

## Importance of inflammatory markers and IL-6 for diagnosis and follow up of patients with type 2 diabetes mellitus

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### ABSTRACT

**Aim** To analyse the long-term impact of altered metabolism on the level of mediators of inflammatory response in female patients with type 2 diabetes.

**Methods** This study included 97 female patients with type 2 diabetes and 107 female, nondiabetic control subjects, who were recruited at the Clinical Centre University of Sarajevo and the General Hospital Tešanj. The effects of glycaemic control on markers of inflammatory response represented by C-reactive protein (CRP), fibrinogen, leukocytes, sedimentation rate, and cytokine IL-6 were tested. All subjects were free of evidence of infections, surgery, thyroid disease, polycystic ovarian syndrome, active liver and kidney damage. All biochemical analyses were performed according to standard International Federation of Clinical Chemistry (IFCC) protocols.

**Results** A significant increase of fibrinogen ( $p < 0.001$ ), CRP ( $p = 0.001$ ), interleukin-6 ( $p = 0.013$ ), leukocytes ( $p < 0.001$ ) and sedimentation rate ( $p = 0.008$ ) in diabetic female population compared to control subjects was found. A significant correlation between CRP and haemoglobin A<sub>1c</sub> ( $p = 0.035$ ), interleukin-6 and glucose ( $p = 0.032$ ), IL-6 and body mass index ( $p = 0.007$ ) was found.

**Conclusion** Our data suggest that inflammation plays an important role in the pathogenesis of diabetes in female diabetic population. A more detailed study on a far larger number of subjects is needed if they were to be used effectively as biomarkers in the primary prevention of type 2 diabetes in this population.

**Keywords:** inflammation, cytokine, hyperglycaemia

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## INTRODUCTION

Type 2 diabetes (T2D) is a major global health problem affecting 415 million people (215 million of men and 199 million of women). It is considered that this number will rise to 642 million in 2040. Of these, 90-95% of cases are T2D (1,2). The tendency of increase of T2D epidemic is present throughout the world, especially in Europe, Southern America, Africa and East Asia. According to the International Diabetes Federation in Bosnia and Herzegovina estimated prevalence of diabetes is 10% with a tendency of continuous increase (3).

As the rates of diabetes increase it is important to study factors associated with late diagnosis of diabetes and whether these determinants differ for males and females. In this sense, it is very important to recognize risk factors for diabetic complications as soon as possible. This is especially the case for female diabetic population since, according to newest data, even though more males have diabetes, females with diabetes have a greater risk of mortality and hospitalizations (4).

Recent research suggests that inflammation could be a crucial factor in the development of a disease that has reached epidemic proportions worldwide. Due to metabolically provoked changes in diabetes, primarily at the cellular level, altered functionality of cells and tissues is to be expected, with proper manifestations at the level of inflammatory reaction and all its components, including inflammatory parameters (high sensitivity C reactive protein (hsCRP) and fibrinogen), mediators, and inflammation regulators (cytokines) (5).

Differences between sexes in the diabetes risk associated with inflammatory markers have been reported in various studies (6-8). Studies on woman population have revealed that CRP was more strongly associated with type 2 diabetes when compared to interleukin-6 (IL-6) (9,10). However, other authors have published contradictory results. Findings in non-obese subjects prove that body fat content is the main predictor of fibrinogen levels as well of hsCRP levels thus supporting the speculation of direct mechanism by which adipose tissue regulates the levels of circulating acute phase reactants (11).

The aim of the study was to analyse the level of inflammatory markers hsCRP, IL-6 and leukocyte count, sedimentation rate as well as anthropometric parameters in a group of female patients

with diabetes type 2 and a group of healthy controls, and to correlate their values with the parameters of glycoregulation such as haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), and fasting glycaemia.

## PATIENTS AND METHODS

### Patients and study design

A total of 204 subjects were enrolled in the study: 97 patients with T2D, recruited from the Clinical Centre University in Sarajevo and General Hospital Tešanj, and 107 female, control nondiabetic patients.

Subjects included in this study were free of evidence of active liver and kidney disease, chronic pancreatitis, gastrointestinal disease, inflammatory bowel disease, endocrine disorders, infection, and were not using hormonal therapy. Non-diabetic controls were of approximately same age (40-60 years old) having normal glucose tolerance (fasting plasma glucose less than 6.2 mmol/L, and two hours postprandial glycaemia less than 7.8 mmol/L). They also had no abdominal obesity as a criteria for insulin resistance.

Each participant gave a written informed consent. The study was performed in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Cantonal Hospital Zenica and International University of Sarajevo.

### Methods

In all the subjects arterial blood pressure and body parameters as height, weight and waist circumference were measured. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest (10). Blood samples were drawn after an overnight fast, at least for 8 hours. HbA<sub>1c</sub> was measured in the whole blood by immunoturbidimetry method using the autoanalyser Dimension X Pand (Siemens, München, Germany). hsCRP was measured at the same autoanalyser with nephelometric method. Fibrinogen was determined using nephelometric method, modified Claus principle in Behring Coagulation Systems (12). For determination of IL-6, flow cytometry was used. For the assay for IL-6, particles with defined fluorescence intensity were used for the detection of soluble cytokine at very low concentrations (10-2500 pg/mL) (Human IL-6 Flex Set, BD™ Cytometric Bead Array)(13).

**Statistical analysis**

Before statistical analysis, normal distribution and homogeneity of the variances were tested using Kolmogorov-Smirnov test respectively. Groups were compared using Student's unpaired t test for parameters with normal distribution or Mann-Whitney test for parameters with non-normal distribution. Correlations between parameters were analysed using the Pearson R test for variables with normal distribution and the Spearman test for variables with non-normal distribution. Data are expressed as mean±standard deviation or medians (interquartile range).  $p < 0.05$  was considered significant.

**RESULTS**

A group of 97 patients with type 2 diabetes mellitus (age>40 years) and 107 healthy controls (age>40 years) were studied (Table 1).

**Table 1. Anthropometric, clinical and biochemical characteristic of female patients with type 2 diabetes mellitus (T2D) and control subjects\***

Characteristic	Healthy controls (n=107)	T2D patients (n=97)	p
Age (years)	55 (53-58)	57 (53-61)	0.282
BMI (kg/m <sup>2</sup> )	26.30 (23.90-27.90)	29.80 (26.80-33.00)	< 0.001†
Waist circumference (cm)	0.88 ± 0.05	0.93 ± 0.07	< 0.05*
Fasting glucose (mmol/L)	4.95 (4.67-5.30)	7.90 (6.95-9.07)	< 0.001†
HbA <sub>1c</sub> (%)	5.05 (2.76-5.40)	7.30 (6.80-8.50)	< 0.001†
hsCRP (mg/L)	2.20 (1.02-3.78)	3.10 (1.92-5.00)	0.001†
Fibrinogen (g/L)	3.28 (2.90-3.50)	3.70 (3.20-4.30)	< 0.001†
IL-6 (pmol/L)	1.23 (0.41-1.90)	1.75 (1.22-3.29)	0.013†
Leukocytes (10 <sup>9</sup> L)	6.00 (4.73-7.23)	7.00 (5.72-8.60)	< 0.001†
Sedimentation rate	10 (5-16)	15 (9-24)	0.008†

\*Data are presented as means ± SD or medians (interquartile range); †Significance of difference in Mann-Whitney test for data following non-normal distributed and t-test for normal distributed date. T2D-Type 2 diabetes mellitus; BMI, body mass index; HbA<sub>1c</sub>, haemoglobin A<sub>1c</sub>; IL6, interleukin-6; hsCRP, high-sensitivity C-reactive protein

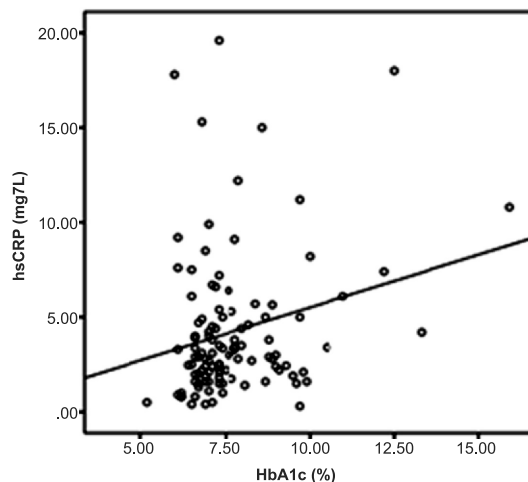
The criteria for the selection of subjects were based on levels of fasting glucose and HbA<sub>1c</sub>. The levels of hsCRP, fibrinogen, IL-6, white blood cell count and sedimentation were determined for all the study participants.

Subjects with T2D were older than subjects without diabetes. The mean age of the subjects in the study group (cases) was 57 years and the subjects in the control group (controls) were aged 55 years. It was observed that among diabetics the mean of body mass index (BMI) (29.80) and waist-hip ratio (WHR) (0.93) were significantly higher compared to non-diabetics ( $p < 0.05$ ), whereas no significant difference was noted in relation to age ( $p = 0.282$ ) among diabetics and non-diabetics. Subjects with T2D had significantly higher fasting plasma glucose and HbA<sub>1c</sub> than those without it (mean value 7.90 versus 4.95 and 7.30 versus 5.05, respectively).

Median levels of IL-6, fibrinogen and hsCRP were significantly higher in diabetic patients: 1.75 versus 1.23 pmol/L for IL-6, 3.70 versus 3.28 g/L for fibrinogen and 3.10 versus 2.20 mg/L for hsCRP ( $p = 0.013$  for IL-6,  $p < 0.001$  for fibrinogen and  $p = 0.001$  for hsCRP).

T2D subjects showed a significant increase in white blood cell count and sedimentation rate (7.00 x 10<sup>9</sup>/L versus 6.00 x 10<sup>9</sup>/L for leukocytes ( $p < 0.001$ ) and 15 versus 10 for sedimentation rate ( $p = 0.008$ ), respectively)

HbA<sub>1c</sub> was positively correlated with hsCRP with a significant p of 0.035 (Figure 1) and BMI was positively and significantly correlated with IL-6 ( $p = 0.007$ ) and fibrinogen ( $p = 0.029$ ) (Figure 2, 3). The glucose levels of the patients was significantly correlated with IL-6 ( $p = 0.032$ ) (Figure 4).



**Figure 1. Correlation between serum levels HbA<sub>1c</sub> and hsCRP in female patients with type 2 diabetes mellitus (T2D)**

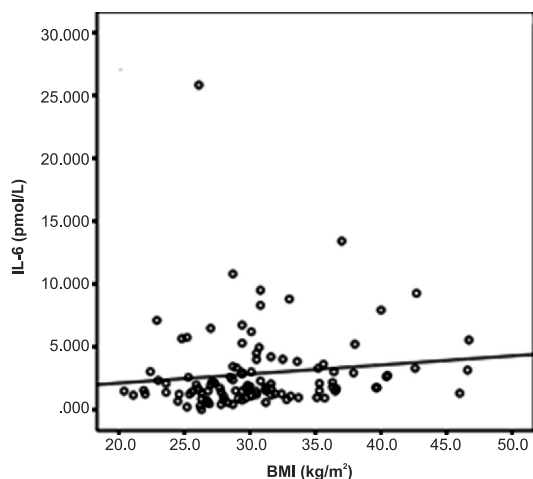


Figure 2. Correlation between serum levels IL-6 and body mass index (BMI) in female patients with type 2 diabetes mellitus (T2D)

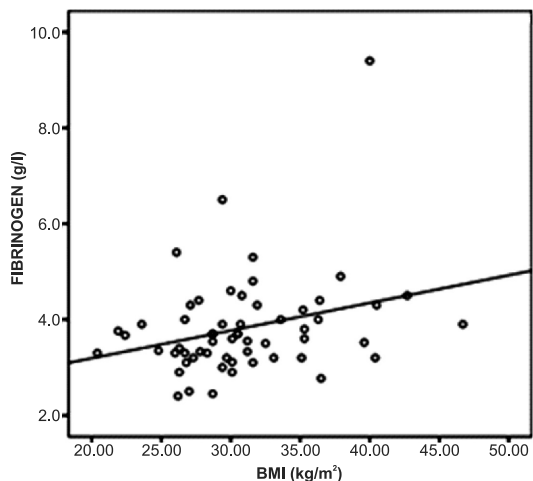


Figure 3. Correlation between serum levels fibrinogen and body mass index (BMI) in female patients with type 2 diabetes mellitus (T2D)

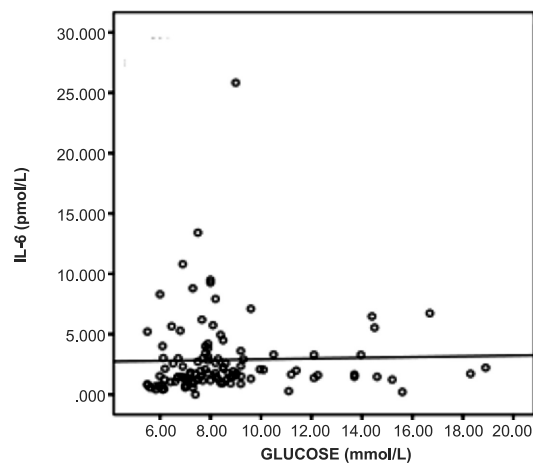


Figure 4. Correlation between serum levels IL-6 and glucose in female patients with type 2 diabetes mellitus (T2D)

## DISCUSSION

It is known for T2D that the concentration of many proteins of the acute phase (CRP, fibrinogen,  $\alpha_1$ -acid glycoprotein, plasminogen activator inhibitor-1, IL-1, IL-6 and tumour necrosis factor-alpha (TNF $\alpha$ ) is increased and that this increase correlates with the development of characteristics associated with this condition (obesity, insulin resistance, impaired glucose tolerance and/or diabetic complications) (14,15), which has been proved in our study.

This research tackled dynamic changes in concentrations of proinflammatory and anti-inflammatory cytokines, concerning change and dynamic course of parameters of inflammation in female patients with T2D. The levels of all of the measured inflammatory parameters (hsCRP, fibrinogen, IL-6, sedimentation, and the white blood cell count) were statistically higher in female T2D patients compared to healthy female population. Already in the 1990s, research on this subjects demonstrated that levels of markers of inflammatory reactions increased with the decrease in insulin sensitivity depending on the severity of T2D and metabolic syndrome (16).

Studies conducted for both sexes have demonstrated the importance of inflammatory mediators in the pathogenesis of T2D, and also that levels of IL-6 rise significantly in both sexes compared to control group even after adjustment for BMI, WHR and smoking, being considered an independent predictor of risk of developing diabetes (17,18). Studies conducted on female population have associated elevated levels of IL-6 and CRP with T2D independent of BMI, physical activity and other risk factors for T2D, provided that CRP is considered to be the most robust predictor (9). However, the results of a Mexico City study group suggest that CRP is an important predictor for the development of T2D and the metabolic syndrome for female, but not male population (19). Magnitude of association between CRP and diabetes seems comparable and even stronger than the association between CRP with coronary heart disease (20,21). These data support the hypothesis that systemic inflammation is a common precursor for T2D (14,22), which is in line with our results. It is believed that IL-6 contributes to the pathology and physiology of T2D through its interactions with insulin-signalling pathways and  $\beta$ -cell

function by stimulating production of CRP in liver (23). In accordance with studies conducted by Pradhan et al. (24) and Mirza et al. (15), it is considered that the predictive role of IL-6 in diabetes is less consistent than the role of CRP, because of greater stability of CRP as an inflammation marker in comparison to IL-6 whose effects are modulated by TNF $\alpha$  production (9). However, in our study, IL-6 concentrations were significantly associated with the levels of glucose, suggesting a role of IL-6 in the process of insulin secretion under certain conditions such as high glucose concentrations, high IL-6 levels or being in synergy with other inflammatory mediators (23). An activation of the immune system and inflammation leads to elevated levels of inflammatory markers, not just cytokines but also leukocytes, as well as to accelerated erythrocyte sedimentation rate (25). Based on the above, one might support the hypothesis that inflammation markers, such as leukocytes and fibrinogen, as well as the erythrocyte sedimentation rate, plasminogen activator inhibitor-1, gamma globulins, and albumin concentration have an extremely important role in the pathogenesis of T2D (26). Ever since Vazarova et al. discovered a positive relationship between the white blood cell count and onset of insulin resistance, their potential mechanisms have been a matter of debate (27). The only possible explanation for elevated white blood cell count and increased insulin resistance lies in the potential activation of the immune system, through IL-6, which is considered to be a potent factor in differentiation of leukocytes, thus associating them with insulin resistance (28,29). In recent years, it has been shown that insulin resistance is associated with CRP levels and the amount of visceral fat, but the relationship is very complex (30). Excessive metabolic activity of visceral fat is associated with insulin resistance, hypercoagulability, dyslipidaemia, hypertension and cardiovascular risk (31). Fat appears to be the most active tissue metabolically that secretes many hormones and cytokines (adipokines, TNF $\alpha$ , IL-6, monocyte chemoattractant protein-1), which participate in inflammatory reactions. Fat tissue is also considered as an important source of inflammation in obese diabetic patients not only because of cytokines secretion from adipocytes, but also because of the infiltration of proinflam-

matory macrophages (32). Our results seem to support these findings.

Interestingly, results of our study showed a high degree of correlation between inflammatory markers (CRP, fibrinogen and IL-6) and BMI. In previous studies, fibrinogen levels were positively correlated with BMI as well as with other components of the metabolic syndrome and a history of diabetes or hypertension in general (33). This could potentially justify the link between BMI and T2D is the presence of insulin resistance, which is considered to be responsible for the elevated levels of inflammatory parameters (34). Strikingly, the association of BMI with fibrinogen levels in women was proven to be approximately two times stronger than in men (35). Our study pointed out the likelihood of elevated CRP concentrations increasing with increase in HbA<sub>1c</sub> levels in female population, thus, further supporting the association demonstrated in previous studies between glycaemic control and systemic inflammation in people with established diabetes (36-38).

In conclusion, our results support the hypothesis that systemic inflammation in moderate, high or subclinical intensity is always present in clinical course of T2D, and the positive correlation between IL-6 and glucose level as well as other inflammatory markers was shown.

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#### TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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## Značaj inflamatornih markera i IL-6 u dijagnozi i praćenju pacijenata s dijabetes melitusom tipa 2

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### SAŽETAK

**Cilj** Analizirati dugoročni utjecaj izmijenjenog metabolizma na nivoe medijatora upalnog odgovora kod žena s dijabetesom tipa 2.

**Metode** Istraživanje je obuhvatilo 97 pacijentica s dijabetesom tipa 2 i 107 žena bez dijabetesa (kontrola) koji su „regrutovani“ na Kliničkom centru Univerziteta u Sarajevu i Općoj bolnici Tešanj. Ispitivani su učinci kontrole glikemije na markere upalnog odgovora mjerenjem nivoa C-reaktivnog proteina (CRP), fibrinogena, leukocita, brzine sedimentacije i citokina interleukina-6. Svi ispitanici su bili bez dokaza o infekcijama, ranijim kirurškim procedurama, bolestima štitnjače, sindromu policističnih jajnika, aktivnom oštećenju jetre i bubrega. Sve biohemijske analize su provedene korištenjem standardnih protokola Internacionalne federacije kliničke hemije (IFCC).

**Rezultati** Utvrđeno je značajno povećanje fibrinogena ( $p < 0.001$ ), CRP ( $p = 0.001$ ), interleukina-6 ( $p = 0.013$ ), leukocita ( $p < 0.001$ ) i brzine sedimentacije ( $p = 0.008$ ) u pacijentica s dijabetesom u usporedbi s kontrolnim ispitanicima. Ustanovljena je signifikantna korelacija između CRP i hemoglobina A1c ( $p = 0.035$ ), interleukina-6 i glukoze ( $p = 0.032$ ), te interleukina-6 i indeksa tjelesne mase ( $p = 0.007$ ).

**Zaključak** Rezultati ovog istraživanja sugeriraju da upala igra važnu ulogu u patogenezi dijabetesa kod dijabetičara ženskog spola. Da bi se ispitivani markeri mogli učinkovito koristiti kao biomarkeri u primarnoj prevenciji dijabetesa tipa 2 u ovoj populaciji, potrebna je detaljnija studija s daleko većim brojem ispitanika.

**Ključne riječi:** inflamacija, citokin, hiperglikemija