EFFECT OF RAMADAN FASTING ON DIABETIC MICRO-VASCULAR COMPLICATION

Mohamed E.G.Kamar , Abbas A.Orabi , Ihab M.Salem and Arafa M.EL- Shabrawy

Diabetes &endocrinology unit, internal medicine department, faculty of medicine, Zagazig University, EGYPT

ABSTRACT

Fasting during Ramadan, one of the five pillars of Islam is an obligatory duty for all healthy adult Muslims. During Ramadan, Muslims must abstain from eating, drinking, taking oral medications, and smoking from the exact time of dawn until time of sunset; there are no restrictions on food or fluid intake between sunset and dawn. Islamic rules allow patients who are diseased and fasting may be hard or harmful for them not to fast. ***This study aimed to*** study the relation between Ramadan fasting and course of micro vascular complication of DM, and to find advices for patient during fasting to help in regression of micro vascular complication of DM. We started the study on 74 diabetic patients but only 64 completed the clinical visits with us and the other 10 missed from the follow up visits. Before Ramadan and After Ramadan fasting all patients were subjected to:. Electroretinogram (ERG), Mean Conduction Velocity (MCV), and Urinary Albumin Creatinine Ratio (UACR) in addition to serum insulin, proinsulin. ***The results showed*** There was increase in the mean oscillatory potentials in the second (OS2) of both eyes from 8.96±3.96 to 9.49±4.77.and other changes in the ERG which indicate significant improvement of diabetic retinopathy after Ramadan fasting , MCV decreased from 43.92± 21.68 to 39.85±13.50 **ms**. and albumin creatinine ratio was increased from 98.41 ±160.49 to 141.49 ±228.62.

Conclusion: Fasting of the whole month of Ramadan has a beneficial effect on β cell function. The relation between Ramadan fasting and micro-vascular complications is variable, with some improvement of diabetic retinopathy. neuropathy show adverse effects. Ramadan fasting increase the albumin creatinine ratio but there is improvement among patients with microalbuminuria.

Key words: Ramadan, Fasting, Diabetes, micro-vascular.

INTRODUCTION

Fasting during Ramadan, one of the five pillars of Islam is an obligatory duty for all healthy adult Muslims. , During Ramadan, Muslims must abstain from eating, drinking, taking oral medications, and smoking from the exact time of dawn until time of sunset; there are no restrictions on food or fluid intake between sunset and dawn. [1]

Although, Ramadan fasting is safe and could not induce any harmful effect in young healthy subjects, those with various diseases should consult their physicians and follow scientific recommendations.[2]

Islamic rules allow patients who are diseased and fasting may be hard or harmful for them not to fast, Despite of this, patients usually insist to fast.[3] Previous studies showed that Ramadan fasting caused significant changes in body weight[4] and different biochemical parameters.[5-6]

Few studies investigated the relation between Ramadan fasting and diabetic microvascular complications. This may be due to the general concept that one month is a short duration not sufficient to affect such chronic complications of chronic disease (diabetes). In this study we tried to explore the effect of Ramadan fasting on diabetic microvascular complications, does Ramadan fasting in diabetic patients affect microvascular complications or not?

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for ~ 10,000 new cases of blindness every year in the United States alone. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes.[7]

Electroretinogram (ERG) and diabetic retinopathy.

Evidence has begun to point to the fact that even before vascular complications begin to manifest, neuronal cell death and dysfunction have already begun.[7]Electrophysiological studies of humans with diabetes could be used to assess alterations [6]; moreover alterations in oscillatory potentials have been shown to predict the onset of proliferative retinopathy better than vascular lesions seen on fundus photographs.[7] (OS1-OS4) were significantly reduced in amplitude and increased in implicit time in the no-DR and NPDR groups. OS4 amplitude correlated significantly with the retinal arteriolar caliber suggesting a correlation between retinal neuronal dysfunction and microvasculature changes.[8]

It has been suggested that the b-wave of the electroretinogram is a particularly sensitive index of retinal ischemia and that, although the amount of reduction in b-wave amplitude during ischemia

corresponds to the severity of the insult, the degree of recovery of the b-wave during reperfusion depends on the duration of ischemia. In this sense the b-wave of the ERG represents a functional measure for potential therapeutic efficacy of drugs interacting with these pathophysiological processes.[9]

Diabetic neuropathy is a common complication of diabetes mellitus with severe morbidity, compromising the quality of life. Nerve conduction studies are one of the important methods for assessing nerve functions in DN.[10]Though both Diabetic Neuropathy Symptom Score and Diabetic Neuropathy Examination Score together can help in prompt evaluation of the diabetic sensorimotor polyneuropathy; nerve conduction study is more powerful test and can help in diagnosing subclinical cases.[13]

Diaetic nephropathy is the major cause of end stage renal disease (ESRD) throughout the world. It is defined clinically as the presence of microalbuminuria or overt nephropathy in patients with diabetes who lack indicators of other renal diseases.[12] Additionally, the reduced glomerular filtration rate (GFR) and albuminuria caused by DN are independent risk factors for CVD and death.[13]

PATIENTS AND METHODS

This study had been carried out in internal medicine outpatient clinic, diabetes and endocrinology outpatient clinic, Rheumatology outpatient clinic, Al-Hekma eye center, and clinical pathology department at Zagazig university hospital. This study was performed during Ramadan of Hijri year 1432 and 1433 (August 2011and July- August 2012). In both years Ramadan was 30 days. The average fasting period was 14 h; the starting and finishing hours of the fasting were approximately 3:30 a.m. and 5:30 p.m., respectively. We started the study on 74 diabetic patients but only 64 completed the clinical visits with us and the other 10 missed from the follow up visits. Their ages ranged from 20 to 64 years; with mean ± SD 44.07± 13.09 years and 25 of them were males and the other 19 were females. All participants provided informed consent to share in this study.

Inclusion criteria: Diabetic patients willing to fast during next Ramadan were included in this study.

Exclusion criteria:

1--Patient with renal impairment (Cr >1.5)
2- Liver dysfunction (ALT > double normal or total bilirubin >1)
3-Women who were pregnant or breast feeding.

Study objectives: The primary objective was to assess the effect of Ramadan fasting on diabetic microvascular complication.

Study methodology: *This is a cross-sectional study in which all patients were subjected to the following:-*

A) Before Ramadan:

Full history taking and detailed clinical examination *with particular consideration on:*

1-Symptoms and sings of diabetes or its complications (Neuropathy, retinopathy, nephropathy).
2-Fundus examination to detect diabetic retinopathy.

Routine laboratory investigations (Liver, kidney function tests and Fasting blood glucose level,)

Specific investigations:

1-Albumin-creatinie ratio (ACR).
2-Sensory conduction velocity.
3-Electroretinogram(ERG)
4-insulin-proinsulin level

B) After Ramadan:

History of the number of fasting days, problems that occurred during fasting (hypoglycemia) and modification in the dose of oral anti-diabetic drugs or insulin.

Laboratory investigations: fasting blood glucose, insulin and proinsulin.

Specific investigations:

1-Albumin-creatinie ratio (ACR).
2-Sensory conduction velocity.
3-Electroretinogram(ERG)

Blood tests:

Blood samples were obtained from all subjects at the beginning in the week before the start of Ramadan (pre-Ramadan) and 4 days later following the fasting period finished, immediately after Bairam (post-Ramadan).

Samples were allowed to clot and the serum centrifuged, divided into aliquots and stored at -80°C until analyzed. All serum samples were analyzed in a single batch to avoid day-to- day laboratory variation.

They were measured in the central laboratory of clinical pathology department, Zagazig University.

Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH).

Serum insulin&***Serum proinsulin*** was measured by ELISA.

HOMA-IR is calculated using the following formula :

International Formula:

Fasting Glucose (mmol/L) x fasting Insulin (mU/L) / 22.5.

US Formula:

Fasting Glucose (mg/dl) x fasting Insulin (µU/mL) / 405.

Insulin sensitivity, resistance and β cell function were calculated using the HOMA Calculator that was released in 2004 by **Hines et al**. This provides quick and easy access to use model-derived estimates of β cell function (HOMA B %) and insulin resistance (HOMA IR), rather than linear approximations.[17]

Albumin-creatinine ratio(ACR):

Urine samples were obtained from all subjects pre-Ramadan post-Ramadan. The second morning Urine samples were collected in serialized urine containers.

UACR is a ratio between two measured substances. UACR is reported in mg/g and approximates the albumin excretion in mg/day.

UACR in mg/g = Urine albumin (mg/dL) / Urine creatinine (g/dL)

Nerve conduction velocity:

+[Nerve conduction study was done in rheumatology outpatient clinic measuring sensory conduction velocity in the right median nerve before and after fasting. Median nerve was chosen because it accessible and easier in examination. Sensory NCS were performed by electrical stimulation of a peripheral nerve and recording from a purely sensory portion of the nerve.

Electroretinogram(ERG)

Full flash ERG was performed according to the standards of the international society for clinical electrophysiology of vision(ISCVE) approved in 2008, for all subjects at the beginning in the week before the start of Ramadan (pre-Ramadan) and 4 days later following the fasting period finished, immediately after Bairam (post-Ramadan).

It were done in Alhekma Eye Center using Roland-consult; The RETI-port33 system. The RETI-port consists of the pattern stimulator unit and computer analyzer system. The bio signal amplifier includes a preamplifier near the patient. All patient data and the results are stored in the data base. The bio signal and averaged curves from all channels can be displayed on the monitor.

6 responses were performed for all patients. The ISCEV Standard specifies five responses:[18]

(1)Dark-adapted 0.01 ERG (rod response);
(2) Dark-adapted 3.0 ERG (combined rod–cone response);
(3)Dark-adapted 3.0 oscillatory potentials;
(4) Lightadapted3.0 ERG (cone response);
(5) Light-adapted 3.0 flicker (30 Hz flicker).
(6) Additional response: Dark-adapted 10.0 ERG

Preparation of the patient

The patient assumes a comfortable position sitting up. The patient's eyes were dilated beforehand with standard dilating eye drops. Anesthetic drops are then placed in the eyes, causing them to become numb.

Pre-adaptation to light or dark: 20 min of dark adaptation before recording dark-adaptedERGs and 10 min of light adaptation beforerecording light-adapted ERGs.

ISCEV standard ERG:

1-Dark-adapted 0.01 ERG (Scotopic or rod response): The Dark-adapted 0.01 ERG is the first signal measured after dark adaptation, because it is the most sensitive to light adaptation. The stimulus is a dim white flash of 0.01 cd.s.m-2; with a minimum interval of 2 s between flashes.

2-Dark-adapted 3.0 ERG (combined rod–cone response): This is produced by a white 3.0 cd.s.m-2 flash in the dark-adapted eye. With an interval of at least 10 s between stimuli.

3-Dark-adapted 3.0 oscillatory potentials: Dark-adapted oscillatory potentials obtained from the dark-adapted eye, using the 3.0 cd.s.m-2 flash stimulus.

*4-Light-adapted 3.0 ERG (**photopic 3.0 ERG GF** or, single-flash cone response):* Use a 3.0-cd.s.m-2 stimulus, with at least 0.5 sbetween flashes. The background luminance of 30 cd.m-2 measured at the surface of the full-field stimulus bowl.

*5-Light-adapted 3.0 flicker ERG (30 Hz flicker) (**photopic 3.0 flicker 30Hz ERG GF**):* Flicker ERGs also reflect activity of the cone system,and it was obtained with 3.0-cd.s.m-2 stimuli,under the same conditions of light-adaptation as theLight-adapted 3.0 ERG. Recording the flicker ERG inthe light-adapted state reduces discomfort and allowsthe light adaptation to be standardized. Flasheswas presented at a rate of approximately 30stimuli per second (30 Hz), and the rate that was chosenconstant for all patient in our study. The first ERGresponse to the flickering stimulus is single flashwaveform; thus, the first few waveforms discarded so that stable conditions are reached.

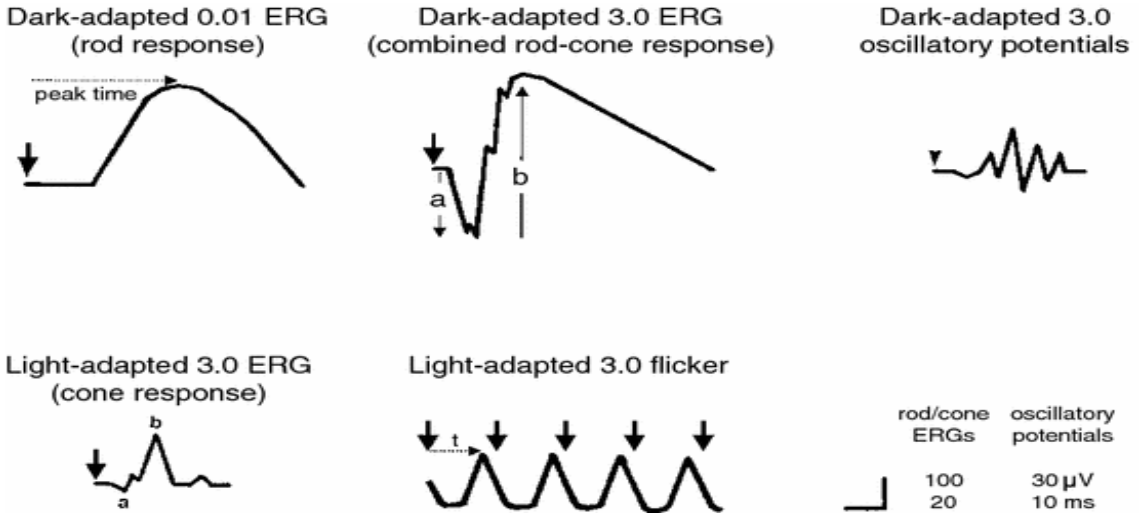
Additional ERG

6-Dark-adapted 10.0 ERG: An additional dark-adapted ERG to a stronger flash , it was obtained with 10.0 cd.s.m-2.This stimulus gives a larger a-wave with better definition (no double trough), larger oscillatory potentials that are easier to characterize, and more distinctive features of negative ERG waveforms (for critical recognition of diseases with related b-wave reduction). Also

this stronger flash may give better signals in patients with opaque media or immature retinae.

ERG analysis and reporting

Single flash ERGs: In general, b-wave amplitude and time-to-peak (implicit time) is measured for all ERGs (except oscillatory potentials), and the a-wave should also be measured when recognizable as a distinct component. According to current convention, the a-wave amplitude is measured from baseline to a-wave trough; the b-wave amplitude is measured from a-wave trough to b-wave peak; the a-wave and b-wave implicit times are measured from the time of the flash to the peak of the wave (see Figure below).



Oscillatory potentials: Their appearance is highly dependent upon adaptation state and filter characteristics of the amplifier, but there are usually three major peaks often followed by a fourth smaller one. Simply observing the presence of the three peaks, and their normality relative to the standards of the laboratory, may be adequate for many clinical purposes in keeping with our present state of knowledge.

*Flicker ERG:*The amplitude of flicker ERG is measured from the trough to the peak (averaging several typical responses). The implicit time is measured from each stimulus onset to the corresponding peak.

Statistical Analysis:

Data entered and analyzed using Microsoft Word. Data were then imported into Statistical Package for the Social Sciences (SPSS version 16.0) software for analysis. Baseline characteristics of the study population were presented as frequencies and percentages (%) or mean values and standard deviations (SD). According to the type of data, the following tests were used to test differences for significance; Paired t-test was used to compare pre and post Ramadan fasting variables. Differences were considered significant when p values were less than 0.05. Chi square for (qualitative variables). Correlation of numeric data was done by person's correlation (r).

RESULTS

Table (1) : the demographic data and clinical characteristics among studied diabetic patients:

Age (years)$\bar{x}$± SD		44.07± 13.09.
Range (years)		(20 - 64)yrs.
		N Percent
Gender	Male	36 56.8%
	Female	28 43.2%
Duration (years)Range		(0.5-35) yrs.
$\bar{x}$± SD		8.90±7.977
Family history of DM		
+ ve		26 (45.5 %)
- ve		38 (54.5 %)
Associated HTN		
Yes		18 (25 %)
No		36 (75 %)

- Table show that 40.6% of the study population have positive family history of DM
- 28.1% have associated HTN with DM

Table (2): changes in biochemical parameters and HOMA score ERG before and after Ramadan fasting:

Parameter	Before Ramadan	After Ramadan		P
FBG(mg/dl)$\bar{x}$± SD	195.08±84.656	197.13±88.218	t =-0.14	**NS**
Insulin(pmol/l)$\bar{x}$± SD	117.730±122.19	166.530±121.0100	Z =1.9	**NS**
Proinsulin(pmol/l)$\bar{x}$± SD	41.493±28.2578	42.03±25.086	Z =0.9	**NS**
PI/I ratio$\bar{x}$± SD	.9775±1.05731	.5803±.91916	Z =2.3	**P<0.05**
HOMA B %$\bar{x}$± SD	62.230 ±103.88	82.42±78.489	Z =1.7	**NS**
HOMA IR$\bar{x}$± SD	3.275±5.1330	3.223±2.8473	Z =1.5	**NS**

-There is significant decrease in PI/I ratio after fasting which indicates decrease in β cell stress.($P < 0.05$)
-There is non-significant change in mean fasting blood glucose, insulin, proinsulin, HOMA B % and HOMA IR after fasting.

Table (3): Fundus examination versus ERG in evaluation of diabetic retinopathy.

Retina	Fundus examination	ERG
Normal	**56.2% (18 patients)**	**16% (4 patients)**
Abnormal	**43.8% (14 patients)**	**84% (21 patients)**
Total	**100% (32 patients)**	**100% (25 patients)**

Table (4): ERG among the study population before and after Ramadan fasting:

	Before Ramadan	After Ramadan
Normal	**19% (4 patients)**	**28.6%(6 patients)**
Abnormal	**81%(17 patients)**	**71.4%(15 patients)**
Total	**100%(21 patients)**	**100%(21 patients)**

- 81% of our patients have features of abnormality and 19% have normal ERG waves as regarding amplitude and duration at the beginning of the study while 71.4% showed features of abnormalities and 28.6 % have normal ERG after fasting.

Table (5): changes of Oscillatory potentials among the study population before and after Ramadan fasting:

	OSCILLATORY POTENTIAL
Improved	40.5% (**8.5)**
Worsened	45.2% (**9.5)**
Not changed	14.3 % **(3)**
TOTAL	**100% (21)**

- 45.2% of our patients become worse (lower voltage)while 40.5% become better and 14.3 % of our patients show no change before and after fasting

Table (6): changes of Oscillatory potentials ERG before and after Ramadan fasting:

Parameter	Before Ramadan	After Ramadan	T	P
Right N2(ms)$\bar{x}$± SD	20.95±1.75	21.29±1.79	-.69	NS
Left N2(ms)$\bar{x}$± SD	20.90±1.34	21.33±2.03	-0.82	NS
Right P2 (ms)$\bar{x}$± SD	25.52±1.57	24.43±3.65	1.31	NS
Left P2 (ms)$\bar{x}$± SD	25.14±1.71	25.48±1.50	-0.92	NS
RightOS2(µv)$\bar{x}$± SD	8.73±4.50	9.24±4.92	-0.47	NS
Left OS2(µv)$\bar{x}$± SD	9.19±3.43	9.74±4.72	-0.66	NS
N2(ms)$\bar{x}$± SD	20.93 ± 1.54	21.31 ±1.89	-1.08	NS
P2 (ms)$\bar{x}$± SD	25.33 ±1.54	21.31 ±1.89	0.83	NS
OS2(µv)$\bar{x}$± SD	8.96±3.96	9.49±4.77	-0.79	NS

The OS2 of both eyes increased from 8.96 ± 3.96 µv to 9.49 ± 4.77 µv. this indicates improvement of the retinal function after fasting.

Table (7): protein dipstick versus ACR in diagnosis of diabetic nephropathy

nephropathy	protein dipstick	ACR
yes	**40% (12 patients)**	**63.3% (19 patients)**
no	**60% (18 patients)**	**36.7% (11 patients)**
total	**100% (30 patients)**	**100% (30 patients)**

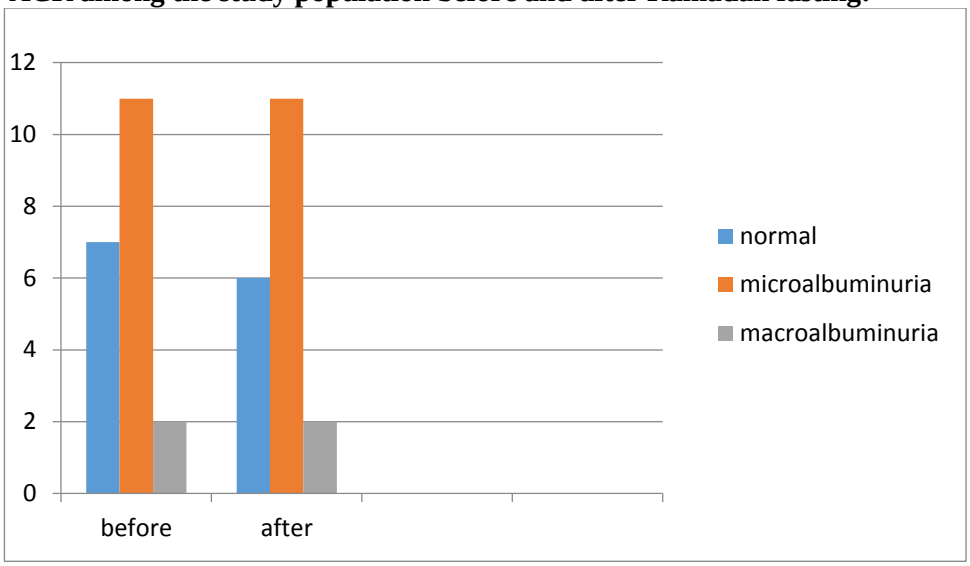
- 30 of our patients by both traditional protein dipstick and Albumin Creatinine Ratio (ACR).
- By protein dipstick: 40 % (12 patients) had proteinuria and 60 % (18 patients) negative for protein in urine.
- By ACR: 63.3% (19 patients) are positive for microalbumin and 36.7 %(11 patients) negative for microalbuminuria .

Table (8): changes in ACR among the study population before and after Ramadan fasting:

	First year	Second year	Total
improved	4	7	11
Worsened	3	5	8
No change	0	1	1
Drop out	4	4	8
No fasting	1	1	2
Total	12	18	30

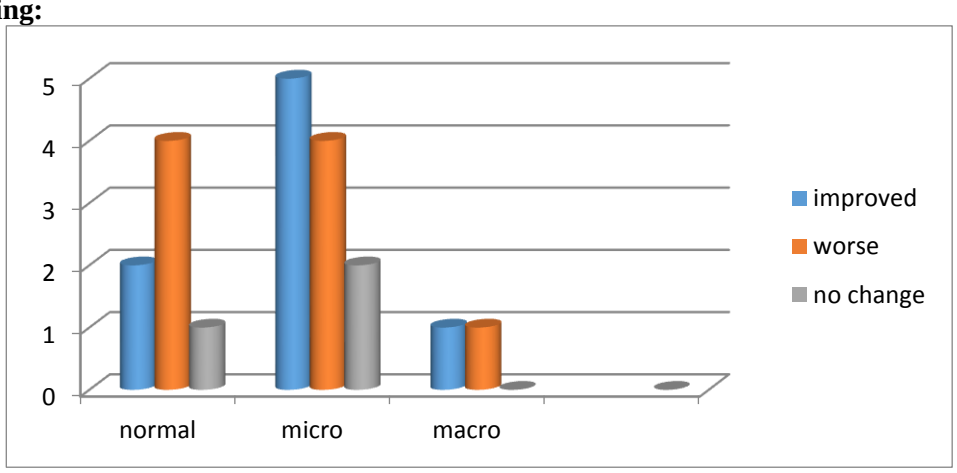
- Of the 20 patients included in the statistical analysis: 7 are found to be negative for micro-albumin(less than 30 mg/gm) before fasting of them 2 improved after fasting, 1 not changed and 4 become worse.
  *11 are found to have microalbumiuria(30-300 mg/gm) before fasting of them 5 improved, 2 not changed and 4 become worse
  *2 are found to have macroalbuminuria (more than 300 mg/gm) one show slight improvement in ACR ratio and the other show increase of the ACR by about 50% of the before fasting value.

Diagram (1): ACR among the study population before and after Ramadan fasting:



- Diagram show 7 are found to be negative for micro-albumin(less than 30 mg/gm),11 are found to have microalbumiuria (30-300 mg/gm) and 2 are found to have macroalbuminuria (more than 300 mg/gm) before Ramadan fasting .
- After Ramadan fasting 6 are found to be negative for micro-albumin, 11 are found to have microalbumiuria and 3 are found to have macroalbuminuria.

Diagram (2): ACR changes among different categories of the study population before and after Ramadan fasting:



- Figure show that the highest number of improved patients is among patients with microalbumiuria.
- Of the 7 patients negative for micro-albumin: 2 improved after fasting, 1 not changed and 4 become worse.
- Eleven patients had microalbumiuria 8 improved, and 3 become worse.
- Two are found to have macroalbuminuria, one show slight improvement in ACR ratio and the other show increase of the ACR.

Table (9): comparison between different categories as regarding change of ACR after Ramadan fasting:

						x^2	P
		ACR			Total		
		Normal	Micro	Macro			
worse	number	5	4	1	10		
	%	71.4%	36.4%	50.0%	50.0%		
Improve	number	2	7	1	10	2.1	NS
	%	28.6%	63.6%	50.0%	50.0%		
Not-changed	number	5	4	1	10	worse	
	%	71.4%	36.4%	50.0%	50.0%		
Total	number	7	11	2	20		
	%	100.0%	100.0%	100.0%	100.0%		

Table (10): comparison between different categories as regarding decrease of ACR after Ramadan fasting

					X^2	P
		ACR		total		
		Normal	Diabetic nephropathy			
improve	count	2	8	10		
	%	28.6%	61.5%	50.0%	12.5	<0.001
total	count	7	13	20		
	%	100.0%	100.0%	100.0%		

Table (11): changes of ACR before and after Ramadan fasting:

Parameter	**Before Ramadan**	**After Ramadan**	Z	**P**
albumin	103.07±138.04	258.17±507.05	-0.936	**NS**
Creatinine	132.27±75.12	131.97±92.82	-0.024	**NS**
ACR	98.41 ±160.49	141.49 ±228.62	-1.328	**NS**

Table (12):Correlation between ACR changes with age and number of fasting days:

		DACR
Fasting days	r	0.447*
	p-value	0.048
Age	r	0.171
	p-value	0.471

Table (13) shows changes of nerve conduction velocity among the study populations:

	Lat2	Cv(m/s)
BETTER	46.2% **(6** patients**)**	7.7% (1 patient)
WORSE	53.8% **(7** patients**)**	69.2 % (9 patients)
Not changed	**-**	23.1%(3 patients)
TOTAL	**100% (13** patients**)**	**100% (13** patients**)**

- 46.2% show reduction of the latency in the 2th second (Lat2) and 53.8% show prolongation of the (Lat2).
- 7.7% show improvement(increase)of mscv while 69.2 % show reduction of the (mscv) and 23.1% show no change

Table (14) :): changes of nerve conduction velocity (MCV) before and after Ramadan fasting:

Parameter	**Before Ramadan**	**After Ramadan**	t	**P**
Lat2	3.68 ±0.61	4.36 ±1.04	-2.13	0.05
Cv(m/s)	51.54± 9.58	43.85±6.69	2.06	**NS**

- Paired t-test comparing Mean sensory conduction velocity (mscv) and the latency in the 2th second (Lat2) before and after Ramadan fasting show increase in the lat2 mean and reduction in the MCV after Ramadan fasting but statistically not significant (p-value > 0.05).

Table (15): Correlation between changes OF MCV and LAT2 with age and number of fasting days:

		Dlat2	DMCV	age	Fasting days
D-lat2	r	1	-.502-	-.445-	-.303-
	p-value		.080	.127	.314
D-MCV	r	-.502-	1	.386	.290
	p-value	.080		.193	.337
Age	r	-.445-	.386	1	.424
	p-value	.127	.193		.149
Fasting days	r	-.303-	.290	.424	1
	p-value	.314	.337	.149	

DISCUSSION

Ramadan fasting is one of the five pillars of Islam. One billion Muslim adults worldwide refrain from food, water and oral drug intake from dawn to sunset during Ramadan fasting. Ramadan fasting could not induce any harmful effect in young healthy subjects[1] . However, it can induce several complications in patients with diabetes. In this study we tried to explore the effect of Ramadan fasting on microvascular complications of DM. [2]

It was observed that There was non-significant change in mean fasting blood glucose which indicates that Ramadan fasting not significantly alter glycemic control and this correlates with different studies that found that Ramadan fasting has been reported not to alter glycemic control[19]. However this is contradictory to the EPIDIAR study, 2001 who reported a decrease in fasting glucose and an increase in the frequency of severe hypoglycemia during Ramadan in a population including both types 1 and 2 patients.[5]This variation may be due to the amount or type of food consumption, regularity of taking medications, engorging after the fast is broken, or decreased physical activities. In most cases, no episode of acute complications (hypoglycemic or hyperglycemic types) occurs in patients under medical management.[20]

This is also contradictory to Norouzy et al, 2012 who showed that fasting during Ramadan deteriorated the glycemic control in Type 2 diabetes patients. This was more evident in patients using oral hypoglycemic medication than diet controlled patients[21].

Also This is contradictory to Fakhrzadeh et al, 2003 who found that fasting plasma glucose decreased significantly in both men and women after Ramadan fasting and to Khaled et al ,2006 who found significant decreases in fasting blood glucose and glycosylated hemoglobin (HbA1c) in obese women with type 2 diabetes mellitus after Ramadan fasting[22].

Our study shows high levels in the mean fasting insulin before Ramadan fasting (Normal value: 57-79pmol/l) and this may be explained by insulin resistance found in type 2 diabetic patients and this correlates with **Bergman et al,** 1997 who provided that the most practical way of assessing insulin resistance is the measurement of plasma insulin levels after overnight fasting condition[23].

Diabetic Retinopathy:

Evidence has begun to point to the fact that even before vascular complications begin to manifest, neuronal cell death and dysfunction have alread begun[8] **(Miranda et al., 2011).**

In our study we observed that oscillatory potentials in the second (OS2) increased from 8.73±4.50 **µv** to 9.24±4.92 **µv** in the right eye and from 9.19±3.43 **µv** to 9.74±4.72 **µv** in the left eye. Also the mean OS2 of both eyes increased from 8.96±3.96 to 9.49±4.77.

Duration of P2 in the right eye reduced from 25.14±1.71 **ms** to25.48±1.50 **ms**, also duration of P2 reduced in the left eye from 25.14±1.71to 25.48±1.50 and the mean duration of P2 decreased from 25.33 ±1.54 to 21.31 ±1.89 but statically not significant (p-value >0.05).

Duration of N2 in the right eye increased from 20.95±1.75 to 21.29±1.79 **ms**, also duration of N2 increased in the left eye from 20.90±1.34to 21.33±2.03 and the mean duration of N2 increased from 20.93 ± 1.54 to21.31 ±1.89.

These changes indicate significant improvement of diabetic retinopathy after Ramadan fasting .this may be due Limitation of fluid intake during the fast, especially if prolonged. And this can be increased by perspiration in hot and humid climates and among individuals who perform hard physical labor.[24]All these may decrease retinal exudation despite increasing the risk of thrombosis.

Saada et al. (2010)[25]; noted that glycosylated haemoglobin (HbA1c) decreased slightly during the last week of the month of Ramadan among the diabetic patients. Also ***Bouguerra et al.***[29]Had found that HBA1c significantly decreased from 8.8 % to 7.4% and from 10.6% to 7.1% correspondingly after Ramadan fasting.

Diabetes Control and Complications Trial (DCCT) found that achieving mean hemoglobin A1C (A1C) of 7.9 % reduced the incidence of new cases of retinopathy by as much as 76 %. The reduction was directly related to the degree of glycemic control as estimated from hemoglobin A1C values. The United Kingdom Prospective Diabetes Study found similar results in patients with type 2 diabetes; each 1 percent point reduction in A1C was associated with a 37 percent reduction in development of retinopathy .[27]

So the improvement of our patients can be explained by the better glycemic control after Ramadan. This consistent with **Frost-Larsen et al** that assessed the effect of short-term strict glycemic control on OS amplitude and reported that OP

amplitudes, which were initially abnormal in a group of a retinopathic subjects with IDDM, were normalized after 11 days of strict glycemic control.[28]

Also we observed that insulin level increased from 117.730±122.19 to 166.530±121.0100 after Ramadan fasting despite being statistically not significant it may indirectly decrease the Aldose reductase activity which is the initial enzyme in the intracellular polyol pathway.

Also both increased insulin level and better glycemic control maydecrease the level of diacylglycerol .This diacylglycerol is thought to activate protein kinase C (PKC),which, in turn, affects retinal blood dynamics, especially permeability and flow, leading to decrease in both fluid leakage and retinal thickening.

Hypertension alone is capable of producing hypertensive retinopathy characterized by macro- and microaneurysms, flame hemorrhages, cotton wool spots, and macular exudates. Tight blood pressure control in patients with hypertension and diabetes is beneficial in reducing visual loss from DR.***Yarahmadi*** found that blood pressure decreased from 122/83 to 118/78 in females and from 130/81 to123/79 this add more benefit to fasting patient[29].

Diabetic neuropathy:

Diabetic neuropathy is a common complication of diabetes mellitus with severe morbidity, compromising the quality of life. Nerve conduction studies are one of the important methods for assessing nerve functions in DN .[13]

Though both Diabetic Neuropathy Symptom Score and Diabetic Neuropathy Examination Score together can help in prompt evaluation of the diabetic sensorimotor polyneuropathy; nerve conduction study is more powerful test and can help in diagnosing subclinical cases.[14]

Kanavi et al., observed that the nerve conduction velocity progressively decreased from the controls (49.0 ± 3.9) to the diabetics with good glycaemic control (47.2 ± 2.8), to the diabetics with poor glycaemic control (45.3 ± 3.1**).**[13]

Bansal et al ., have suggested that the slowing of NCV indicates the ongoing damage to the myelin sheaths and they are also of the opinion that the amplitude decreases with the rising HbA1c levels, thus suggesting the onset of axonopathy.[30]

In our study we observed that: Of the 13 patient completed the study 46.2% (6 patients) show reduction of the latency in the 2th second (Lat2) and 53.8% (7 patients) show prolongation of the (Lat2).As regarding (mscv) 7.7% (one patient) show improvement while 69.2 % (nine patients) show reduction of the (mscv) and 23.1%(3 patients) show no change.

Also Lat2 increased significantly from 3.68 ±0.61 to 4.36 ±1.04 and MCV decreased from 43.92± 21.68 to 39.85±13.50 ms this may be due to dehydration and/or post breakfast hyperglycemia.

Also we found no significant correlation between these changes neither with Fasting days nor age of the studied group.

Diabetic nephropathy

In our study we observed that albumin creatinine ratio was significantly increased from 98.41 ±160.49 to 141.49 ±228.62 this contradictory to ***El-Gendy et al,2012*** as they found that Ramadan fasting for 4 weeks without vitamin E supplementation lowered ACR insignificantly by 3.9 and 5.6% in control and diabetic groups.[31]

Our results can be explained by the Limitation of fluid intake during the fast, especially if prolonged, a cause of dehydration is. The dehydration may become severe as a result of excessive perspiration in hot and humid climates and among individuals who perform hard physical labor. In addition, hyperglycemia produces an osmotic diuresis, further contributing to volume and electrolyte depletion. In addition, contraction of the intravascular space can further exacerbate the hypercoagulable state.[24]

Increased blood viscosity secondary to dehydration may enhance the risk of thrombosis.[32]

In conclusion: effects Ramadan fasting on diabetic microvascular are variable, diabetic retinopathy better after fasting .ACR increase after fasting also latency of the 2nd second prolonged with decrease of the MCV. Further studies needed for more conclusive data about Ramadan fasting and diabetic micro vascular complication.

Limitations of this study The relatively small number of the study populations , Poor patient compliance to attend the follow up visit, The equipment for this study present in different place and of high cost and Lack of accurate data about the patient dietary habits and blood glucose control.

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