Original Article

Effects of the Fast of Ramadan on Endothelial Function and High-Sensitivity C - Reactive Protein in Newly Diagnosed Type 2 Diabetic Patients

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Kuwait Medical Journal 2008, 40 (1): 53-58

ABSTRACT

Objective: To evaluate the effect of fasting during Ramadan on the endothelial function and high-sensitivity C-reactive protein as a marker of inflammation in newly diagnosed type 2 diabetic patients.
Design: Prospective study.
Setting: Tertiary Center, Kuwait
Subjects: Fifty-two patients (29 male and 23 female) with newly diagnosed type 2 diabetes were examined, before and after the Ramadan fasting.
Intervention: A high resolution ultrasound scanner
Main Outcome measures: Assessment of endothelial function was done by ultrasound assessment of flow-mediated dilatation of the brachial artery. Also, both high-sensitivity C-reactive protein and waist circumference were measured.
Results: Fasting during Ramadan significantly improved the brachial artery flow-mediated dilatation (7.27 ± 3.4 Vs. 5.27 ± 2, $p < 0.05$) as well as significantly reduced both high-sensitivity C-reactive protein (0.26 ± 0.07 Vs. 0.48 ± 0.13, $p < 0.001$) and waist circumference in both male and female group (94.68 ± 11.01 Vs. 92 ± 10.07 & 89.76 ± 17.52 Vs. 87.18 ± 17.53, respectively, $p < 0.0001$)
Conclusion: Fasting during Ramadan has a beneficial effect on the endothelial function and on the reduction of low-grade inflammation and waist circumference.

KEY WORDS: C-reactive protein, endothelial dysfunction, high-sensitivity, Ramadan fasting, waist circumference

INTRODUCTION

Arterial inflammation has emerged as central to the progression of atherothrombosis[1]. Of the markers of inflammation, the high-sensitivity C-reactive protein "hs-CRP" is the most studied, with evidence that it may also play a direct pathogenic role in atherosclerotic lesion formation[2-9]. CRP, at concentrations known to predict adverse cardiovascular outcomes, directly inhibits the production of nitric oxide (NO) and angiogenesis, which could impair the response to ischemia[10]. Serum CRP measured by a highly sensitive assay (hs-CRP) has become an important marker of vascular inflammation and predictor of atherosclerosis[2,11-14]. Recent data suggest that hs-CRP is as important a predictor of atherosclerosis as circulating LDLC[15]. Thus inflammation may be potentially as important as cholesterol in contributing to atherosclerosis. High levels of hs-CRP in obesity also predict development of diabetes later[16].

Endothelium plays a vital role in vascular homeostasis, vascular tone regulation, vascular smooth muscle cell proliferation, trans-endothelial leukocyte migration and thrombosis and thrombolysis balance. In response to various mechanical and chemical stimuli, endothelial cells synthesize and release a large number of vasoactive substances, growth modulators, and other factors that mediate these functions[17]. Endothelial dysfunction is now regarded as an early pivotal event in atherogenesis and has been shown to precede the development of clinically detectable atherosclerotic plaques in the coronary arteries[18]. This event was important in the development of microvascular complications in diabetes[19].

Over the past decade, a non-invasive technique has evolved to evaluate flow-mediated vasodilatation (FMD) an endothelium-dependant function, in the brachial artery[20-23]. This stimulus provokes the endothelium to release nitric oxide (NO) with subsequent vasodilatation (index of vasomotor function). This technique is attractive because it is non-invasive and allows repeated measurements.

Endothelial dysfunction in the brachial artery

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highly correlates with endothelial dysfunction in the coronary circulation, which is emerging as an independent risk factor for the cardiovascular disease[24].

Diabetes is an atherosclerotic risk equivalent. Both are the end results of two important parallel pathways:

1. The progression of insulin resistance to the metabolic syndrome, pre-diabetes and ultimately diabetes and

2. The progression of endothelial dysfunction with progressive inflammation, thrombosis, and oxidation at the vessel wall to fatty streak formation and ultimately to the development of advanced atherosclerotic plaques[25].

There has been much contention about the effect of Ramadan fasting on health. The majority of Muslims fast from dawn to sunset during the whole month of Ramadan. Ramadan is the ninth month in the lunar calendar. The daily fast (neither food nor drink) lasts about 12-19 hours depending on the season in which Ramadan falls and on the geographic location of the country.

The aim of our study was to evaluate the effect of Ramadan fasting on the link between endothelial function, inflammation and atherothrombosis.

PATIENTS AND METHODS

Study Population:

We recruited 52 patients with non-insulin dependant type 2 diabetes mellitus who were recently discovered (less than 3 years). None of our patients had documented coronary artery disease or history of myocardial infarction. A 12-lead resting ECG showed no ischemic ST-T wave changes and no pathological Q-wave. All patients had normal sinus rhythm. Also, none of our patients had cerebro-vascular disorders, dysthyroid disease, heart failure, infection, vasculitis or peripheral vascular disease.

There were 29 male (age range 31-67 years, mean ± SD 45 ± 17) and 23 female (age range 29 – 54 years, mean ± SD 41 ± 15) patients. Seven out of 29 male patients were hypertensive (24.13%) and 18 were smokers (62.1%). Also, there were six hypertensives (26.1%) and seven current smokers (30.4%) in the female group.

Test samples were collected from all patients five and one week before Ramadan fasting and then one week after the beginning of Ramadan so that patients acted as their own control. Ethical Committee in the hospital approved the study.

All patients were educated about medications, hypoglycemia and hyperglycemia complications. They were asked to fill out a questionnaire about their meals, quantity, quality and they were advised to avoid the common practice of overfeeding with sweets. They were asked to adopt a protein-low fat-energy restricted three meals before fasting (Iftar at sunset and Sohor before dawn). They were suitably monitored by a dietician.

Assessment of Flow Mediated Dilation in the Brachial Artery:

The ultrasound procedures for assessing endothelium function by FMD was performed as described in the guidelines by Corretti *et al*[26]. The patients were examined in the morning after an overnight fast. None of our patients used long-acting nitroglycerine or calcium antagonist.

A high resolution ultrasound scanner (system Five GE Vingmed, Horton, Norway) with a 10.0 MHz linear array transducer was used. After a 10 minute equilibration period at rest in the recumbent position, scans of the brachial artery were taken proximal to the antecubital fossa and saved on videotapes. Baseline diameter recordings were obtained after which arterial occlusion was performed by inflating the forearm blood pressure cuff to 50mm Hg above systolic blood pressure for 4 - 5 minutes. After cuff release, diameter recordings were repeated during the post-occlusive increase in brachial artery blood flow.

Measurements of the brachial artery diameter was defined as the distance from the leading edge of the near wall intima-lumen echo to the leading edge of the far wall intima-lumen echo along a line perpendicular to the arterial long axis. A computer system with ultrasound tracing of echo interfaces was used for measurement of distance between the wall echoes within a 5 mm long section of the brachial artery. The brachial artery diameter was calculated in diastolic frames taken coincidently with the R-wave on the ECG twice at rest and then 45, 60 and 75 seconds after cuff deflation. The average diameter at baseline and post inflation was calculated.

Guidelines expressed diameter changes as the percentage change relative to the mean baseline value. When baseline rest image was acquired, we estimated blood flow by time averaging the pulsed Doppler velocity signal obtained from a mid-artery sample volume. To assess the hyperemic velocity, we obtained the mid-artery pulsed Doppler signal upon immediate cuff release and no later than 15 s after cuff deflation.

Assessment of the Waist Circumference:

We measured the waist circumference at the narrowest point (between the highest point of iliac crest and the lower costal margin)[27]. The normal values of waist circumference differ in both male and female population. Normal values for waist circumference in the male population should be

Table 1: Comparison of Pre and Post-fasting study parameters in the study group (n = 52).

Parameters	5-Weeks Pre-Fasting	1-Week Pre-Fasting	1-Week Post-Fasting
Baseline brachial artery diameter (mm)	3.52 + 0.81	3.67 + 0.79	3.59 + 0.56*
Peak hyperemic blood flow (ml / min)	431 + 135	434 + 132	541 + 95*
Blood flow increase (ml/min)	379 + 82	365 + 92	411 + 87*
Flow-mediated dilatation (%)	5.25 + 2.1	5.27 + 2	7.27 + 3.4*
High-sensitivity CRP (mg / dl)	0.47 + 0.12	0.48 + 0.13	0.26 + 0.07*
Waist circumference in cm (Male group)	94.68 + 11.01	95.1 + 10.81	92 + 10.07*
Waist circumference in cm (Female group)	89.67 + 17.52	90.01 + 17.34	87.18 + 17.53*
Fasting blood glucose (mmol)	5.68 + 0.38	5.63 + 0.34	5.64 + 0.38
Systolic blood pressure (mmHg)	123 + 8	124 + 9	122 + 10
Diastolic blood pressure (mmHg)	80 + 6	81 + 4	79 + 5

* = statistically significant

less than 102 cm, while that value in the female population should be less than 88 cm.

Assessment of hs – CRP:

High sensitivity C-reactive protein was processed with the use of latex- enhanced immuno nephelometric assays (Date Behring, Newark, Del.)[28].

In patients without known cardiovascular disease, the range of hs-CRP for the subjects with the lowest (quintile 1) to the highest (quintile 5) vascular risk were 0.01 - 0.069, 0.07 - 0.11, 0.12 - 0.19, 0.2 - 0.38, and more than 0.38 mg/dl respectively. A risk estimate appears to be linear across the spectrum of inflammation and these sequential quintiles considered in clinical terms represent individuals with lowest, mild, moderate, high, and highest relative risks of future cardiovascular diseases.

Statistical Analysis

The statistical analysis was performed using SPSS[11] software. Quantitative data were reported as mean ± standard deviation and compared using the students T-test. A linear regression analysis was used to study the relationship between the endothelial function and both the hs-CRP and waist circumference. A probability level of < 0.05 was considered statistically significant.

RESULTS

Effect of Ramadan Fasting on Endothelial Function

We studied 52 patients with recently diagnosed (less than 3 years, range 8-35 months) diabetes mellitus type 2 with no documented coronary artery, cerebro-vascular or peripheral vascular disease.

We examined patients twice before the Ramadan, by ultrasound to detect the endothelial dependant flow mediated vasodilatation in the brachial artery. The examination showed impaired flow mediated dilatation in the brachial artery both five weeks and one week before the Ramadan (5.25 ± 2.1 Vs. 5.27 ± 20 $p > 0.05$). Ramadan fasting significantly improved flow mediated dilatation in the brachial artery diameter (7.27 ± 3.4 Vs. 5.27 ± 20 $p < 0.05$, post-fasting Vs. pre-fasting, percent change in brachial artery diameter , mean ± SD),

Pre-fasting blood sugar ranged between 5.1 - 6.5 mmol at five weeks and 5.0 - 6.2 mmol one week pre-fasting. Fasting blood glucose showed no significant difference after fasting (5.3 - 6.6 mmol, $p > 0.05$). Body weight was reduced post-fasting as compared to the week before fast (post-fasting 76.3 + 5.6 Vs. pre-fasting 78.8 + 4.98 kg).

Effect of Ramadan Fasting on hs-CRP:

The two test samples at five and one week prior to Ramadan were similar (0.47 ± 0.12 Vs. 0.48 ± 0.13, $p > 0.05$, mean ± SD). The third test sample (post Ramadan fasting) of hs – CRP showed significantly lower values than the second test sample (0.26 ± 0.07 Vs. 0.48 ± 0.13, mean ± SD, $p < 0.001$)

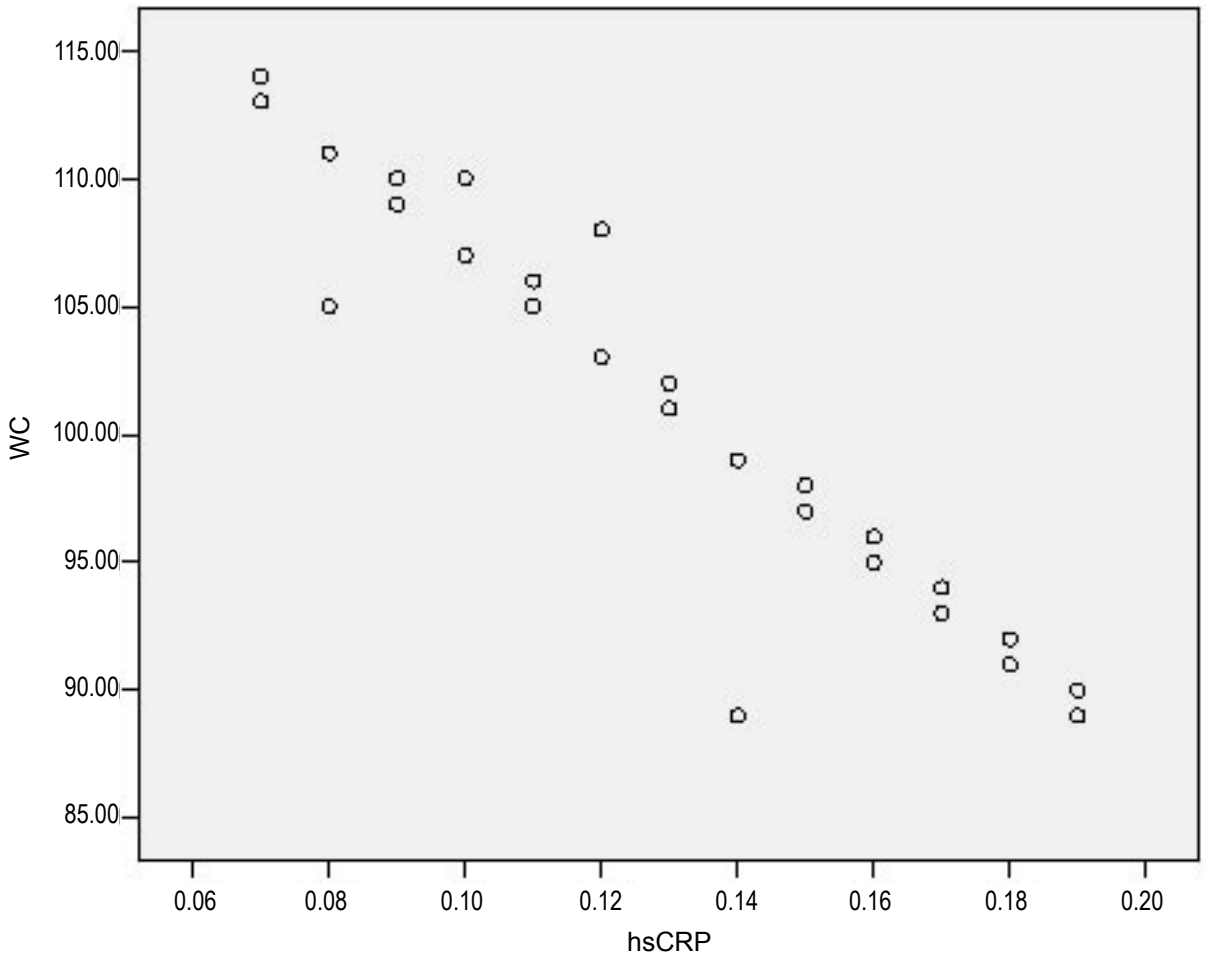
Effect of Ramadan Fasting on Waist Circumference:

In the male group, the waist circumference was significantly reduced after the Ramadan fasting (94.68 ± 11.01 Vs 92 ± 10.07, $p < 0.0001$, mean ± SD) with no significant difference between the waist circumference measurement at five weeks Vs. one week pre fasting (95.12 ± 10.9 Vs 94.68 ± 11.0, $p > 0.05$).

In the female group, the waist circumference was reduced significantly after the Ramadan fasting (89.76 ± 17.52 Vs 87.18 ± 17. 53, $p < 0.0001$, mean ± SD) with no significant difference between the measurements of waist circumference at five weeks and one week before Ramadan (90.1 ± 16.9 Vs 89.76 ± 17.52, $p > 0.05$).

Relation between Endothelial Function, Hs- CRP and Waist Circumference:

There was an inverse relationship between



r = 0.842; p < 0.0001

Fig.1: Correlation between hs-CRP and waist circumference

the improvement in flow mediated dilatation in the brachial artery after Ramadan fasting and the reduction in the levels of hs - CRP ($r = -0.63$, $p < 0.0001$) as well as the reduction in the measurement of waist circumference ($r = -0.49$, $p < 0.001$).

DISCUSSION

We studied 52 patients with recently diagnosed type 2 diabetes (within the last three years) and no clinically evident macro-vascular disease (cardiovascular, cerebro-vascular or peripheral vascular disease). All our patients had impaired flow-mediated dilatation in the brachial artery (5.27 ± 2.0 baseline percent increase in brachial artery diameter, mean ± SD)

A study by Williams *et al*[29] as well as another study by Lim *et al*[30] concluded that people with type 2 diabetes almost invariably have abnormal endothelial function as determined by the assessment of vascular reactivity and / or by the measurement of plasma markers of endothelial activation, coagulation, fibrinolysis, or inflammation. They have been consistently found to have abnormal small and large vessel reactivity for both endothelium dependant and independent vasodilatory pathways, demonstrating that there is not only a reduction in nitric oxide production in diabetes but also decreased response to its effect in vascular smooth muscle cells.

In a study by Caballero *et al*[31], they reported that, micro and macro-vascular reactivity were markedly reduced in type 2 diabetic patients as well as impaired reactivity was present in relatives of type 2 diabetes patients and in subjects with impaired glucose tolerance.

Our study results showed a significant improvement in the brachial artery diameter change in response to reactive hyperemia (7.72 ± 3.4 Vs. 5.27 ± 2, $p < 0.05$, post fasting Vs. pre-fasting, percent increase in brachial artery diameter, mean ± SD).

There is a life style modification during fasting in the month of Ramadan. Muslims fast from dawn to sunset (they neither eat nor drink). They have two meals per day (Iftar at sunset and Sohor before dawn). They exert more physically during the usual five prayers plus the added prayers specific for the

Ramadan. This adds up to an average of two hours per day. They also walk five times to the mosque which adds to the physical activity.

Hamdy *et al*[32] studied the effect of life style modification on the improvement of endothelial function in obese subjects with the insulin resistance syndrome through the effect of a six month weight loss program and reported that this intervention significantly improved flow-mediated dilatation in the brachial artery (12.9 ± 1.2% Vs 7.9 ± 1.01%, final Vs. baseline respectively, $p < 0.0001$) with a linear relationship with percentage weight reduction.

This is in agreement with our study results, wherein our intervention (fasting during Ramadan) significantly improved the flow mediated dilation in brachial artery and showed a linear relationship with reduction in the waist circumference in both the male and the female group (94.68 ± 11.01 Vs. 92 ± 10.7, $p < 0.0001$ and 89.76 ± 17.52 Vs. 87.18 ± 17.53, $p < 0.0001$ respectively). The effect of Ramadan fasting on the waist circumference in males and females, as a reflection of abdominal adiposity, was in agreement with Soliman N[33], Azizi F[34] and Takruri HR[35], who reported a significant decrease in body weight during Ramadan fasting. The decrease in body weight was due to efficient utilization of body fat during fasting. El-Ati *et al*[36] reported that overweight persons lose more weight than normal or underweight subjects during the Ramadan.

As inflammation began to be recognized as a major contributor to the pathogenesis of atherosclerosis, cardiologists started to ask whether markers of inflammation could be used to predict the clinical outcome. Our study results revealed that fasting during the Ramadan significantly reduces the level of hs - CRP (0.26 ± 0.07 Vs. 0.48 ± 0.13, $p < 0.001$ post fast Vs pre-fast, mean ± SD) and shows a linear relationship with improved percentage FMD in the brachial artery.

These findings compare well with the study of Pasceri *et al*[4] who studied the direct pro-inflammatory effect of CRP in human endothelial cells, and reported that CRP has a significant pro-inflammatory effect in both umbilical vein and coronary artery endothelial cells, inducing high levels of expression of ICAM-1, VCAM – 1 and E-selectin.

Our findings compare well with the results of Ridker *et al*[11], who reported that even small increments in serum levels of CRP are associated with higher risk of atherosclerosis and ischemic heart disease in apparently healthy subjects.

Lowering of CRP levels may have beneficial effect on the evolution of atherosclerosis and may reduce the risks of coronary events. In our study, this was achieved with a non-pharmacological intervention (Ramadan fasting). Ridker *et al*[38] found that the reduction of serum CRP by statins was associated with a better clinical outcome after acute myocardial infarction.

CONCLUSION

We observed that fasting during the Ramadan had a favorable effect on endothelial function. It also reduced the direct pro-inflammatory effect of CRP on human endothelial cells as well as waist circumference which is a measure of abdominal adiposity. Hence, Ramadan fasting can affect the link between atherosclerosis, inflammation and adiposity with a non-pharmacological intervention in type 2 diabetes.

These favorable effects have occurred in spite of the short period of fasting (29-30 days per year). We, therefore, suggest that a systematic fasting of one to two days per week even after the Ramadan period would serve as an excellent part of healthy lifestyle.

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