British Journal of Science
March 2014, Vol. 10 (2)

The Effect of Ramadan Fasting on Beta Cell Secretory Efficiency in a Sample of Egyptian Diabetic Patients

Mohamed E.G.Kamar[1];Nagwa S Said[1];Ihab M. Salem[1];
Ayman Abd-Elrahman M.N.[1]; and Mervat M.M. Azab [2]
[1]Internal Medicine and [2] Clinical Pathology Departments,
Faculty Of Medicine, Zagazig University, Egypt

ABSTRACT

During the holy month of Ramadan, Muslims fast during daytime hours and restrict food and drink intake to the period after sunset.Two main meals are eaten during Ramadan, one before dawn (Suhur) and the other at sunset (Iftar).In diabetic patients, fasting may influence diabetes control and biochemical parameters.However, nothing is known about the effect of Ramadan fasting on insulin secretory efficiency. ***Aim Of The Study:*** to evaluate insulin secretory efficiency before and after Ramadan fasting in a sample of egyptian type 2 diabetic patients using proinsulin:insulin (PI/I) ratio. ***Patients and Methods:*** The present study included 44 type 2 diabetic patients either were fasting or not. Patients were classified into 3 groups: Group (A):8 Diabetic patients who did not fast the whole month. Group (B): 18 Diabetic patients who were fasting (18-22) days. Group (C): 18 Diabetic patients who were fasting the whole month. ***The Results showed:***Significant weight gain after Ramadan fasting ($P<0.05$).There was significant decrease in PI/I ratio after fasting the whole month of Ramadan ($P<0.05$).There were significant positive correlations between PI/I ratio with fasting blood glucose ($r= 0.811$, $P<0.05$),weight gain($r=0.482$,$P<0.05$) and HOMA IR($r= 0.417$, $P<0.05$).There were significant negative correlations between PI/I ratio and the number of fasting days ($r= -0.462$, $P<0.05$) and HOMA B% ($r=-0.346$,$P<0.05$).There was highly significant negative correlation between fasting blood glucose and HOMA B% ($r=-0.709$,$P<0.001$). ***Conclusion:*** Reduction of PI/I ratio indicates the beneficial effect of fasting on β cell secretory efficiency and reduction of β cell stress especially in patients fasting the whole month of Ramadan .

Keywords: Ramadan,Fasting,Insulin,Proinsulin,B cell secretory efficiency,HOMA IR, HOMA B%.

INTRODUCTION

Diabetes mellitus is becoming a worldwide disease. Its prevalence in adults was 4% in 1995 and is expected to rise up to 5.4% by the year 2025 **(1).** Egypt is among the top ten countries in diabetes prevalence **(2).**Ramadan is the holy month for Muslims. The timing of this month varies each year as it is linked to the sighting of the new moon. During this month foods and fluids are only allowed at night so fasting extends from dawn to sunset. The exact length of time dependent on geographical location and season, in August, fasting can last over 15 hours a day **(3)**. However, some patients with diabetes fasting may induce several complications **(4)**,islamic rules allow such patients not to fast, although they usually insist on fasting. Patients with type 1 are among those who are exempted to fast. The risk of glycemic imbalance and diabetes control is questioned during Ramadan fasting due to changes in meal times, type of food, lifestyle

and the use of medications[4]. Several studies have studied the biochemical changes occurring during Ramadan fasting both in normoglycemic subjects [5,6] and in subjects with diabetes [7,8,9]. Most of these studies have shown little change in glycemic control been shown to occur [10,11]**.** In patients with type 2 diabetes, it is clearly obvious that once hyperglycemia exists, beta-cell dysfunction is present.One of the consequences of this change is the inefficient proinsulin processing to insulin [12,13,14]. Proinsulin and insulin are not released equimolarly, and the plasma concentration of proinsulin is usually only a small proportion of that of insulin, with clearance of proinsulin being lower than that of insulin [15]. Thus, fasting proinsulin concentration may be considered a possible indicator of β-cell dysfunction. [16]. Its predictive value has been confirmed in other studies, and its measurement in individual diabetic patients provides a reliable index of insulin resistance. In addition to its role as an early indicator of the disease, it may also provide an important marker for selecting and monitoring an appropriate therapeutic regimen[17]. **Grill et al, (2002)** [18] suggested that elevated proinsulin and proinsulin/insulin ratios are secondary to increased demands on β-cell secretion induced by hyperglycemia and insulin resistance while, other prospective studies have demonstrated that the determination of the proinsulin-to-insulin ratio may be used to predict deterioration in glucose tolerance [19,20]. Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) using fasting glucose and insulin. It is first described 1985 by **Matthews** [21]. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells and is the physiological mechanism behind HOMA model. HOMA-%B is a measure of β-cell activity, not of β-cell health or pathology [22]. **This study aimed to** explore the effect of Ramadan fasting on insulin secretory efficiency in a sample of egyptian diabetic patients.

PATIENTS AND METHODS

This study had been carried out in Internal Medicine Outpatient Clinic and Clinical Pathology department- Zagazig University hospitals. This study was performed during Ramadan of Hijri year 1432 (August 2011). In this year Ramadan was 30 days. The fasting period was 14h and 50 min at the beginning of the month and 14h at the end of the month; 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 56 diabetic patients but only 44 completed the clinical visits with us and the other 12 missed from the follow up visit. Their age ranged from 26 to 64 years; with mean ± SD 44.07± 13.09 years. 19 of them were males and 25 were females. All participants provided informed consent to share in this study.

The study participants were type 2 diabetic patients on oral antihyperglycemic drugs whether fasting or not. Patients were classified into 3 groups: **Group (A):**8 Diabetic patients who did not fast the whole month. They were 6 males and 2 females. Their age ranged from 26 to 60 years. **Group** (B): 18 Diabetic patients who were fasting the month (18-22 days), but miss some days due to menses or sickness. They were 6 males and 12 females.Their age ranged from 41 to 57 years. **Group (C):** 18 Diabetic patients who were fasting the whole month. They were 8 males and 10 females. Their age ranged from 42 to 60 years.

Type 1 diabetic patients, type 2 diabetic patients on insulin therapy, patients with renal disease or liver dysfunction, confirmed by

laboratory testing of liver and kidney functions and women who were pregnant or breast feeding were excluded.

A) Before the beginning of Ramadan:

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

1-Symptoms and signs of diabetes or its complications (Neuropathy, retinopathy, nephropathy).2-Body weight before the beginning of Ramadan fasting.3-Fundus examination to detect diabetic retinopathy.

Routine laboratory investigations:

1-Liver and kidney function tests.

2-Fasting blood glucose level.

Specific investigations:

1-Serum insulin and proinsulin measured by ELISA.

2-Nerve conduction velocity to detect diabetic neuropathy.

B) After the end of Ramadan:

* History of the number of fasting days.

* Body weight after the end of Ramadan.

* Laboratory investigations : fasting blood glucose,insulin and proinsulin.

Blood tests:

Blood samples were obtained from all subjects at the beginning 1 or 2 days before the start of Ramadan (pre-Ramadan) and 4 days later following the fasting period finished.

HOMA-IR is calculated using the following formula: Fasting Glucose (mg/dl) x fasting Insulin (μU/mL) / 405. [(21)]

HOMA β is calculated using the following formula: 360 x insulin (uU/mL) / glucose (mg/dl)- 63[(21)]

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. ANOVA was used to analyze repeated measures.Non parametric Sign test used to compare paired samples. Differences were considered significant when p values were less than 0.05 and highly significant when p values were less than 0.001. Differences between means (quantitative variables) in groups were compared by Student's t-test.Chi square for (qualitative variables). Correlation of numeric data was done by pearson's correlation (r).

RESULTS

Table (1) : shows the clinical characteristics of all our groups ; the studied patients were 44 (25 females and 19 males), their age ranged from 26 to 64 years; the mean age was 44.07± SD 13.09. All patients were type 2 DM on oral anti-diabetic drugs, 20 patients (45.5%) they were not complicated, mean duration of DM was 8.9 years ±7.977 (SD) and ranged from 1-35 years 45.5% of patients had positive family history of DM and 25% had hypertension with DM.There where no statistical difference between groups regarding the age,duration of DM,neuropathy,retinopathy hypertension and family history of DM.

Table (2): Group (A) there was non-significant increase in mean body weight, fasting blood glucose, insulin, proinsulin and proinsulin: insulin ratio. While in group (B) there were significant increase in mean body weight and non-significant changes in other parameters. And group (C) showed significant increase in mean body weight, significant decrease in proinsulin: insulin ratio and non-significant changes in other parameters. There was significant improving in insulin secretory efficiency in group C only (complete fasting),

indicated by the significant decrease in PI/I ratio.

Table (3): There was significant positive correlation between proinsulin:insulin ratio and fasting blood glucose, weight gain and HOMA IR% (P<0.05) .There was negative correlation between proinsulin : insulin ratio and HOMA B% and the number of fasting days (P<0.05) which indicates the beneficial effect of fasting on β cell secretory efficiency and reduction of β cell stress and non-significant correlation between PI/I ratio and the duration of DM or the age of patients **.**

Table (4) there was highly significant negative correlation between fasting blood glucose and HOMA B% (P<0.001) and highly significant positive correlation between insulin level and HOMA B% and HOMA IR (P<0.001). These may indicate that good glycemic control helps to improve the β cell function(HOMA B%) . .

Table (1): Patients' clinical characteristics:

Clinical Characteristics	**Group A N=8**	**Group B N=18**	**Group C N=18**	**F** / x^2	**P**
Age (years) $\bar{x}$ ± SD Range(years)	48.75±16.029 (26-60)	49.3±8.8 (41-57)	51.1±8.922 (42-60)	**F=0.013**	**NS**
Duration of DM $\bar{x}$ ± SD Range(years)	12.25±13.351 (1-30)	6.33±5.018 (1-20)	10.72±8.73 (2-35)	**F=1.82**	**NS**
Complications					
Neuropathy	2 (25 %)	3 (16.7 %)	7(38.9 %)		
Retinopathy	1 (12.5%)	0 (0%)	1 (5.6%)	x^2**=5.8**	**NS**
Neuropathy with Retinopathy	2 (25 %)	4 (22.2 %)	4 (22.2 %)		
None	3 (37.5%)	11(61.1 %)	6 (33.3 %)		
Family history of DM					
+ ve	5 (62.5 %)	9 (50 %)	6 (33.3 %)	x^2**=1.1**	**NS**
- ve	3 (37.5 %)	9 (50 %)	12(66.7 %)		
Associated HPN					
Yes	2 (25 %)	2 (11.1 %)	7 (38.9 %)	x^2**=4.6**	**NS**
No	6 (75%)	16 (88.9 %)	11 (61.1 %)		

- ***Table (2) mean± SD of body weight and biochemical parameters among 3 groups before and after fasting***:

Parameters	Group A			Group B			Group C		
	before	**after**	**P**	**before**	**after**	**P**	**before**	**after**	**P**
Body weight (kg)	96.25± 5.67	96.37± 5.7	**t=1.00 NS**	76.61± 13.72	77.56± 13.78	**t= -2.7 P<0.05**	84.83± 11.18	87.8± 11.62	**t= -2.50 P<0.05**
FBG (mg/dl)	200.7± 63.184	233± 122.6	Sign test **NS**	220.83 ± 86.55	227.5 ± 98.6	Sign test **NS**	168.06 ± 82.23	158.78± 51.35	Sign test **NS**
Insulin(pmol/l)	62.32± 74.32	240.27 ± 182.75	Sign test **NS**	124.55 ±124.4	112.6± 67.23	Sign test **NS**	123.21 ±130.3	204.011 ±131.67	Sign test NS
PI (pmol/l)	48.85± 34.14	62± 19.39	Sign test **NS**	33.6± 26.38	33.03± 23.18	Sign test **NS**	48.66± 27.94	46.59± 25.26	Sign test **NS**
PI/I ratio	1.37± 1.28	1.46± 2.14	Sign test **NS**	0.59± 0.70	0.52± 0.84	Sign test **NS**	1.26± 1.22	0.38± 0.51	Sign test **P<0.05**

- ***Table (3) shows the correlation between different patient parameters and PI/I ratio in the studied patients:***

Patient Parameters	PI/I ratio	
	Pearson correlation	**P**
Age	-0.026	NS
Duration of DM	-0.002	NS
Number of fasting days	-0.462	<0.05
Body weight changes	0.482	<0.05
Fasting blood glucose	0.811	<0.05
HOMA B%	-0.346	<0.05
HOMA IR	0.417	<0.05

- ***Table (4) shows the correlation between HOMA B and HOMA IR and biochemical parameters in the studied patients:***

Biochemical Parameters	HOMA B%		HOMA IR	
	r	**P**	**R**	**P**
Fasting Blood Glucose	-0.709	<0.001	0.152	0.348
Insulin	0.705	<0.001	0.769	<0.001
Proinsulin	-0.160	0.325	0.236	0.143

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 [(23)] and may have beneficial effect on waist circumference and lipid profile [(24)]. While in patients with type 2 diabetes studies have shown that Ramadan fasting did not alter biochemical parameters and however, it may induce hypoglycemia. In this study we tried to explore the effect of Ramadan fasting on insulin secretory efficiency in 44 type 2 diabetic patients on oral anti-diabetic agents through measurement of insulin, proinsulin and PI/I ratio in diabetic patients before and after the month of fasting. The baseline clinical data of the patients were recorded including duration of DM, complications and associated hypertension. Patients were divided into 3 groups according to the number of fasting days.

Ramadan can be an opportunity for obese diabetic patients to reduce their weight through individualized prepared dietary plan. Despite several reports have shown that body weight does not change during the fasting period [(25,26)] and others showed even reduction in body weight, our diabetic patients showed significant increase in body weight after Ramadan fasting. This may be explained by the changing dietary pattern during Ramadan. People, who fast from dawn to sunset, may take large quantities of sugary fluids (juice and carbonated drinks). Also fried foods, carbohydrate rich meals and sweet food specially prepared for Ramadan during nonfasting hours. [(3)] These foods Pattern during Ramadan may increase the risk of hyperglycaemia and weight gain for Muslim diabetic patients [(27)]. Furthermore, most diabetics reduce their daily activities for fear of hypoglycemia [(28)].

In this study, there was non-significant change in mean fasting blood glucose which indicates that Ramadan fasting not significantly alter glycemic control and this in agreement with different studies that found that Ramadan fasting has been reported not to alter glycemic control. [(26)]

This is contradictory to **Fakhrzadeh et al**, **(2003)** [(29)] who suggested that fasting plasma glucose decreased significantly in both men and women after Ramadan fasting and to **Khaled et al** ,**2006** [(30)] who found significant decrease in fasting blood glucose and glycosylated hemoglobin (HbA1c) in obese women with type 2 diabetes mellitus after Ramadan fasting.

The present study results showed high levels in the mean fasting insulin before Ramadan fasting and this may be explained by insulin resistance found in type 2 diabetic patients and this correlates with **Bergman et al**, **1997** [(31)] who provided that the most practical way of assessing insulin resistance is the measurement of plasma insulin levels after overnight fasting condition. It also showed non-significant increase in mean insulin level after Ramadan fasting while **M'guil et al**, 2008 [(32)] who studied the effect of fasting on clinical and biochemical parameters, blood pressure, and glycemic control in type 2 diabetic patients and found significant increase in mean insulin level.

Abnormally high levels of proinsulin before fasting were found in this study and this correlates with **Tura et al, 2003** [(33)] who found that type 2 DM is characterized by higher circulating concentrations of intact and split proinsulin, in absolute amounts and as proportions of total insulin secretory products. Although the cause of disproportional hyperproinsulinaemia in diabetes is unknown, it may arise from inefficient proinsulin processing within the beta cell secretory granules or the premature release of proinsulin as a result of increased demand for insulin in insulin-resistant states. [(19)]. While **Pfützner, et al. (2010)** [(34)] suggested that elevated intact proinsulin seems to indicate an advanced stage of β cell exhaustion and is a highly specific marker for insulin resistance. These findings indicate that elevated proinsulin and proinsulin/insulin ratios are secondary to

increased demands on β cell secretion induced by hyperglycemia and insulin resistance. In our study, there was non-significant decrease in the proinsulin level after Ramadan fasting, so it was measured as a proportion to insulin (PI/I ratio) to asses changes in β cell function after Ramadan fasting. Elevations in the ratio of proinsulin to insulin as well as absolute proinsulin concentrations adjusted for fasting insulin have been proposed as early markers of beta cell dysfunction.[31]

In this study, PI/I ratio had positive correlation with fasting glucose and this indicates that better glycemic control leads to decreased β cell stress and production of proinsulin and this correlates with **Yanbing et al, 2004** [35] who found that long term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β cell function. In this study, Proinsulin-to-insulin ratio showed decreased levels after Ramadan fasting especially in the group who fasted the whole month,which may act as indicator for β cell stress as it was found to be a marker of the degree of reduced maximum beta-cell secretory capacity.

It was found in this study that proinsulin-to- insulin ratio positively correlates with HOMA IR and negatively with HOMA B% and this correlates with **Thomas et al**, **2004** [36] who supposed that HOMA IR is accepted with some limitations as a standard method for the determination of insulin resistance in epidemiological studies. However, the determination of insulin resistance by HOMA IR is limited to the early stage of type 2 diabetes because β cell secretion in later stages is also comprised of intact proinsulin and split products and this makes PI/I ratio measurement superior to it. Also HOMA B seems to give misleading results when used as a diagnostic tool for β cell function in diabetic patients treated with sulfonylurea drugs. [34]

This study also explored the factors that may affect β cell function and found that there is a positive correlation between fasting blood glucose and proinsulin-to- insulin ratio which refers to the beneficial effect of DM control on β cell secretory function and this was in agreement with **Grill et al, 2002** [18] who found a strong association between blood glucose and proinsulin-to-insulin ratio in Swedish non-diabetic men.

It also showed positive correlation between body weight and PI/I ratio which indicates that weight gain leads to increased β cell stress. According to this study there is non-significant correlation between the age of type 2 diabetic patient or the duration of diabetes and proinsulin-to-insulin ratio, this is contradictory to **Bryhni et al, 2010** [37] who found that proinsulin and PI/I ratio declined significantly with advanced age but in non-diabetic patients.

Limitations of the study: In addition to the small sample size, our study lacks of periods where the patients could be followed up before and after fasting. Timing of sampling, number of fasting hours and climate made our data incomparable with other researchers' findings as Ramadan is a lunar month and its time changes each year.

In conclusion: Fasting of the whole month of Ramadan has a beneficial effect on β cell function and β cell secretory efficiency evidenced by reduction in proinsulin-to-insulin ratio while insulin resistance and glycemic control not significantly affected. However; further studies are recommended to evaluate the effect of Ramadan fasting on diabetes complications and co morbidities as cardiovascular, renal or liver diseases.

References:

1- **King H, Aubert R, Herman W**: Global burden of diabetes, 1995–2025: Prevalence, numerical estimates, and projections. *Diabetes Care 1998, **21**:1414-1431.*

2- **International Diabetes Federation.** ***Diabetes Atlas*** The Global Burden ***available at http://www.idf.org/diabetesatlas/5e/the-global-burden*** *accessed on 24\9\2012*

3- **Benaji B, Mounib N, Roky R, Aadil N, Houti IE, Moussamih S, et al.** Diabetes and Ramadan : Review of the literature. *Diabetes Res Clin Pract.2006; 73:117–25.*

4- **Al-Arouj M,Bouguerra R, Buse J,Hafez S,Hassanein M**. Recommendations for management of diabetes during Ramadan. *Diabetes Care 2005; 28:2305–2311.*

5- **Haouri M, Haourai-Oukerro F, Mebazaa A, Nagati K:***Circadian Evolution of Serum Level of Glucose, Insulin, Cortisol and Total Proteins in Healthy, Fasting Volunteers*. Istanbul, Turkey, Second International Congress on Health and Ramadan, 1997, p. 31.

6- **Hojlund K, Wildner-Christensen M, Eshoj O, Skjaerbaek C, Holst JJ, Koldkjaer O, Moller Jensen D, Beck-Nielsen H:** Reference intervals for glucose, beta-cell polypeptides, and counterregulatory factors during prolonged fasting. Am J Physiol Endocrinol Metab. 2001 Jan; 280(1):E50-8.

7- **Bouguerra R, Ben Slama C, Belkadhi A, Jabrane H, Beltaifa L, Ben Rayana C, Doghri T:** *Metabolic Control and Plasma Lipoprotein During Ramadan Fasting in Noninsulin Dependent Diabetes*. Istanbul, Turkey, Second International Congress on Health and Ramadan, 1997, p. 33.

8- **Ramadan J, Telahoun G, Al-Zaid NS, Barac-Nieto M:** Responses to exercise, fluid, and energy balances during Ramadan in sedentary and active males. *Nutrition* , 1999;15: 735–739.

9- **Mohsen Nematy,Maryam Alinezhad-Namagh, Masoud mahdavi Rashed,et al.;** Effect of Ramadan fasting on cardiovascular risk factor ;Prospective Observational Study:Nutrition Journal 2012,11:69 .

10- **Akanji AO, Mojiminiyi OA, Abdella N:** Beneficial changes in serum Apo A-1 and its ratio to apoB and HDL in stable hyperlipidaemic subjects after Ramadan fasting in Kuwait. *Eur J Clin Nutr*, 2000; 54:508–513.

11- **Mafauzy M, Wan Mohamad WB, Zulkifli A, Ruhani AH:** A study of fasting diabetic patients during the month of Ramadan. *Med J Malaysia* , 1990;45:14–17, 1990.

12- **Saad MF, Kahn SE, Nelson RG et al.** Disproportionately elevated proinsulin in Pima Indians with noninsulin- dependent diabetes mellitus. *J Clin Endocrinol Metab **1990;**70:1247–1253*

13- **Kahn SE, Leonetti DL, Prigeon RL, Bergstrom RW, Fujimoto WY** Relationship of proinsulin and insulin with noninsulin-dependent diabetes mellitus and coronary heart disease in Japanese American men: impact of obesity. *J Clin Endocrinol Metab **1995;**80:1399–1406*

14- **Kahn SE, Halban PA** Release of incompletely processed proinsulin is the cause of the disproportionate proinsulinemia of NIDDM. *Diabetes* **1997;***46:1725–1732.*

15- **Carson ER, Cobelli C, and Finkelstein L.** *The Mathematical Modeling of Metabolic and Endocrine Systems, 1983: New York; John Wiley & sons.*

16- **Alarcon C, Leahy JL, Schuppin GT, Rhodes CJ**. Increased secretory demand rather than a defect in the proinsulin conversion mechanism causes hyperinsulinemia in a glucose-infusion rat model of non-insulin dependent Diabetes Mellitus. *J. Clin. Invest 1995: 95:1032-1039.*

17- **Wareham N J, Byrne C D, Williams R, Day N E, Hales C N .**Fasting proinsulin concentrations predict the development of type 2 diabetes. *Diabetes Care 1999; 22(2):262-70.*

18- **Grill V, Dinesen B, Carlsson S, Efendic S, Pedersen O, Ostenson C-G.** Hyperproinsulinemia and proinsulin-to-

insulin ratios in Swedish middle-aged men: association with glycemia and insulin resistance but not with family history of diabetes. American journal of epidemiology. *2002 May 1; 155(9):834–41.*

19- **Haffner SM, Gonzalez C, Mykka¨nnen L, Stern M:** Total immunoreactive proinsulin, immunoreactive insulin and specific insulin in relation to conversion to type 2 diabetes: the Mexico City Diabetes Study. *Diabetologia.* 1997. 40:830–837.

20- **Nijpels G, Popp-Snijders C, Kostense PJ, Bouter LM, Heiner RJ:** Fasting proinsulin and 2-h post-load glucose levels predict the conversion to type 2 diabetes in subjects with impaired glucose tolerance: the Hoorn study. Diabetologia . 1996 39:113–118.

21- **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC**. "Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man". *Diabetologia* 1985; 28 (7): 412–9.

22- **Wallace TM, Levy JC, Matthews DR.** Use and abuse of HOMA modeling. *Diabetes care. 2004 Jun;27(6):1487–95.*

23- **Roky R., Houti I., Moussamih S. Qotbi S, Aadil N.,** Physiological and chronobiological changes during Ramadan intermittent fasting, *Ann. Nutr. Metab 48 (2004) 296–303.*

24- **Saleh, S. A. Elsharouni, S. A. Cherian, B. Mourou, M.** Effects of Ramadan fasting on Waist Circumference, Blood Pressure, Lipid Profile, and Blood Sugar on a Sample of Healthy Kuwaiti Men and Women Mal *J Nutr 200511(2): 143-150.*

25- **Beshyah, S.A. Jowett, N.I. Burden, A.C.** Effect of Ramadan fasting on metabolic control in diabetes, *Diabet Med 5 (Suppl. 2) (1988) 32–33.*

26- **Sari, R. Balci, M.K. Akbas, S.H. Avci, B.** The effects of diet, sulfonylurea, and Repaglinide therapy on clinical and metabolic parameters in type 2 diabetic patients during Ramadan, *Endocr. Res. 30 (2) (2004) 169–177.*

27- **Rashed, H.** The fast of Ramadan: no problem for the well; the sick should avoid fasting, *BMJ 304 (1992) 521–522.*

28- **Ewis A,Afifi NM**.Ramadan fasting and NIDDM,effect of regular exercise.*Second international congress on health and Ramadan.December13,1997.Istanbul,Turkey p76.*

29- **Fakhrzadeh H, Larijani B, Sanjari M, Baradar-Jalili R, Amini MR.** Effect of Ramadan fasting on clinical and biochemical parameters in health adults. *Ann Saudi Med 2003; 23: 223-6.*

30- **Khaled B, Bendahmane M, Belbraouet S.** Ramadan fasting induces modifications of certain serum components in obese women with type 2 diabetes. *Saudi Med J 2006; 27:23–26.*

31- **Bergman RN, Finegood DT, Kahn SE.**The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes.*Eur J Clin Invest 2002; 32(Suppl 3):S35–S45.*

32- **M'guil M, Ragala MA, El GuessabiL, Fellat S, Chraibi A, Chabraoui L, Israili ZH , Lyoussi B**.Is Ramadan fasting safe in type 2 diabetic patients in view of the lack of significant effect of fasting on clinical and biochemical parameters ,blood pressure and glycemic control? *Clin Exp Hypertens.2008; 30(5)339-57.*

33- **Tura A, Pacini G, Kautzky-Willer A, Ludvik B, Prager R, Thomaseth K.** Basal and dynamic proinsulin–insulin relationship to assess beta-cell function during OGTT in metabolic disorders.*Am J*

PhysiolEndocrinolMetab 2003; 285:E155–E162.

34- **Pfützner A, Derwahl M, Jacob S, Hohberg C, Blümner E, Lehmann U, Fuchs W, Forst T**. Limitations of the HOMA-B score for assessment of beta-cell functionality in interventional trials–results from the PIOglim study. *Diabetes Technol Ther. 2010;12(8):599–604.*

35- **Yanbing L, Wen XU, Zhihong I, Bin Y, Xiahua C, Zhimen H, Guoliang H, JianpingW**.Long term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β cell function.*Diabetes care 2004; 27: 2597-2602.*

36- **Thomas R Gest , Thrainsdottir I,Malmberg K, Olsson A,Gutniak M,Ryden L.:**Initial experience with GLP-1 treatment on metabolic control and myocardial function in patients with type 2 diabetes mellitus and heart failure.Diab Vasc Dis Res 2004;1:40-43.

37- **Bryhni B, Arnesen E and JensssenTG**.Association of age with serum insulin, proinsulin and proinsulin-to-insulin ratio: a cross sectional study.*BMC Endocrine Disorders 2010;10-21.*