The Relationship between Inflammation, Oxidative Stress, and Metabolic Risk Factors in Type 2 Diabetic Patients

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Abstract

Objective: Globally, 3-5.2 percent of people suffer from diabetes which is one of the most serious metabolic disorders resulting in an increase in inflammatory biomarkers e.g. interleukin-6, tumor necrosis factor-alpha, and C-reactive protein. The aim of this study was to investigate the relationship between inflammation, oxidative stress and fasting blood glucose, lipid profile and anthropometric parameters in patients with type 2 diabetes.

Material and methods: This study was conducted as a cross-sectional study in Tehran through 2009-2010 on 45 men and women aged 35-65 years old with type 2 diabetes. Blood glucose, lipid profile, C-reactive protein, and malonedialdehyde were measured. Independent sample T-test and linear regression analysis were used.

Results: Fasting blood glucose, malonedialdehyde, total cholesterol and body mass index were higher in women than in men; but there was no difference between two sexes in other factors. Malonedialdehyde, neither directly nor after adjustment for sex was not related to fasting blood glucose, total cholesterol, triglycerides and anthropometric indices (weight, body mass index, and body fat mass).

Conclusion: This study showed that oxidative stress had not any relationship with blood glucose, lipid profile, and anthropometric index, but inflammation was related to glycemia, body mass index, and fat mass. Control of inflammation and oxidative stress is necessary for accelerating treatment process and preventing complications due to them.

Keywords: Type 2 diabetes mellitus, Inflammation, Fasting blood glucose, Body mass index, Cholesterol

Introduction

Diabetes mellitus is a metabolic disorder which is associated with severe hyperglycemia, impaired metabolism of carbohydrates, fats, as well as proteins, and is a result of relative or absolute insulin deficiency (1). Globally, 3-5.2 percent of people suffer from diabetes (2). Type 2 diabetes accounts for over 90% of diabetic cases (3). Based on a national Iranian survey on non-communicable diseases in 2005, the prevalence of diabetes mellitus in 25-64 years old urbans was 7.7 percent (2 million people)

(4). In addition to reduced quality of life and treatment costs, late complications such as vascular diseases in diabetic patients can increase mortality rate by 4.2 percent (2). Diabetes has other complications like heart diseases and atherosclerosis (5). Positive association has been shown between diabetes and systemic inflammation in non-smoker white men (5). Great deal of research have been done on the relationship between type 2 diabetes and inflammatory biomarkers; the results have demonstrated that this biomarkers increase in diabetes, especially CRP, IL-6 and TNF-alpha. The majority of patients with type 2 diabetes are overweight, and they need to decrease 15-30 percent of their calorie intake in order to lose 5-15 percent of their body weight and reduce their blood sugar, blood pressure, and blood lipids (6). Oxidative stress can accelerate the incidence of clinical manifestation of diabetes in patients. Body has some series of antioxidant systems (including vitamin E, vitamin C, enzymes like catalase and superoxide dismutase, and molecules such as glutathione) in order to prevent the accumulation of free radicals. This system can neutralize free radicals, but increased production of free radicals due to the imbalance between free radicals and antioxidants load may reduce antioxidants levels, partial clearing of free radicals, and cause oxidation of lipids, sugars, proteins and nucleic acids which eventually leads to widespread pathological consequences of diabetes (7). One of the factors that facilitate formation of atherosclerosis in diabetes is oxidative stress (8).

Although the role of oxidative stress and inflammation in diabetes complications and pathogenicity is well known nowadays, there are few studies on their association with blood sugar, blood lipids and anthropometric indicators in Iran; so the purpose of the present study was to investigate the relationship between inflammation, oxidative stress and blood sugar, lipid profile and anthropometric parameters in patients with type 2 diabetes.

Materials and Methods

45 non-smoker males and females aged 65-35 years old with type II diabetes were recruited from Iranian Diabetes Association and the Institute of Endocrinology and Metabolism, Firoozgar hospital, between 2009 and 2010, after written consents were obtained. People were excluded if they had cardiovascular disease, liver diseases, kidney disorders, thyroid problems, macroproteinuria, neuropathy, smoking during the past two years, non-steroidal anti-inflammatory drugs use and more than 3 kg weight change during past 3 months. Height was measured by stadiometer and weight was measured with Seca scale. Body fat mass was measured with Bioelectric impedance (BIA). After overnight fasting, venous blood samples were taken for determination of FBS, TG, TC, MDA and CRP. Blood glucose level was measured using colorimetric enzymatic method (Pars Azmoon, Tehran, Iran) and TG and TC were assessed by an enzymatic method (ParsAzmoon, Tehran, Iran). MDA was determined by chemical colorimetric assay (Cayman, MI, USA) and CRP was evaluated with ELISA (BiochemCanada Ontario, Canada). Blood pressure was measured in the sitting position, 2 times after a 10-minute rest from the right arm using a mercury sphygmomanometer and the mean values were used. The study protocol was approved by the ethics committee of Iran University of Medical Sciences. Statistical analysis was performed using the SPSS software, version 17. Independent sample T-test and linear regression analysis were used to compare the results.

Results

Demographic characteristics of participants are shown in Table 1. The mean age of patients was 54.97± 8.26 years and the mean duration of diabetes was 4.05 ± 5.40 years. FBS, MDA, TC and BMI were higher in women than in men (*P*-value: <0.001, 0.019, 0.005, and 0.031, respectively). There was no difference between both sexes in other cases (*P*-value>0.05). MDA neither directly, nor after

Table 1. Demographic characteristics of the study population

Variable	Mean ± SD
Age(years)	54.97 ±8.26
Sex*	
Women	22 (48.89)
Men	23 (51.11)
Height (cm)	163.06 ± 9.80
Weight (kg)	73.30 ± 11.87
BMI (kg/m^2)	27.44 ± 4.11
Duration of diabetes (years)	5.40 ± 4.05

*Data are presented as n (%).

adjustment for sex had any relationship with FBS, TC, TG and anthropometric indices (weight, BMI, and body fat) (*P*-value>0.05). However, blood glucose, body mass index and body fat mass had a significant role in predicting CRP (*P*-value: 0.012, <0.001, and 0.027, respectively).

Discussion

This study showed that in diabetic patients, oxidative stress which was measured by MDA, was not significantly associated with fasting blood glucose, lipid profile and anthropometric parameters. However, fasting plasma glucose, body mass index and body fat mass were significant predictors of the inflammatory factor, CRP.

The study of Franzini on diabetic men and women with and without abdominal obesity showed that HDL level in women was significantly higher than men (*P*-value=0.01); while triglyceride and blood pressure had no significant differences between both sexes (*P*-value>0.05) and fasting blood glucose level was higher in diabetic women (*P*-value=0.042) which are inconsistent with our results. In this study, body mass index in males without abdominal obesity were significantly higher than females (*P*-value=0.001) (9). This outcome is contrary to our results, which can be related to considering abdominal obesity as a confounder. In Mahmoudi et al study that was performed on patients suffering from heart attack, diabetes rate was significantly higher in women than men; in addition, hyperlipidemia, hypertension, cholesterol, and fasting blood glucose were higher in women than men (16). In a study conducted on patients with angina, levels of HDL, TG, FBS, and BMI were significantly higher in women with coronary artery disease than men with this disease, but systolic and diastolic blood pressures were not significantly different in two sexes which partly confirms the results of our study (18).

Lipid peroxidation contributes to the formation of toxic aldehydes such as malondialdehyde (14). Oxidative stress because of hyperinsulinemia can have consequences like β-cell death or dysfunction in diabetic patients. It has revealed that diacron reactive oxygen metabolites (dROMs) have significantly positive relation to age, fasting plasma glucose, and body mass index and a negative correlation with HDL (20). Chung et al study found higher levels of free oxygen radicals (FORT) in metabolic syndrome patients with higher levels of FBS or lower HDL (21). In the present study, we could not find such a relationship maybe because of small sample size. It was displayed that dROMs have a positive relationship with BMI and percent body fat in adolescents but biological antioxidant potential (BAP) did not (22) that is

Table 2. Comparison of biochemical and anthropometric measures in men and women

Variable	Women	Men	*P*-value
FBS (mg/dl)*	96.77± 15.76	95.85±16.95	<0.001
Systolic BP (mmHg)*	121.00±11.75	121.27±10.88	NS
Diastolic BP (mmHg)*	77.60±9.97	79.50±8.50	NS
Fat Body mass (percent)	40.10±6.1	25.70±4.32	NS
MDA (nM/µL)§	3.78±0.78	3.28±0.36	0.019
CRP(mg/L)§	2630.54±2951.82	2110.33±2663.36	NS
Weight (kg)	71.02±12.88	75.69±10.48	NS
Total cholesterol (mg/L)§	180.47±34.76	153.50±25.88	0.005
TG (mg/dL)§	159.86±80.14	147.45±55.23	NS
BMI (kg/m^2)§	28.98±4.67	26.04±2.81	0.031
Duration of diabetes (year)*	7.17±4.64	5.59±3.23	NS

*Independent sample T-test; §Non-parametric 2 independent sample T-test
NS: Not significant

similar to the present findings. Body fat excretes adipokines, which may be the most important factors in reactive oxygen species (ROS) production.

Increased pro-inflammatory cytokines and activation of the inflammatory cascade are important factors in the development of insulin resistance and type 2 diabetes, so the new approach in control of diabetes is modulating or inhibiting inflammation (12). We found that FBS, BMI, and body fat mass could predict CRP in diabetic patients. In Shivananda et al study, it was found that CRP levels had no significant difference in diabetics compared to control group. Sialic acid levels in this study, an acute phase inflammation marker, was higher in diabetic patients than in controls (*P*-value=0.01). Serum sialic acid was also significantly correlated with waist/hip ratio (r=0.226, *P*-value<0.05) which is in agreement with our results (10). In Taghdir et al study, inflammatory cytokines, IL-6 and malonedialdehyde were not different in diabetic and non-diabetic participants (11). One study on healthy adults revealed that CRP level was significantly higher in subjects with BMI ≥ 25 kg/m² (OR 6.9; 95% CI: 3.6-13.3), abdominal obesity (OR 4.6; 95% CI: 2.2-7.3) and high body fat (OR 10.2; 95% CI: 5.1-20.3) (*P*-value<0.001) (23). Pitsavos and colleagues showed that diabetic subjects had 57% higher mean levels of CRP, 15.9% higher level of hypercholesterolemia, 22% higher mean levels of interleukin-6 and 60% higher levels of tumor necrosis factor-alpha compared to non-diabetic subjects. They also revealed a positive association between blood glucose, C-reactive protein and interleukin-6 levels, after adjustment for several lifestyle factors (19). Adipose tissue secretes adipokines like TNF-α, IL-6, leptin, visfatin, resistin, angiotensin II, and plasminogen activator inhibitor which affect energy and glucose metabolism, as well as, immunity. They can phosphorylate insulin receptor substrate (IRS) on serine through c-Jun N-terminal kinase (JNK) and I-kappa B kinase β (IKKβ)/NFκB pathways which results in insulin signaling pathway disruption and finally insulin resistance (24).

Nutritional factors play an important role in increasing or decreasing inflammatory factors like CRP. In Krojcovicova et al study, an inverse relationship between vitamin C intake and C-reactive protein levels was observed (15). In another study by Ajani et al, an inverse association was found between fiber consumption and C-reactive protein levels (17). In Mirmiran et al study investigating the effect of broccoli sprout powder consumption on blood sugar and inflammatory factors in diabetic patients, a reduction in fasting blood glucose, interleukin-6 and C-reactive protein was seen that could be related to its sulforaphane content (3). Inflammation and oxidative stress are two important factors in development and progression of diabetes-related complications such as CVD. While it is evident that inhibition of insulin receptor signaling pathways is a key mechanism through which inflammatory and stress responses mediate insulin resistance, it is possible that other relevant pathways, molecules, and alternative mechanisms be involved in this interaction that have not yet been cleared. Given increased inflammation and oxidative stress present in type 2 diabetic

Table 3. The relationship between CRP and MDA with biochemical measures

Independent variable	Dependent variable: MDA						Log CRP		
	B		SE		*P*		B	SE	*P*
	Model 1§	Model 2¶	Model 1§	Model 2¶	Model 1§	Model 2¶			
FBS*	0.152	0.123	0.004	0006	0.355	0.450	0.381	0.005	0.012
TC*	0.096	-0.014	0.002	0.002	0.560	0.936	0.281	0.111	0.068
TG*	0.007	-0.024	0.001	0.001	0.968	0.881	0.231	0.001	0.136
weight*	0.034	0.108	0.005	0.008	0.519	0.342	0.295	0.006	0.055
BMI*	0.219	0.148	0.015	0.016	0.181	0.387	0.518	0.017	<0.001
Fat mass*	0.269	0.170	0.010	0.017	0.098	0.529	0.336	0.008	0.027

*linear regression; §Regression crude model; ¶Regression after adjustment for sex.

patients, it can be a useful strategy to incorporate foods with anti-inflammatory properties and rich in antioxidants into their diets to prevent deterioration of diabetes and progression of diabetes-related complications. The positive association between fasting blood glucose, lipid profile, anthropometric indices and the inflammatory markers may well highlight the clinical importance of targeting inflammation and oxidative stress lowering in treatment and/or prevention of type 2 diabetes. This study has some limitations, which should be considered in future. Small sample size and inability to measure other inflammatory and oxidative stress indicators are the main points.

Conclusion

To sum up, it was observed that oxidative stress had not any relationship with FBS, lipid profile, and anthropometric index, but inflammation was related to glycemia, BMI, and fat mass. Control of these two conditions can play an important role in the reduction of diabetes related complications.

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