Ramadan-Like Fasting Reduces Carbonyl Stress and Improves Glycemic Control in Insulin Treated Type 2 Diabetes Mellitus Patients

Abir Zakaria[1], Inas Sabry[2], and Amal El Shehaby[3]

[1]Internal Medicine Department, Faculty of Medicine - Cairo University, Cairo, Egypt
[2] Internal Medicine Department, Faculty of Medicine - Ain Shams University, Cairo, Egypt
[3]Clinical Biochemistry Department, Faculty of Medicine -Cairo University, Cairo, Egypt
drabirzakaria@yahoo.com

Abstract: Aim: To assess the effect of a culturally-tailored Ramadan-like fasting model on carbonyl stress and glycemic control in insulin treated patients with type 2 diabetes. **Methods:** In a single group non-randomized controlled multicentric trial 90 out of 200 insulin treated type 2 diabetic patients, were enrolled in a Ramadan-like fasting model. After two sessions of interactive patient-centered general diabetes education held for 200 patients, only 90 fulfilled the minimal reasonable glycemic control, defined as HbA1c of 9% or less after three months, and were considered eligible to participate in fasting, after a Ramadan-oriented session. Each participant commenced Ramadan-like fasting for 3 consecutive days, under close medical in-hospital supervision. Post-meal culturally-based moderate exercise was integrated, with adjusted insulin regimen, and dietary control. **Results:** Ramadan-like fasting was found to be beneficial for insulin treated patients with type 2 diabetes, with reduction of carbonyl protein stress, mean amplitude of glycemic excursion, mean post-prandial glycemic excursion, and average glucose. The risk for hypoglycemia was mild with one self-detected and managed event, but no hyperglycemic crises. **Conclusions:** Ramadan fasting may be beneficial in uncomplicated, properly educated, insulin treated patients with type 2 diabetes through reduction of carbonyl stress, over and above its glycemic control.

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1. Introduction:

Both intermittent fasting and dietary restriction were found to delay age related brain dysfunction in animal models (1) due to reduction of oxidative stress. A state of adaptive preconditioning (2) with slowing down of end organ damage in animals was attributed to partial restoration of anti-oxidant status (3). It was also suggested to increase longevity of animals (2) and humans (4).

Type 2 diabetes mellitus is characterized by insulin resistance, which induces oxidative stress (5). In addition to the toxic effect of chronic hyperglycemia as a cause of microvascular and macrovascular diabetic complications, there is growing evidence that postprandial glycemic spikes (6) play an important role in the pathogenesis of these complications through associated oxidative stress.

Ramadan is a lunar-based month during which an adult Muslim should practice daily intermittent fasting with abstinence from food, drink, or any oral intake from pre-dawn to after sunset, then allowance of food and drink from after sunset to pre-dawn. Chronically ill patients including those with diabetes are exempted from Ramadan fasting from a religious point of view, but many patients insist to participate (7). According to the population-based EPIDAR study (8) more than 50 million Muslim patients with diabetes mellitus fasted during Ramadan. Hypoglycemia and hyperglycemia remain risks for every patient with diabetes who wishes to fast during Ramadan, particularly in insulin-treated patients.

Objectives of the Study

In the current study we invented a Ramadan-like fasting model. We postulated that we can benefit from fasting hours to limit glycemic excursions, as meals are usually reduced to two meals. We also tried to blunt post-meal glycemic spikes by integrated post-meal moderate culturally-based exercise, in addition to proper dietary control and adjustment of insulin regimen. We aimed at figuring out the effect of this Ramadan-like fasting model on oxidative stress in insulin treated, uncomplicated, reasonably controlled patients with type 2 diabetes, who were under close medical supervision in an inpatient context. Carbonyl protein (CP) level was used as an indicator of oxidative stress. Our second objective was to assess the influence of this Ramadan-like fasting model on glycemic variability as assessed by mean amplitude of glycemic excursion (MAGE), mean postprandial glycemic excursion (MPPGE) and average glucose level in comparison to the pre-fasting levels, as well as the hypoglycemic and hyperglycemic risks during this intermittent fasting regimen.

2. Participants and Methods:

2. i. Study Design:

In a single group non-randomized controlled multicentric trial two hundred insulin treated patients with type 2 diabetes, whose age ranged from 40-60 years, were recruited from the outpatient clinic of both Kasr El Ainy and Ain Shams University hospitals, Cairo, Egypt. All attended 2 educational interactive sessions held in one month and each lasted for 60 minutes. These sessions included basic knowledge about type 2 diabetes mellitus pathogenesis, dietary principles, exercise protocols, encouragement of self monitoring of blood glucose SMBG, symptoms suggestive of hypoglycemic or hyperglycemic attacks and their management.

Three months later HbA1c was ordered for all patients. Only 90 patients with reasonable overall glycemic control defined as HbA1c of 9 % or less were considered eligible to participate in a Ramadan-like fasting. Initially seven blood glucose readings were collected from each patient by SMBG, a pre-meal, and 2 hours postprandial reading for each meal, and one at dawn time, for each day for three consecutive regular non-fasting days. Oxidative stress was assessed for each patient by monitoring of CP level after an overnight fast.

Another hour of Ramadan-fasting focused educational session was held with special emphasis on healthy diet, meal planning, moderate exercise, liberal fluid intake after sunset, and frequent SMBG. Afterwards each participant out of the 90 patients was admitted to hospital, according to his/her preferred time schedule, to commence Ramadan-like fasting.

Under medical supervision and for 3 consecutive days each patient was allowed to abstain from food and drink and any oral medication for about 14 hours per 24 hours from pre-dawn to after sunset. Appropriate plans were put before commencement of fasting for both correction of insulin doses with 20% to 25% reduction of the total dose and redistribution of administration time, as well as change of other medications' timing during the days of fasting. SMBG was carried out during fasting hours at 8 am, 12 pm, and 3 pm. A pre-meal, and 2 hours postprandial reading for each of the two daily meals, one after sunset and the other at pre-dawn, were also recorded.

Meal planning during fasting was individualized for each patient taking his/her needs into consideration, while still keeping the carbohydrate content representing 50%, proteins 20% and fat 30% of each meal, with predominance of poly-unsaturated fat.

A total period of 50 minutes of moderate exercise was carried out after sunset meal similar to those performed by most Muslim individuals in Ramadan. It included 30 minutes of prayers preceded and followed by 10 minutes of walking. Muslim prayers normally include repeated movements of standing, bowing, kneeling, and rising. Another SMBG reading was taken at 12 am to access the delayed effect of this integrated moderate exercise. Blood samples were collected for detection of CP level at the end of the 14 hours fast of the third day.

The study protocol was approved by the scientific board of Internal Medicine Department and Committee of Research Ethics; Faculty of Medicine - Cairo University, and an informed consent was obtained from each participant.

2. ii. Assessment of glycemic variability:

Glycemic variability was estimated by the mean amplitude of glycemic excursion MAGE by calculating the arithmetic mean of differences between consecutive peaks and nadirs (9) of SMBG readings recorded in the three consecutive days before fasting and those recorded during Ramadan-like fasting days.

2 iii. Assessment of average glucose level:

Average glucose level was estimated by dividing the algebraic sum of blood glucose measurements detected by SMBG over the number of readings in three consecutive days before fasting. These figures were compared to the average calculated during the three Ramadan-like fasting days.

2.iv. Mean post-prandial glycemic excursion:

Mean postprandial glycemic excursion MPPGE was calculated by dividing the algebraic sum of the differences between pre-meal and 2 hours post-prandial reading of each meal by the number of meals for the three consecutive non-fasting days, compared to the Ramadan-like fasting days. Taking into consideration that the number of meals was three in each usual day, we divided the sum by nine in the three pre-fasting days to calculate the MPPGE. But only two meals existed in each fasting day, so we divided by six in the three consecutive fasting days.

2. v. Indications of breakfasting:

Instructions were given to patients, physicians, and nurses to stop fasting if the patient complained of hypoglycemic symptoms, or if any SMBG reading was 75mg/dl or less before 12 p.m. or 70 mg/dl or less afterwards. Fasting was also terminated if SMBG showed a reading of 300mg/dl or more with assessment of arterial blood gases and urine samples for ketones.

2.vi. Exclusion Criteria:

Excluded from the study were patients with type 1 diabetes mellitus or type 2 with history of myocardial infarction, cerebrovascular stroke, peripheral arterial disease, proliferative diabetic retinopathy, or creatinine clearance < 60 ml/min. Patients who developed more than three attacks of mild or moderate hypoglycemia, or a single attack of severe hypoglycemia evidenced by neuroglucopenic symptoms, over the last three months, were exempted from the study. Also pregnant ladies or those exceeding 60 years were excluded. In patients with evidence of acute illness fasting was postponed.

2.vii. Carbonyl Protein Measurement:

Serum Carbonyl protein CP was measured by a kit provided by Cayman Chemical Company, Ann Arbor, USA. Cayman's Protein Carbonyl Assay Kit could utilize dinitrophenylhydrazine reaction to measure the protein carbonyl content in plasma, serum, cell lysates, or tissue homogenates. In the present study protein carbonyl content was measured in serum. The amount of protein-hydrozone produced was quantified spectrophotometrically at an absorbance between 360-385 nm. The carbonyl content was standardized to protein concentration in mg/ ml. The intra-assay coefficient of variation was 4.7%, and the inter-assay coefficient of variation was 8.5%. According to the manufacturer's instructions the utilized assay worked best when samples had protein concentrations in the range of 1-10 mg/ml.

2 viii. Statistical Analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between equivalent data before and during fasting was done using Student *t-test* for independent samples. Within group comparison between before and during data was done using paired t-test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between variables was done using Pearson's correlation equation for linear relations and Spearman Rank correlation for non-linear relations. *P*-value less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results:

Only 45% (90/200) of the initially enrolled group of patients achieved a reasonable glycemic control as a pre-requisite for participation in fasting (Fig. 1). Fasting patients' characteristics were summarized in table 1. Compared to pre-fasting data significantly lower values of CP level and glycemic variables were recorded during fasting (Table 2).

Linear correlations were detected between HbA1c and glycemic variables (Table 3), as well as between average glucose and MAGE, before and during fasting (Table 4).

In comparison to the significant correlations between CP level and (MAGE and MPPGE) before fasting, correlations between CP level and (MAGE and MPPGE) during fasting did not reach statistical significance (Table 5). Figure 2 shows a linear correlation between CP level and MPPGE before fasting.

Table 1 showed that hypoglycemia necessitating termination of fasting occurred in 1 out of the 90 participating patients (1.1%). This patient was on premixed insulin. None of the participants terminated fasting due to hyperglycemia.

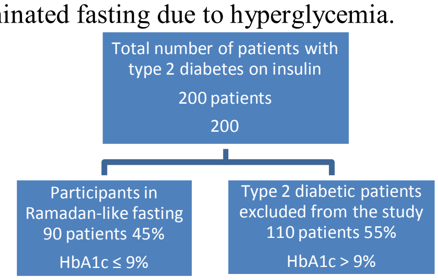

Figure 1: Steps of selection of insulin treated patients with type 2 diabetes mellitus to participate in the medically supervised Ramadan-like fasting

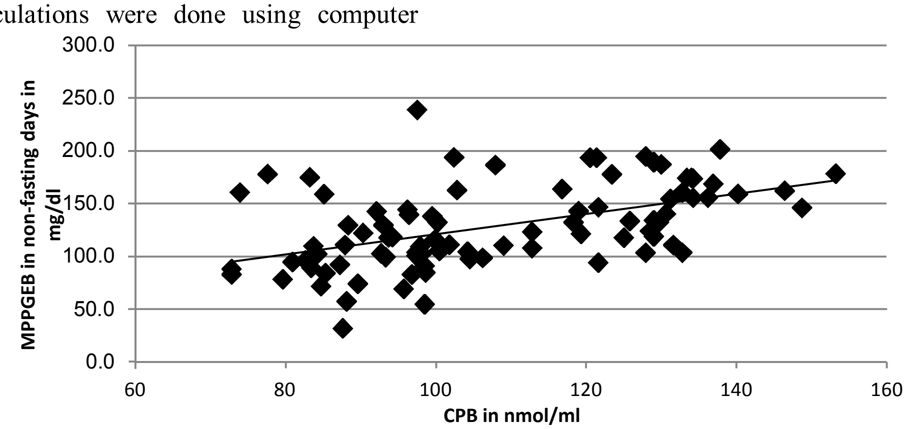

Figure 2: Correlation between CPB and MPPGEB in regular non-fasting days
CPB: carbonyl protein level before fasting; MPPGEB: mean post-prandial glycemic excursion before fasting.

Table 1: Characteristics of Ramadan-like fasting participants with type 2 diabetes mellitus (n= 90)

Parameter	Data	Percentage
Age (mean ± SD)	49.03 ± 5.652	
Sex	Males: n = 47	52.2%
	Females n = 43	47.8%
Insulin Regimen	Premixed insulin: n = 22	24.4%
	Basal Bolus insulin : n = 68	75.6%
Hypoglycemia with termination	n = 1	1.1%
Hyperglycemia with termination	null	0%

SD: standard deviation; n= number

Table 2: Comparison between carbonyl protein level and glycemic changes before and during Ramadan-like fasting.

	Mean ± SD (mg/dl)	*p*-value
MAGED MAGED	115.826 ± 37.0963 49.189 ± 11.9823	0.000
MPPGED MPPGED	128.46 ± 38.998 80.86 ± 19.421	0.000
AGB AGD	160.675 ± 27.4659 136.535 ± 21.4599	0.000
CPB CPD	107.780 ± 20.210 61.873 ± 17.3149	0.034

MAGEB: mean amplitude of glycemic excursion before fasting, MAGED: mean amplitude of glycemic excursion during fasting, MPPGEB: mean post-prandial glycemic excursion before fasting, MPPGED: mean post-prandial glycemic excursion during fasting, AGB: average glucose before fasting, AGD: average glucose during fasting, CPB: carbonyl protein before fasting, CPD: carbonyl protein during fasting. Significant p-value is < 0.05.

Table 3: Correlations (linear dependence) between HbA1c and glycemic variables before and during fasting:

Glycemic parameter	Pearson's Correlation with HbA1c (r)	*p*-value
MAGEB	0.735	0.000
MAGED	0.510	0.000
AGB	0.761	0.000
AGD	0.408	0.000
CPB	0.620	0.000
CPD	0.219	0.038

HbA1c: glycated hemoglobin; MAGEB: mean amplitude of glycemic excursion before fasting, MAGED: mean amplitude of glycemic excursion during fasting; AGB: average glucose before fasting; AGD: average glucose during fasting; CPB: carbonyl protein level before fasting; CPD: carbonyl protein level during fasting. Significant p-value is < 0.05.

Table 4: Correlations (linear dependence) between different glycemic parameters before and during fasting:

Glycemic parameter before fasting	Pearson's Correlation with AGB (r)	*p*-value
MAGEB	0.671	0.000
Glycemic parameter before fasting	Pearson's Correlation with AGD (r)	
MAGED	0.339	0.001

MAGEB: mean amplitude of glycemic excursion before fasting, MAGED: mean amplitude of glycemic excursion during fasting AGB: average glucose before fasting; AGD: average glucose during fasting. Significant p-value is < 0.05.

Table 5: Correlations between carbonyl protein level and glycemic variables before and during fasting:

Glycemic parameter before fasting	Correlation with CPB	*p*-value
MAGEB	0.480 (Pearson)	0.000
MPPGEB	0.534 (Spearman)	0.000
Glycemic parameter before fasting	Correlation with CPD	
MAGED	0.113 (Pearson)	0.290
MPPGED	- 0.099 (Spearman)	0.351

MAGEB: mean amplitude of glycemic excursion before fasting, MAGED: mean amplitude of glycemic excursion during fasting; CPB: carbonyl protein level before fasting; CPD: carbonyl protein level during fasting. Significant *p*-value is < 0.05.

3. **Discussion:**

Ramadan is a lunar-based month during which fasting is rigorously observed by Muslims all over the world from pre-dawn to after sunset. According to the EPIDAR study the prevalence of fasting among patients with diabetes was 43% for type 1 and 86% for type 2 (8). Diabetes management during fasting is a challenge for both the physician and the patient, due to fear from daytime hypoglycemia (10), or night hyperglycemia (7). Insulin treated patients with type 2 diabetes mellitus are justified to be exempted, however many of them insist on fasting. In the current study we tailored a Ramadan-like fasting model to detect its effect on carbonyl protein, glycemic control and variability, and hypoglycemic or hyperglycemic risks.

The currently innovated Ramadan-like fasting model, with adjusted insulin regimen, dietary control, and post-meal culturally-based moderate exercise, was found to be beneficial for insulin treated patients with type 2 diabetes with reduction of carbonyl stress, MAGE, MPPGE and average glucose. Hypoglycemic risk was minimal, presented with mild event, and was easily self-diagnosed by SMBG and self-managed. Hyperglycemic crises never occurred.

In addition to the overall glycemic control, there is growing evidence that postprandial glycemic excursion is an independent risk factor for cardiovascular diseases among patients with diabetes through production of oxygen free radicals (11), which induce endothelial damage by oxidative and carbonyl stress (12), with the later being also considered among other mechanisms as polyol pathway, advanced glycation end products, and activation of protein kinase C, playing an important role in the pathogenesis of diabetic microvascular complications (13, 14). During normal physiological conditions enzymatic and non-enzymatic defense mechanisms interfere with production of reactive carbonyl species. In some pathological conditions as diabetes mellitus these protective mechanisms become overwhelmed (15). Having a long half life and being easily detected, reactive carbonyl species, including carbonyl protein, have been used as biomarkers of oxidative stress (15).

In the current study significant reduction of serum carbonyl protein CP level after Ramadan-like fasting was observed. CP correlated positively with HbA1c, suggesting being influenced by the overall glycemic control. *Before beginning of fasting, carbonyl protein level* (CPB) correlated positively with *mean amplitude of glycemic excursion before fasting* (MAGEB), and *mean post-prandial glycemic excursion before fasting* (MPPGEB). In spite of significant reduction in *mean amplitude of glycemic excursion during fasting* (MAGED) and *mean post-prandial glycemic excursion during fasting* (MPPGED), their correlation *with carbonyl protein level estimated at the end of fasting* (CPD) did not reach statistical significance, suggesting another element to play a role in lowering CP level. This might be the mere effect of prolonged fasting hours with less frequent glycemic spikes, as the number of meals during Ramadan-like fasting was reduced to two instead of three in regular non-fasting days. Frequency, as well as amplitude of glycemic excursions, was suggested by previous investigators to play a pivotal role in microvascular and macrovascular diabetic complications (16). Moreover integrating exercise after the main meal might have reduced the oxidative stress (17) suspected to reach its peak in the post-prandial period (18).

Fasting of a healthy individual was divided by Felig in 1979 into post-absorptive phase ranging from 6 to 24 hours from commencement of fasting associated with reduction of insulin secretion, with increase of glucagon and catecholamines, both enhancing glycogenolysis, then gluconeogenesis phase with a fast extending for 2 to 10 days, and protein sparing phase with more protracted fasting (19). Fasting in a patient with diabetes for the same time interval was found to be associated with exaggeration of the normal phenomenon, with excessive hyperglycemia due to insulin deficiency, with the possibility of gluconeogenesis to occur earlier due to unclear cut point between the phases, and ketogenesis to take place to guarantee an energy source (7). However in the current study patients were supplied with sufficient insulin to suppress these processes in a basal or a premixed preparation. Moreover proper redistribution and individualized tailoring of insulin doses, together with adequate patient education about insulin preparations as regards onset, peak, and duration of action, avoided them from just omitting doses from fear of hypoglycemia (7).

There is no accurate data about the exact rate of hypoglycemic events during Ramadan fasting among patients with diabetes (20). The famous EPIDAR study was concerned about the risk of severe hypoglycemia necessitating hospitalization, which was estimated to reach 4.5 folds in patients with type 1 and 7.5 folds in those with type 2 diabetes (8). In the present study hypoglycemia was mild, and was self-managed. This might be attributed to the adherence to SMBG and termination of fasting in the proper time.

Blunting post-meal glycemic excursion after the post-sunset meal, which is considered the mean meal after about 14 hours fast, was a real challenge in the present study. Long term (21) and short term (22) effects of different exercise regimen including culturally-based exercises as the T'ai Chi exercise

(21) were addressed in previous studies. Considering cultural barriers, which may prevent implementing regular exercise regimen in real life after prolonged fasting hours, compelled us to integrate an exercise model simulating that occurring in real life of most Muslim individuals after sun-set in Ramadan, in the post-prandial period, in an attempt to reduce the post-meal glycemic spike as suggested by previous investigators (23). Being well known for every Muslim, prayer movements were performed with no need for education and could be repeated as much as one can, so extending prayers to 30 minutes in the post-prandial period was easy. Moreover they were preceded and followed by 10 minutes of walking simulating the walk needed to reach a mosque in real life. This was successful in limiting MPPGE, which could be explained by the effect of muscle contraction on increasing glucose transporter 4 (GLUT4) translocation to the skeletal muscle cell membrane, with consequent enhancement of glucose transport by facilitative diffusion independent on insulin (24). Moreover exercise was suggested to improve insulin sensitivity (22) and to increase absorption of the administered insulin from its subcutaneous site (25). Being a moderate exercise prevented immediate or delayed hypoglycemic events (26).

As regards meal planning we faced two problems. First we could not prohibit Ramadan drinks taken by the patients in the main meal after sunset, as they guarantee proper hydration. But sugar added to these drinks was partially replaced by sugar substitutes. So that some of the carbohydrate daily requirements were supplied as simple sugar, which was found according to the American Dietetic Association (27) evidence based guidelines not to have a substantial difference in glycemic response; so long the total amount of carbohydrates was kept constant. We also distributed the fluid requirements over the period from sunset to predawn to supply the 24 hours fluid recommendations, reaching up to 2.7 liters for women and 3.7 liters for men as recommended by Institute of Medicine (28). The second problem was the rest of carbohydrates, which was recommended to be supplied from whole grain, fruits, vegetables, and low fat milk. Being preferred in the Egyptian community and also considered a major source of resistant starch (29), legumes were added to both meals in an attempt to limit both MPPGE and hypoglycemia during fasting (30).

In the current study we made use of the spiritual need of reasonably controlled insulin treated patients with type 2 diabetes to encourage their adherence to SMBG, dietary control, and regular moderate exercise. We limited hazards of fasting by strict exclusion criteria, and by selection of those who made benefit from the initial general diabetes education sessions by lowering their HbA1c, which reduced our sample size.

Conclusion:

Conditioned by proper education and reasonable glycemic control, enrollment of uncomplicated, insulin-treated patients with type 2 diabetes, was feasible in the current Ramadan-like fasting model, to show that benefits might overweigh risks. This model succeeded in lowering carbonyl stress over and above its beneficial effect in lowering MAGE, MPPGE, and average glucose. Hypoglycemic events were mild, and easily self-managed. We would suggest larger scale similar models to detect the long term effect of Ramadan-like fasting on oxidative stress and its impact on vascular complications.

Competing interests: Nothing to declare.

Corresponding author
Abir Zakaria
Internal Medicine Department, Faculty of Medicine-Cairo University, Cairo, Egypt
Email: drabirzakaria@yahoo.com

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