause a reduction in serum fructosamine and does not cause formation of beta hyroxybutirate.*

Key words: *ramadan fasting, type 2 diabetes mellitus, fructosamine, beta hydroxybutirate.*

INTRODUCTION

Fasting generally refers to the condition of not eating for a varying duration of time.[1] Aside from being used as medical treatment for several conditions, fasting is also a spiritual activity for several religions, such as Islam, Christianity, Buddha, and Judaism.[1,2]

The Ramadan fast is a form of worship that is a part of the five pillars of Islam, and is required of every healthy adult Muslim for a complete month (between 28-30 days) for approximately 14 hours/day in Indonesia. In addition, the fast also has the benefit of encouraging individual discipline,[3] which is very useful for diabetes patients.

Diabetes mellitus (DM) is a chronic incurable illness, but if blood glucose levels could be controlled, acute as well as chronic diabetes mellitus complications may be avoidable. Patients with diabetes mellitus are always advised not to take a different attitude as non-diabetics around them and in their community.

In the Diabetes Atlas 2000 (International Diabetes Federation), it is noted that the estimated number of diabetes patients in Indonesia is 5.6 million (with an assumed prevalence of diabetes mellitus of 4.6%).[4] Most of these diabetes patients are Muslim and a large number of them carry out the Ramadan fast. Thus, the Ramadan fast has potentially great benefit to be studied to determine several metabolic aspects of the diabetes mellitus patients who carry out the fast.

During fasting, there is a reduction in calorie intake, which results in a drop of blood glucose. Under normal conditions, during fasting, blood glucose is maintained within the narrow range of 60-126 mg/dL through the action of insulin and insulin contra-regulatory hormones such as glucagon, epinephrine, growth hormone and cortisol, through the processes of glycogenolysis and gluconeogenesis. The gluconeogenesis process results in the formation of keton bodies (20% acetoacetate, 75-85% beta hydroxybutirate, and 2% acetone).[5-9]

In several studies, Ramadan fasting in type 2 diabetes mellitus does not demonstrate pathological changes or clinical complications in several observed parameters, such as body weight and body mass index

** Department of Internal Medicine of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo General Hospital, Jakarta*
*** Division of Metabolic Endocrinology, ***Division of Hematology-Medical Oncology, Department of Internal Medicine of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo General Hospital, Jakarta*

(BMI), blood glucose, glycate hemoglobin (A1C), C-peptide, insulin, serum fructosamine, cholesterol, and triglyceride.[8] Actually, from several studies, the Ramadan fast has been shown to improve some of the metabolic control measures mentioned above. In order to evaluate diabetes control, A1C or serum fructosamine, which is the result of protein glication found in hemoglobin and albumin, could be used. A1C is a blood glucose control evaluation parameter for the preceding 120 days, while serum fructosamine could be used as a parameter to evaluate the preceding 2-3 weeks.[10, 11] Several studies demonstrate insignificant change in A1C levels, while Mafauzy, in 2 previous studies, found adequately significant changes in the serum fructosamine of patients with type 2 diabetes mellitus carrying out the Ramadan fast. Such condition may be because A1C is a parameter for the preceding 120 days, while serum fructosamine is a parameter for the previous 2-3 weeks, which approximate the duration of the Ramadan fast.[8,12,13]

For diabetes mellitus patients, dietary and drink regulation as well as modification of the time and dose of drug administration must be performed prior to them undergoing the Ramadan fast, in order to achieve the desired metabolic control. In uncontrolled diabetes mellitus, the liver glycogen is not sufficient, resulting in precipitated fat metabolism, resulting in ketosis.[8,14,15] In this study, we would like to see whether Ramadan fast can improve metabolic controls evaluated through serum fructosamine and whether beta hydroxybutirate is formed in patients with type 2 diabetes mellitus.

METHODS

The study was designed as a one-group before and after (self-controlled) study. The study was conducted from November to December 2001. The sample consisted of type 2 diabetes mellitus outpatients from the outpatient clinic of the Division of Metabolic Endocrine that carry out the Ramadan fasting, have A1C levels of ≤ 8%, and are undergoing repaglinide treatment. The sample obtained were continued from previous studies, because they have had a relatively satisfactory metabolic control (high or medium control), and has received adequate and regular education. The exclusion criteria were subjects who are unable to or not recommended to fast, and those undergoing steroid and lipid reduction treatment. All subjects that has been selected based on the inclusion and exclusion criteria underwent anamnesis, physical examination, and supporting examinations (ECG, fasting blood glucose and 2 hour post meal blood glucose, serum fructosamine and lipid profile) 1 week prior to fasting (week -1). Every week during the fast (weeks 1, 2, 3, and 4), history-taking and physical examination were conducted. On the 4th week, fasting blood glucose, serum fructosamine, lipid profile, and beta hydroxybutirate assessments were conducted. On the 6th week (2 weeks following fasting), history-taking and physical examination as well as fasting blood glucose and 2 hour post meal blood glucose and serum fructosamine assessments were repeated. During every visit, food recall was performed, and hypoglycemia recorded. The data was entered using SPSS version 10.0. Statistical analysis was performed using t-test.

RESULTS

Twenty four subjects participated in the study, comprising of 10 males and 14 females with an age range of 34 to 68 years (median 52.6 years), 12 employed, and 12 unemployed.

The demographical and clinical characteristics of the subjects can be found in Tables 1 and 2.

In Table 3 we can see that there was a significant reduction in the level of serum fructosamine from week -1 (pre-Ramadan) compared to the fourth week (the end of Ramadan), with a non-significant increase on the 6th

Table 1. Demographical Characteristics

Variable		N	Mean	SD	Notes
Age (years)		24	52,6	8	Min 34 Max 68
Sex	Male	10			41,7%
	Female	14			58,3%
Education level	Primary	6			25,0%
	Secondary	11			45,8%
	Tertiary	7			29,2%
Employment status	Employed	12			50%
	Unemployed	12			50%

Table 2. Clinical Characteristic

Variable	Mean	SD	Notes	
			Min	Max
Duration of DM (months)	26,7	34,3	5	120
Height (cm)	156,0	7,8	142	166
Weight (kg)	62,3	10,7	47	76,5
Initial BMI (kg/m^2)	25,5	3,5	20,6	35,8
Systolic blood pressure (mmHg)	132,9	16,8	110	170
Diastolic blood pressure (mmHg)	77,9	9,8	60	100

week (2 weeks post Ramadan). There was no formation of beta hydroxybutirate in all subjects, as evaluated at the end of Ramadan.

From the mean blood glucose level evaluated at the laboratory at weeks -1, 4, and 6, a significant reduction was found between blood glucose on weeks -1 and 4 (130.8 ± 27.3 mg/dL dengan 110.8 ± 15.7 mg/dL; p=0.001), while an insignificant increase was found in blood glucose level from the 4th to the 6th weeks (110.8 ± 15.7 mg/dL dengan 117.9 ± 21.4 mg/dL; p=0.085). This finding can be found in Figure 2.

Table 3. Observed Changes in Dependent Variable

Variable	Week 1	Week 4	p	Week 6	p
Serum fructosamine (umol/L)	344,2	303,9	0,02	313,6	0,16
β hidroxybutirate (mmol/L)		≤ 0,3			

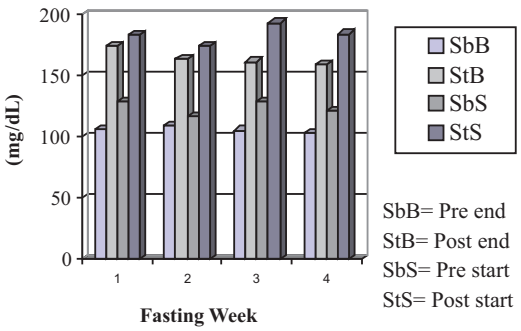

Figure 1. Mean Daily Self-measured Fasting Blood Glucose Level

There were 8 complaints of hypoglycemia, consisting of weakness and cold sweat, 5 of whom were found with blood glucose levels between 60-80 mg/dL, while the remaining 3 were found with a blood glucose level of over 80 mg/dL.

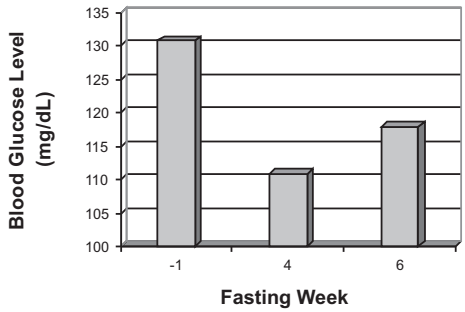

Figure 2. Mean Laboratory-assessed Blood Glucose Level

In this study, we also observed changes in lipid profile. No significant change in total cholesterol level was observed between week -1 and week 4, but there was a significant increase in LDL cholesterol level, reduction in HDL cholesterol level, and a reduction in triglyceride level between week -1 and week 4.

Table 4. Several Biochemical Parameters that were Also Assessed

	Week 1	Week 4	*p*
Total cholesterol (mg/dL)	218,0	222,6	0,471
LDL cholesterol (mg/dL)	134,8	153,0	0,005
HDL cholesterol (mg/dL)	51,4	43,1	0,001
Triglyceride (mg/dL)	176,8	132,0	0,008

In Table 5, Figure 3, and Figure 4, a significant reduction in BMI could be observed between week -1 and weeks 2, 3, and 4, and there is a significant increase in BMI between the fourth and six weeks. Calorie intake is also significantly reduced between week -1 and weeks 1, 2, 3, and 4, and there is a significant increase between fourth and six weeks. Protein intake is significantly reduced between week -1 and weeks 1, 2, 3, and 4, and significantly re-increases between the fourth and sixth weeks. Fat intake is significantly reduced between week -1 and weeks 1, 3, and 4, and significantly re-increases between the fourth and sixth weeks. Fiber intake is significantly reduced between week -1 and week 4, and a non-significant increase was found between the fourth and sixth weeks.

Table 5. Changes in BMI and Nutrient Intake

	Week 1	Week 1	Week 2	Week 3	Week 4	Week 6
BMI (kg/m^2)	25,5	25,4	25*	25,1*	24,7*	25,1**
Calorie intake (kal)	1670	1330*	1402*	1299*	1326*	1667**
Protein intake (g)	56	42,7*	42,6*	39,5*	43,5*	54,1**
Fat intake (g)	51,1	39*	42,1	35,8*	40,2*	53,8**
Fiber intake (g)	27,1	20,5	20,5	20,2	18,4*	20,3

Week * p < 0,05; when compared to values from week-1
** p < 0,05, if compared to values from week-4

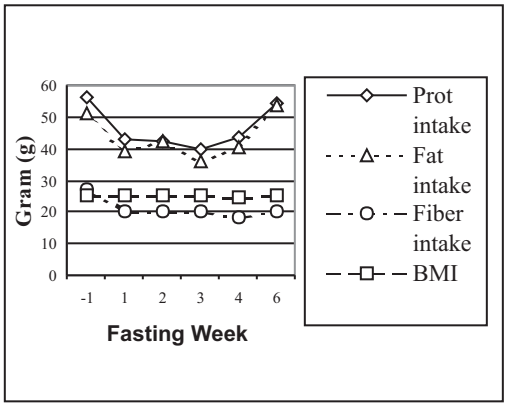

Figure 3. Protein, Fat, and Fiber Intake and BMI Prior to, during, and Following Fasting

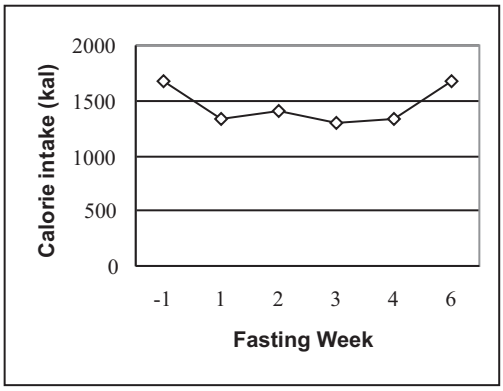

Figure 4. Calorie Intake Prior to, During, and Following Fasting

DISCUSSION

This study was a prospective study on an observed group. The patients with type 2 diabetes mellitus who were included in the study were observed from one week prior to the Ramadan fasting until 2 weeks after the end of the Ramadan fasting. The sample was a continuation of a previous study on repaglinide treatment to observe metabolic control in type 2 diabetes mellitus patients. This sample was selected due to a relatively satisfactory metabolic control, A1C levels of ≤ 8% (high or medium control), and have received adequate and regular education.

Based on sample size calculation, 18 subjects were obtained. In this study 24 subjects were selected, all of whom were followed until the end, but 2 subjects did not undergo assessment of laboratory parameters at the final visit due to technical reasons, but they still underwent history-taking, physical examination, and nutritional analysis. Due to technical reasons as well, out of the 24 subjects, only 15 subjects could undergo beta hydroxybutirate assessment.

Another limitation in the study was the lack of consistency in the study subjects' occupation and activity, which becomes a significant confounding factor, since they influence the assessed metabolic control.

This study demonstrated a significant reduction in serum fructosamine between prior to and at the end of the Ramadan fast (p=0.02). This condition is in line with the study by Mafauzy, who found a significant reduction in serum fructosamine in type 2 diabetes mellitus patients carrying out the Ramadan fast.12 In another study, Mafauzy found a significant reduction in serum fructosamine level in 116 patients treated with repaglinide, while no significant reduction was found in the serum fructosamine level of 119 patients treated with glibenclamide.[13] Belkhaidir et al also did not find a significant change in the level of serum fructosamine prior to and at the end of the Ramadan fast in 591 patients with type 2 diabetes mellitus treated with glibenclamide.16 Unlike serum fructosamine, A1C levels during almost the entire study demonstrated a non-significant change prior to and at the end of Ramadan. This can be explained by the fact that serum fructosamine is a parameter to indicate the conditions in the preceding 2-3 weeks, which approximates the duration of the fast, while A1C level is a blood glucose control parameter for the preceding 120 days.[8]

The significant reduction in serum fructosamine levels found in this study demonstrate a satisfactory blood glucose control during the Ramadan fast, even though the serum fructosamine levels were still higher than normal (344.1 ± 45.7 umol/L prior to Ramadan and 303.9 ± 34.5 umol/L at the end of Ramadan, compared to normal levels of 205-285 umol/L). In this study there was also a re-increase in serum fructosamine following Ramadan (313.6 ± 45.9 mmol/L), even though the increase was not significant. This may be caused by a significant calorie restriction between week -1 and week 4, and return of calorie intake to pre-Ramadan levels, while other nutritional intakes could be seen in Figure 3 and 4, influencing blood glucose levels as seen from the increase in serum fructosamine.

Beta hydroxybutirate evaluation could only be performed on 15 subjects in this study due to a technical problem when utilizing the instrument. This condition influenced the statistical calculations, causing an increase in error level to 15%. In this study, beta hydroxybutirate formation was not found in patients with type 2 diabetes mellitus executing the Ramadan fast, evaluated immediately preceding the meal to break the fast (after approximately 14 hours of fasting) on the 4th week of Ramadan. However, Sadraoui[17] found a significant increase in beta hydroxybutirate between the first and the 28th day of fasting in 9 healthy adults executing the Ramadan fast. Theoretically, glycogenolysis occurs after we fast for approximately 12 hours, and accelerates in patients with type 2 diabetes mellitus with poor blood glucose control. [5,18,19] The lack of beta hydroxybutirate formation in this study was due to a relatively normal blood glucose level during fasting, where the processes of glycogenolysis and gluconeogenesis did not occur, and thus no keton bodies were formed. [5-8]

In this study, there was a significant reduction in laboratory assessed blood glucose level 10 hours following the last meal from week -1 and week 4. However, there was a non-significant increase in fasting blood glucose from week 4 to week 6. There were no significant changes in self-administered blood

glucose level assessment performed prior to breaking the fast, 2 hours following the meal to break the fast, prior to the meal preceding the fast and 2 hours following the meal preceding the fast at weeks 1, 2, 3, and 4. Similar variation in blood glucose level was found in previous studies. Lajam, Mafauzy, Sulimani and Deghan [8,12] found non-significant changes in blood glucose level. Meanwhile, Bouguerra found a significant reduction in blood glucose level, and Bagraicik found a significant increase in blood glucose level.[8] The variation in blood glucose control may be due to the amount and type of food consumed and the patient's cooperation with drug administration and individual differences in energy metabolism and regulation.[8]

There were 8 reports of hypoglycemia, comprising of weakness and cold sweat, 5 of which were found with blood glucose levels between 60 – 80 mg/dL, and the other 3 with blood glucose levels of over 80 mg/dL. The presence of a hypoglycemic complaint in different blood glucose levels is caused by different body adaptation capacity in responding to drops in blood glucose level.[20] Hypoglycemic complaints unaccompanied by a blood glucose level reduction below 60 mg/dL should still be considered as hypoglycemia, and the patient should be advised to break his or her fast. Such action needs to be taken because hypoglycemia could persist and cause dangerous acute complication.[20]

The lipid profile observed in this study demonstrated varying results. Total cholesterol levels demonstrated a non-significant increase prior to and following Ramadan. Previous studies by Uysal et al[21] and Fattah et al[22] found non-significant increase of total cholesterol levels, while Azizi et al found a significant reduction in total cholesterol levels.[8] In this study, we found a significant increase in LDL cholesterol levels prior to and following Ramadan. A previous study by Uysal et al[21] found a non-significant increase in LDL level prior to and following Ramadan. In this study, there was a significant decrease in HDL cholesterol levels. This differed from the finding of Uysal et al, who found a significant increase in HDL levels prior to and following Ramadan.[21] Triglyceride levels were significantly reduced in this study. This is in line with the study by Fattah et al[22] but different from the findings of Uysal et al,[21] who found a non-significant decrease in triglyceride levels. The varying changes in lipid profile observed in this study compared to other studies could be explained by the difference in dietary type and pattern among the subjects of these various studies.[8] This could be observed from the fact that even though in this study fat intake decreased at the end of Ramadan, there was an increase in total cholesterol and LDL cholesterol levels. The significant increase in triglyceride levels in this study was due to increased calorie intake, in this case carbohydrate. The significant reduction in HDL cholesterol in this study may be due to a relative reduction in activity during the Ramadan fast, even though the subjects' activities were not assessed in this study.

In this study, a significant reduction in body mass index (BMI) was found between week -1 and weeks 2, 3, and 4, and a significant increase found between weeks 4 and 6. This finding is similar to that of Soewondo et al.[23] However, Uysal et al[21] did not find a significant change in BMI levels. The significant reduction and increase in BMI prior to, at the end, and 2 weeks following Ramadan may be associated with changes in bodyweight influenced by calorie, protein, and fat intake, which were also significantly reduced at the end of Ramadan, causing an increase in bodyweight, followed by a significant increase 2 weeks following Ramadan. This condition was found in almost all of the previous studies.[8,21,23] However, the fiber intake that was significantly reduced at the end of Ramadan and then non-significantly increased again after Ramadan was not in line with the findings of Soewondo et al. [23]

CONCLUSION

The Ramadan fast in patients with well-controlled and medium-controlled type 2 diabetes mellitus could cause a reduction in serum fructosamine and does not cause formation of beta hyroxybutirate.

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