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Effect of Ramadan Fasting on Microvascular Complications in Type 1 Diabetic Patients

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ABSTRACT

Background: Ramadan holy month fasting is part of Muslims faith that involves abstaining from food and drink intake as well as oral and injected medications from the dawn to dusk. An appreciable percent of type 1 diabetic patients insists on Ramadan fasting though exempted religiosly and medically.

Objective: To evaluate the effect of Ramadan fasting primarily on eGFR and microalbuminuria in people with type 1 diabetes and secondarily on neuropathy and retinopathy**.**

Patients and Methods: This study was conducted on 60 type 1 diabetic patients with microalbuminuria intending to fast Ramadan. Patients were recruited from diabetes outpatient clinics at Ain Shams University; all patients were on mutiple daily insulin injection (MDI). Before and after Ramadan fasting blood glucose (FBG), 2hPPBG, HbA1c%, fructosamine, Serum creatinine, BUN, urinary albumin/creatinine ratio (UAC ratio) and estimated GFR were measured to all patients in addition to fundus examination and DN4 questionnaire.

Results: Among 60 patients who joined the study, 53 patients completed the study visits. The end of Ramadan fasting follow up showed a significant rise of serum creatinine and UAC ratio (0.87±0.14 vs 0.93±0.16 mg/dl, p=0.003; 125.5±101.1 vs 132.7±107.8 ugm/mg creatinine, p=0.003), while systolic and diastolic blood pressure showed no significant change (p=0.56; 0.58 respectively). Fifty percent of the patients exhibited a significant decrease of eGFR after Ramadan fasting (96.3±21.5 vs 89.7±22.7 ml/min/1.73 m^2, p= 0.002). There was no difference across all studied variables upon subgrouping of patients according to eGFR state (Decreased, stationary and increased). There was a significant improvement of glycemic parameters, FBS (p<0.001), post-prandial blood sugar (PPBS) (p< 0.001) and fructosamine (p= 0.02) with a significant reduction in hypoglycemic attacks by the end of Ramadan.

Conclusion: Ramadan fasting decreased eGFR but within normal range among 50% of the studied population with a significant increase of UAC ratio inspite of improved glycemia.

Keywords: Ramadan fasting, Type 1 DM, Fructosamine, Albumin/creatinine ratio (UAC ratio), Estimated GFR.

INTRODUCTION

One of the five pillars of Islam is to fast during the holy month of Ramadan. Between sunrise and dusk, one must abstain from eating and drinking. Biological differences occur throughout this holy month as a result of lifestyle and dietary habits changes [(1)].

The length of Ramadan might vary. As the Islamic calendar is lunar and the Islamic year has 354 days, (instead of 365, as in the Gregorian or solar calendar). Because of this, the month of Ramadan starts 11 days earlier each year and can fall at any time of the year, making a full rotation every 33 years. Hence, the average length of a fast is 12 to 14 hours, but depending on the location and the time of year, it may potentially go up to 18 or even 22 hours in the most northern latitudes [(2)].

Any Muslim adolescent who is intellectually capable and does not qualify for any religious exceptions is required to fast throughout Ramadan, according to the Quran. Also, if a person's health is in danger, fasting is not permitted. The Jurisprudence established laws that shield Muslims with chronic illnesses from harm and agony based on the Quran and the Sharia [(3)]**.**

A decrease in blood glucose levels brought on by fasting results in less insulin being produced. Moreover, the levels of glucagon and catecholamine increase, increasing glycogen breakdown while gluconeogenesis is enhanced. Glycogen stores become depleted during a prolonged fast, and low levels of circulating insulin allow for an enhanced release of fatty acids from adipocytes. A prolonged fast can cause excessive glycogen breakdown, increased gluconeogenesis, and accelerated ketogenesis in those with severe insulin insufficiency, leading to hyperglycemia and ketoacidosis [(4)].

Special consideration should be given to pregnant women who insist on fasting and those with type 1 diabetic mellitus (T1DM). The ideal method for managing diabetes during Ramadan is to customise medication choices. Pre-Ramadan patient evaluation, Ramadan medication modification, and post-Ramadan follow-up are some of the phases that make up this procedure [(5)].

Twenty to forty percent of people with diabetes develop diabetic kidney disease, which is the main cause of end-stage renal disease (ESRD). Urinary albumin-to-creatinine ratio (UACR), which may be measured in a random spot urine sample, is the most straightforward method for screening for kidney injury (albuminuria). However, there is little information available, and there are no standards or defined methods [(6)].

The consequences of Ramadan fasting on renal physiology are not just a matter of academic study or of particular concern to Arab nations. As more and more

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Muslims are settling in Western nations, doctors in a globalised world must deal with problems like managing chronic kidney disease (CKD) in Muslim patients who desire to fast throughout Ramadan. However, there is little information available, and there are no standards or defined methods [7].

The aim of the study was to evaluate the effect of Ramadan fasting primarily on estimated glomerular filtration rate (eGFR) and microalbuminuria in people with type 1 diabetes and secondarily on neuropathy and retinopathy.

PATIENTS AND METHODS

This study was conducted on 60 type 1 diabetic ranging from 16 to 35 years old with microalbuminuria diagnosed more than 5 years intending to fast Ramadan. Patients were recruited from diabetes outpatient clinics at Ain Shams University. All patients were on mutiple daily insulin injection (MDI).

Exclusion criteria included patients with estimated GFR <60 ml/min/1.73m², major hypoglycemic episodes and / or hyperglycemic crisis within the past 3 months to Ramadan and pregnancy.

Full clinical examination was performed including BMI, measurement of systemic blood pressure, fundus examination and DN4 questionnaire

Laboratory studies:

Before and after Ramadan FBG, 2hPPBG, HbA1c%, fructosamine, serum creatinine, blood urea nitrogen (BUN), Urinary albumin/creatinine ratio (UAC ratio) and estimated GFR were measured to all patients in addition to fundus examination and DN4 questionnaire. Before to Ramadan 2017, they all received health education, with follow-up occurring during the month and after Ramadan. **Ethical approval:**

This experiment was ethically approved by Ain Shams University. After being fully informed, all participants provided written consent. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

Using SPSS software version 18, data analysis was carried out. Mean±Standard deviation (SD), range, median and interquartile range (IQR) were employed to describe quantitative data, whereas percentages and numbers were utilised to represent qualitative data. Wilcoxon Signed Ranks Test (nonparametric test): is a test of significance used for comparison between paired data not normally distributed having nominal variables. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P values lower than 0.05 were regarded as significant.

RESULTS

This prospective observational study was conducted on 60 type 1 diabetic ranging from 16 to 35 years old with microalbuminuria. Among 60 patients who joined the study 53 patients completed the study visits. The end of Ramadan fasting follow up showed a significant rise of serum creatinine and UAC ratio, while systolic and diastolic blood pressure showed no significant change. Fifty percent of the patients exhibited a significant decrease of eGFR after Ramadan fasting. Also, there was a significant decrease in weight and BMI **(Tables 1, 2 and figure 1).**

Table (1): Comparison between clinical and lab. data before and after Ramadan (N= 53)

Variable	Before Ramadan Mean±SD	After Ramadan Mean±SD	Paired mean difference	T	P-value
Weight (kg)	68.2±10.3	67±9.9	1.2	5.377	**<0.001***
Waist circumference	79.1±8.3	79.1±8.3	0	0	-
BMI (kg/m²)	25.7±2.5	25.2±2.5	0.5	5.688	**<0.001***
Systolic bl. pr. (mmHg)	112.3±11.7	111.4±10.2	-0.6	-0.588	0.560
Diastolic bl. Pr. (mmHg)	72±8.7	71.8±9.1	0.4	0.552	0.584
FBS (mg/dl)	173.3±42.3	131.9±29.2	-41.42	-4.62	**<0.001***
2hr PPBG	216.1±51.4	178.1±38.3	-37.98	-4.49	**<0.001***
BUN (mg/dL)	13.1±3.1	14.2±3.2	-1.1	-2.608	**0.012***
S. Creatinine (mg/dl)	0.87±0.14	0.93±0.16	-0. 06	-3.148	**0.003***
A/C ratio	125.5±101.1	132.7±107.8	-7.2	-3.158	**0.003***
éGFR (ml/min)	96.3±21.5	89.7±22.1	6.6	3.320	**0.002***
Dose of basal insulin (unit)	26.5±6.6	19.3±4.5	7.2	17.921	**<0.001***
Dose of bolus insulin (unit)	46.8±11.1	30.3±7.3	16.4	16.769	**<0.001***

Table (2): Categorizing of the study group according to éGFR

éGFR (ml/min)		
	N	**%**
Stationary	17	32. 1
Decreased	27	50.9
Increased	9	17
Total	53	100.00

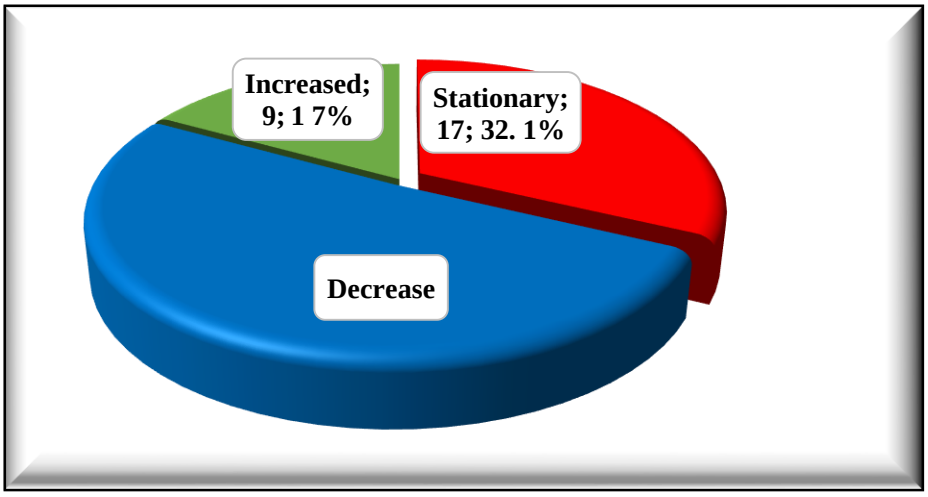

Figure (1): Categorizing of the study group according to éGFR.

There was no significant difference between pre and post Ramadan fundus examination and there was a mild significant increase of DN4 questionnaire score **(Tables 3, 4).**

Table (3): Comparison between before and after Ramadan regarding fundus examination

Fundus examination	Before Ramadan		After Ramadan		Chi-Square	
	N	%	N	%	X^2	P-value
Normal	51	96.2	51	96.2	0.000	1.000
Foveal atrophy	2	3.8	2	3. 8		
Total	53	100	53	100		

Table (4): Comparison between DN4 Q and fructosamine before and after Ramadan (N= 53)

Data	Time	Median	IQR	Wilcoxon Signed Ranks Test	
				Z	P-value
DN4 Q	**Before**	0.00	0.00	-2.000	0.046*
	After	0.00	1.00		
	Ramadan 2017	1.00	2.00		
Fructosamine	**Before**	267.8	91.2	-2.519	0.012*
	After	259.9	93.6		

There was a significant improvement of glycemic parameters, FBS, PPBS and fructosamine **(Tables 1, 4),** with a significant reduction in hypoglycemic attacks by the end of Ramadan **(Table 5)**.

Table (5): Comparison between Ramadan 2016 and 2017 regarding attacks of hypoglycemia (N= 53)

Variable		Ramadan 2016	Ramadan 2017	Z	P-value
Attacks of hypoglycemia	**Median**	4.00	1.00	-5.694	<0.001*
	IQR	3.00	2.00		

DISCUSSION

Regarding the impact of the Ramadan fast on renal function, our study revealed that serum creatinine, blood urea nitrogen (BUN), and urine albumin-creatinine ratio (ACR); all significantly increased after the Ramadan fast (p value = 0.003, 0.012 and 0.003 respectively) with a mean difference of 0.063 mg/dl, 1.125 mg/dl and 7.197 mg/dl respectively, in a maintained glycemic control so that hyperglycemia is not the cause of post Ramadan increase of microalbuminuria, also fifty percent of the patients exhibited a significant decrease of eGFR after Ramadan fasting (96.3±21.5 vs 89.7±22.7 ml/min/1.73 m2p= 0.002). These findings are explained by the dehydration-causing restriction on fluid intake during the fast, particularly if it is extended. In hot, humid conditions and among those who engage in strenuous physical activity, excessive sweating can exacerbate dehydration.

This agreed with the study of **Marbut *et al.*** [8] who observed a non-significant increase in blood urea toward the end of Ramadan in a study conducted on 30 normal healthy male doctors aging between 26 to 30 years in the month of Ramadan from 26 of Oct. to 24 of November 2003. Average duration of the fast was about 12 hours and maximum temperature ranged from 10 to 15^{o}C. In their short review, **Abedini *et al.*** [9] highlighted the significance of proper hydration in diabetes patients planning to fast by demonstrating a non-significant rise in BUN following Ramadan. **Kamar *et al.*** [10] also noted that the albumin creatinine ratio dramatically rose from 98.41±160.49 to 141.49±228.62 following Ramadan fasting in a research including 74 diabetes patients (whose ages varied from 20 to 64 years). According to **El-Gendy *et al.*** [11] who conducted a research on 20 type 2 diabetes patients, fasting throughout Ramadan for four weeks had a negligible impact on ACR, dropping it by 3.9 and 5.6% in the control and diabetic groups, respectively.

It is important to understand the mechanism by which fasting causes these changes. Blood and urine samples were taken in the early morning, when it appeared that participants were hydrated. It is also possible that participants had reduced their dietary intake and were more aware of potential problems and how to handle proteins during Ramadan [11].

El-Wakil *et al.* [12] demonstrated, in contrast to our study, that Ramadan did not significantly alter the GFR of CKD patients who were not diabetic (baseline eGFR 33.321.1 ml/min/1.73m^2). Nevertheless, just a limited sample size was used for the investigation (15 subjects).

There was no statistically significant difference between the pre- and post- Ramadan fundus examinations. This may be because there wasn't enough time to observe significant fundus changes throughout the research period.

In contrast to our study, **Kamar *et al.*** [10], who examined 74 diabetic individuals with ages ranging from 20 to 64 years, found that diabetic retinopathy significantly improved following Ramadan fasting. 14 hours on average were spent fasting. Limiting fluid intake during the fast, especially if it is extended, may be the cause of this. Moreover, this can be aggravated by sweat in hot, muggy environments and in those who engage in strenuous physical activity. All of them, although raising the risk of thrombosis, may reduce retinal exudation.

Regarding the effect of Ramadan fasting on neuropathic pain measured by DN4 Q our study showed a mild significant increase of DN4 questionnaire score (p = 0.046).

In our study we found that there was a significant improvement of glycemic parameters, FBS (p<0.001), PPBS (p< 0.001) and fructosamine (p= 0.02) with a significant reduction in hypoglycemic attacks by the end of Ramadan.

This was in keeping with **Fakhrzadeh *et al.*** [13] findings from 2003, that by following Ramadan fasting, fasting plasma glucose considerably dropped in both men and women. Also, **Khaled *et al.*** [14] discovered that following Ramadan fasting, obese women with type 2 diabetes mellitus had substantial drops in their fasting blood glucose and HbA1c levels.

This was consistent with research by **El-Hawary *et al.*** [15] on T1DM children who fasted for 29 days during Ramadan 1434/2013 and received comprehensive pre-Ramadan instruction, which revealed a substantial drop in post-Ramadan fructosamine levels (p 0.001).

On the other hand, **Hassan *et al.*** [16] showed non-significant changes in FBG after Ramadan among patients with adequate baseline glycemic control. They conducted a research on 63 people with continuous glucose monitoring before, during, and after Ramadan. **Sahin *et al.*** [17], in a research including 122 individuals with type 2 diabetes, also demonstrated that there was no variation in PPBG following Ramadan fasting.

The same was found by **Bouguerra *et al.*** [18], who investigated how fasting during Ramadan affected glycemic control and found that patients with fructosamine levels above 340 micromol/l before Ramadan experienced an increase in plasma fasting glucose and serum fructosamine (p 0.003), whereas patients with fructosamine levels below 340 micromol/l experienced no change in glycemic control during Ramadan.

CONCLUSION

In summary, the study concluded that Ramadan fasting decreased eGFR but within normal range among 50% of the studied population with a significant increase of UAC ratio inspite of improved glycemia.

It is important to respect a person with T1DM's decision to fast during Ramadan. There is some evidence to support the idea that they can do so safely as long as they are otherwise stable and healthy. Nevertheless, type 1 diabetics with microalbuminuria

should be counselled on proper hydration and dietary protein modification during pre-Ramadan health education. They should also be under careful medical supervision and get specific teaching on how to regulate their glucose levels.

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