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ORIGINAL ARTICLE

C-Reactive Protein And Fibrinogen In Type 2 Diabetes Mellitus*

ABSTRACT

Introduction. Chronic, low-grade inflammation is important in the development and progression of type 2 diabetes mellitus (T2DM). Indicators of increased inflammatory activity include elevated values of circulating acute phase proteins like C-reactive protein (CRP) and fibrinogen. The aim of the study was to test sex-related differences in CRP and fibrinogen blood levels in T2DM patients.

Patients and Methods. The cross-sectional study included 40 T2DM patients, both sexes (19 males and 21 females), median age 70 (36-90) years. Patients were hospitalized at the Clinic of Endocrinology, Clinical Center University of Sarajevo. The fasting glucose levels, glycated haemoglobin, fibrinogen and CRP in the blood of T2DM patients were determined by standard laboratory methods. The data were analysed by statistical software SPSS 19.

Results. The median values of CRP and fibrinogen in blood were not statistically different between female and male T2DM patients, although values had tendency to be higher in female patients [17.30 mg/L (3.40-61.35) vs. 9.60 mg/L (3.50-28.90); $p=0.573$]; [5.70 g/L (4.20-6.35) vs. 3.80 g/L (3.60-6.00); $p=0.078$]. A positive correlation between CRP and fibrinogen was found in samples from female T2DM patients ($\rho=0.606$; $p<0.01$).

Conclusion. Elevated CRP and fibrinogen indicate the presence of inflammation in T2DM patients. Female patients had higher values of both inflammatory markers in blood in comparison to males, but we did not prove statistically significant sex-related differences.

KEY WORDS

Type 2 diabetes mellitus; inflammation; C-reactive protein; fibrinogen.

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One of important factors in the pathogenesis of type 2 diabetes mellitus (T2DM) is a state of subclinical chronic inflammation.¹ It is considered that inflammation is a key factor in insulin resistance.² Except for the disease development, chronic low-grade inflammation is important in the progression of T2DM. Hyperglycemic condition and proinflammatory state in T2DM patients are responsible for the development of a wide spectrum of atherosclerotic complications.³ Indicators of increased inflammatory activity are elevated values of circulating acute phase proteins like C-reactive protein (CRP) and fibrinogen. These proteins play a significant role in initiation, aggravation and progression of atherosclerosis in diabetic patients.⁴ The endothelial dysfunction, promotion of foam cell formation, inhibition of endothelial progenitor cell survival and differentiation,

activation of the complement system in atherosclerotic plaque are major mechanisms of proatherosclerotic action of CRP.⁵⁻⁸ In addition, CRP further contributes to the progression of atherosclerosis by stimulation of monocyte interleukin-6 production.⁹ There are several mechanisms by which fibrinogen increases cardiovascular risk such as stimulation of platelet aggregation, promotion of fibrin formation and increase in plasma viscosity.^{10,11} Sex-related differences exist in CRP and fibrinogen blood values among the healthy population.¹² Accordingly, our aim was to examine if sex-related differences in CRP and fibrinogen blood levels also exist in T2DM patients.

Patients and Methods

Patients. Forty ($n=40$) T2DM patients hospitalized at the Clinic of Endocrinology, Clinical Center University of Sarajevo were included in the study. Patients were divided in sex-based groups: T2DM-males ($n=19$) and T2DM-females ($n=21$). The median age of T2DM patients was 70 (36-90) years. All data were taken from patients' medical histories.

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Table 1. Clinical and biochemical parameters of type 2 diabetic patients

Parameters	T2DM (n=40)	T2DM-females (n=21)	T2DM-males (n=19)	P
Age (years)	70 (36-90)	70 (36-82)	69 (54-77)	0.520
BMI (kg/m ²)	27.05 (23.85-29.67)	26.20 (22.80-29.40)	28.70 (24.30-29.70)	0.236
Disease duration (years)	9.5 (4-20)	10 (4-20)	9 (4-17)	0.810
STA (mmHg)	135(120-160)	140 (130-160)	130 (120-145)	0.196
DTA (mmHg)	80 (80-90)	80 (75-90)	80 (80-90)	0.872
FBG (mmol/L)	9.6 (7.8-14.5) [†]	9.5 (7.70-15.90) [†]	11.40 (8.0-14.50) [†]	0.810
HbA1c (%)	8.45 (7.15-9.15) [†]	8.50 (7.20-9.10) [†]	7.90 (7.10-9.30) [†]	0.851
CRP (mg/L)	16.5 (3.57-30.10) [†]	17.30 (3.40-61.35) [†]	9.60 (3.50-28.90) [†]	0.573
Fibrinogen (g/L)	4.82 (3.7-6.3) [†]	5.7(4.20-6.35) [†]	3.80 (3.60-6.0) [†]	0.078

Abbreviations: T2DM-type 2 diabetes mellitus; BMI-body mass index; STA-systolic blood pressure; DTA-diastolic blood pressure; FBG-fasting blood glucose; HbA1c-glycated haemoglobin; CRP-C-reactive protein; n-number of the patients included in the study; P-probability; [†]-biochemical parameters which are out of the reference range.

Clinical examinations and laboratory measurements.

Systolic and diastolic blood pressures were determined by standard protocol using mercury manometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Glucose hexokinase method (Dimension RXL, Siemens, Munich, Germany) was used for fasting blood glucose measurement (reference range 3.3-6.1mmol/L). CRP and HbA1c were analysed by immunoturbidimetric methods on the Dimension Xpand Plus Analyzer (Siemens, Munich, Germany). The CRP reference range was 0-5 mg/L and values less than 6% for HbA1c were considered normal. Fibrinogen measurement was done using immunonephelometric method using BN II nephelometer (Siemens, Munich, Germany) (reference range 1.8-3.5 g/L).

Statistical analysis. Results of descriptive statistics are presented by median with range from first to third quar-

tile. Differences of parameters between two groups were analysed using non-parametric Mann-Whitney U test because the criteria of normal data distribution were not satisfied. Spearman's correlation test was used to analyse the association between studied parameters. For data analysis, we used SPSS Statistics software version 19.0 (SPSS Inc, Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

Results

Characteristics of clinical and biochemical parameters of type 2 diabetes mellitus patients are presented in Table 1. There were no age-related differences between T2DM patients of both sexes. We found that type 2 diabetic patients were overweight with a poor control of glycaemia. No statistically significant differences were found with regard to glucose and HbA1c levels, duration of disease and blood pressure among men and women. Concentrations of CRP

Table 2. Gender related inflammatory markers and parameters of the type 2 diabetic patients

Biochemical tests	T2DM patients				
		Females		Males	
		CRP (mg/L)	Fibrinogen (g/L)	CRP (mg/L)	Fibrinogen (g/L)
FBG (mmol/L)	Rho	0.360	0.205	0.506	0.183
	P	0.109	0.372	0.027 [†]	0.453
HbA1c (%)	Rho	-0.120	-0.299	-0.143	-0.083
	P	0.605	0.189	0.559	0.736
Fibrinogen (g/L)	Rho	0.606	-	-0.086	-
	P	0.004 ^{††}	-	0.725	-

Abbreviations: T2DM-type 2 diabetes mellitus; CRP-C-reactive protein; FBG-fasting blood glucose; HbA1c-glycated haemoglobin; Rho-Spearman's coefficient of correlation; p-probability.

[†]correlation is significant at 0.01 level. ^{††}correlation is significant at 0.05 level

and fibrinogen in blood were increased in both male and female T2DM patients. The median blood values of CRP and fibrinogen had tendency to be higher in female T2DM compared to male patients, without statistical significance.

Analyses of CRP and fibrinogen correlation and association of inflammatory markers with glycemic control parameters in the blood of male and female patients are presented in Table 2. Significant positive correlation was found between inflammatory markers in females while glucose and CRP correlated significantly in male diabetic patients. The insignificant correlations were found between inflammatory markers and glycemic control parameters in female patients. In male T2DM patients, no significant correlations were observed between blood values of CRP and fibrinogen and between fibrinogen and HbA1c (Table 2).

Discussion

Poorly controlled diabetes with elevated CRP and fibrinogen was found in the patients studied. Analysis of sex-related difference in achieving glycemic control has shown that male patients had a higher glucose values than females. A poorer long-term glycemic control was noted in female patients but sex-related differences were not statistically different. A separate analysis of CRP and fibrinogen in females and males has revealed a higher value in female patients. Gender related differences in CRP and fibrinogen were insignificant, but positive correlations between CRP and fibrinogen values in females ($p < 0.01$) and glucose and CRP in males ($p < 0.05$) were found. The mechanisms associated with insulin resistance and accelerated atherosclerosis development in patients with T2DM include impaired vasodilatation, increased oxidative stress, low-grade inflammation and thrombus formation, just to name a few.¹³

Inflammation markers are indicators of risk for cardiovascular complications development in diabetic patients. CRP and fibrinogen are hallmarks of the chronic inflammation and indicators of adipose dysfunction and insulin resistance.¹⁴ There are published data that the relative risk for cardiovascular disease onset is more pronounced in female diabetic patients compared to male.¹⁵ Lakoski and associates have shown a higher blood value of high sensitivity CRP (hs-CRP) in women compared with men and this gender difference was maintained across all ethnic subgroups.¹² The results of Lai and associates and Ahonen and coauthors studies have shown the existence of stronger association of elevated hs-CRP concentration and metabolic syndrome in women.^{16,17} A higher circulating levels of CRP in women are well established and can be related to differences in visceral and subcutaneous fat and oestrogen levels.^{18,12,19,20} Study of Ilić and associates have shown that women with T2DM and clinically manifest coronary artery disease have more prominent lipid and inflammatory disorder and they are more susceptible for cardiovascular complication development.¹⁴ A reduced susceptibility to plasmin degradation and increase of fibrinogen synthesis

rate are possible mechanisms of elevated fibrinogen in diabetic patients.²¹ Study of Alzahrani and associates found higher values of fibrinogen in female T2DM patients compared to male patients. They have shown the existence of variant type of clots with compromised fibrinolysis in female T2DM patients. There was gender specific association between clotting parameters and cardiometabolic risk factors in this population.²²

The results obtained implicate the need for further evaluation of gender difference in these markers by larger study group and use of high sensitivity immunoassays. The findings in this study showed that the presence of elevated CRP and fibrinogen indicates the existence of inflammation in T2DM patients as possible risk factors for complication development. Female patients had tendency for higher values of both inflammatory markers in the blood, but the differences were not statistically significant.

Authorship statement

SH takes full responsibility for the study design, the manuscript writing and accuracy of the data analysis, MD is responsible for data collection, DK, DDS are responsible for data interpretation and critical revision of the manuscript.

Financial disclosure

We declare that we have no conflict of interest.

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C-reaktivni protein i fibrinogen u tipu 2 diabetes mellitus-a

APSTRAKT

Uvod. Hronična inflamacija niskog stepena je značajna za razvoj i progresiju tip 2 diabetes mellitus-a (T2DM). Pokazatelji inflamatorne aktivnosti su povišene vrijednosti proteina akutne faze u cirkulaciji kao što su C-reaktivni protein (CRP) i fibrinogen. Cilj studije je bio ispitati postojanje spolnih razlika u vrijednostima CRP-a i fibrinogena u krvi pacijenata sa T2DM.

Metode. U presječnoj studiji je uključeno 40 pacijenata oboljelih od T2DM, oba spola (19 muškaraca, 21 žena), medijana starosne dobi je bila 70 (36-90) godina. Pacijenti su bili hospitalizirani na Klinici za endokrinologiju, Kliničkog centra Univerziteta u Sarajevu. Standardnim laboratorijskim metodama su određivani nivoi glukoze na tašte, glikiranog hemoglobina, fibrinogena i CRP-a. Podaci su statistički obrađeni sa SPSS 19. programom.

Rezultati. Medijane vrijednosti CRP-a i fibrinogena u krvi nisu bile statistički značajno različite između T2DM pacijenata ženskog i muškog spola, i ako je postojala tendencija viših vrijednosti kod žena u odnosu na muškarce. [17.30 (3.40-61.35) mg/l vs. 9.60 (3.50-28.90) mg/l; $p=0.573$]; [5.70 (4.20-6.35) g/l vs. 3.80 (3.60-6.00) g/l; $p=0.078$]. Pozitivna korelacija je utvrđena između CRP-a i fibrinogena kod T2DM pacijenata ženskog spola ($\rho=0.606$; $p<0.01$).

Zaključak. Povišene vrijednosti CRP-a i fibrinogena ukazuju na prisutnu inflamaciju kod pacijenata oboljelih od T2DM. Utvrđene su više vrijednosti oba inflamatorna markera u krvi pacijenata ženskog spola, ali statistički značajne razlike nisu dokazane.

KLJUČNE REČI

Diabetes mellitus tip 2; upala; C-reaktivni protein; fibrinogen.