ORIGINAL ARTICLE

# Influence of C-reactive protein on the occurrence and assessing of albuminuria severity in diabetics

**Lamija Pojskić[1], Sabaheta Hasić[2], Ema Tahto[3], Vildana Arnautović-Torlak[1], Belma Pojskić[1]**

[1]Department of Internal Diseases, Cantonal Hospital Zenica, Zenica [2]Department of Medical Biochemistry, Faculty of Medicine, University of Sarajevo, Sarajevo [3]Clinic for Cardiovascular Surgery, University Clinical Center Tuzla, Tuzla; Bosnia and Herzegovina

## ABSTRACT

**Aim** To asses relation of serum high sensitive C-reactive protein (hsCRP) level with albumin concentration in daily urine in patients with diabetes mellitus type 2 (T2DM).

**Methods** The prospective study included 69 patients with T2DM, both sexes (24 males, 45 females), aged 30-82 years. They were divided into two groups: patients with T2DM and normoalbuminuria (T2DM-NA; n=40) and patients with T2DM and microalbuminuria (T2DM-MA; n=29). Patients were hospitalized at the Department of Internal Medicine, Cantonal Hospital Zenica, in the period January-April 2014. Immunonephelometry measurement of hsCRP was performed on the Nephelometer Analyzer BN II (Siemens, Germany).

**Results** Frequency of patients in T2DM-NA and T2DM-MA groups was not significantly different in relation to sex and age. There was significant difference in relation to duration of diabetes ( p=0.001). Average glucose and HbA1c levels were significantly higher in T2DM-NA group comparing to T2DM-MA group (p=0.008 and p=0.047, respectively). Serum creatinine (p=0.011), urea (p=0.009) and hsCRP (p=0.005) were significantly higher in T2DM-MA group compared to T2DM-NA group. Urinary albumin showed significantly positive correlation with the hsCRP (rho=0.286; p=0.017), urea (rho=0.503) and creatinine (rho=0.438) (p<0.0005). A one unit (mg/L) increase in hsCRP concentration was associated with 11.5% increase of odds of microalbuminuria OR=1.115; 95% CI 1.014-1.225; p=0.025).

**Conclusion** Significantly higher values of serum hsCRP in patients with type 2 diabetes mellitus and microalbuminuria in comparison to those with normoalbuminuria as well as the correlation of values of inflammatory marker with urinary albumin implicate a low grade inflammation in the progression of diabetic nephropathy.

**Key words:** diabetic nephropathy, endothelium, inflammation

**Corresponding author:**
Lamija Pojskić
Department of Internal Diseases, Cantonal Hospital Zenica
Crkvice 67, 72000 Zenica, Bosnia and Herzegovina
Phone +387 32 222 052;
fax: +387 32 226 576;
E-mail: lamija.pojskic@gmail.com
ORCID ID: orcid.org/0000-0002-1728-0649

**Original submission**:
27 June 2017;
**Revised submission:**
13 August 2017;
**Accepted:**
10 October 2017
doi: 10.17392/919-18

Med Glas (Zenica) 2018; 15(1):

## INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine disorders affecting nearly 6% of the world's population (1). It is believed that by 2030 the number of patients is likely to rise to 360 million (2) and more than 97% of patients will suffer from type 2 diabetes mellitus (T2DM) (1). Diabetes is a major cause of early morbidity and mortality in the world (3) and is the leading cause of renal failure, non-traumatic amputations and blindness in adults (2). Chronic hyperglycemia causes irreversible structural and functional changes in cells leading to the development of microvascular and macrovascular complications (4). Poor blood glucose control increases the risk of complications of diabetes causing endothelial dysfunction; low level vascular inflammation (subclinical inflammation), defined using C-reactive protein (CRP) value and microalbuminuria (5). The main characteristic of endothelial dysfunction is a low-grade chronic vascular inflammation (subclinical inflammation). Endothelial dysfunction and subclinical inflammation play a key role in the pathophysiology of atherosclerosis and are associated with microalbuminuria (6,7). C-reactive protein is one of the most sensitive markers of subclinical inflammation, and its serum concentration is an indicator of intensity of low-grade chronic inflammation of the arterial wall (5). Microalbuminuria (albumin in 24-hour urine between 30-300 mg) is one of the first symptoms of diabetic nephropathy (DN), and it progresses to macroalbuminuria (> 300 mg in 24-hour urine) and renal failure (2). Measurement of total albuminuria in 24-hour urine is the gold standard for early detection of nephropathy and its prevention (8), and the most sensitive prognostic factor for assessing the risk of developing clinical nephropathy (proteinuria / macroalbuminuria) (4). Microalbuminuria is associated with an increased risk of cardiovascular events and increased mortality (2).

Some prior studies have shown significant correlation between CRP and microalbuminuria (9-11) but other studies have conflicting results (12,13). Early detection of microalbuminuria in diabetics can significantly reduce the progression of renal complications (14). Although microalbuminuria remains the gold standard marker for early detection of diabetic nephropathy, it is not routinely done in our patients. We decided to investigate a correlation between hsCRP, sensitive marker of inflammation, and microalbuminuria in order to establish its impact on the development of microalbuminuria in diabetics. Advantage of CRP is that it is a stable compound and it can be measured at any time of the day (15).

Since microalbuminuria and CRP are markers of low-grade inflammation, which is present in T2DM, the aim of this study was to explore the values and mutual correlation of CRP with the albuminuria values in T2DM, influence of CRP on the albumin concentration in 24-hour urine, as well as the occurrence of microalbuminuria in patients with T2DM.

## PATIENTS AND METHODS

### Patients and study design

A prospective clinical comparative descriptive study included 84 patients of both genders (31 males and 53 females), aged 30-82 years. All T2DM patients were admitted at the Department of Internal Medicine, Cantonal Hospital in Zenica (CHZ) in the period 24 January to 25 April 2014. Patients with diagnosed type 1 diabetes mellitus, patients with new-onset T2DM and patients with chronic or acute systemic inflammatory diseases, infectious or septic conditions were excluded from this study. Based on the given exclusion and inclusion criteria, the final sample included 69 T2DM patients. Participants were divided into two groups: 40 patients with T2DM and normal albuminuria (T2DM-NA) and 29 patients with T2DM and microalbuminuria (T2DM-MA). Monitored parameters included age, gender, type of therapy for diabetes (oral antidiabetic drugs or insulin therapy), creatinine, urea, HbA1c, blood glucose (random sample), high-sensitivity CRP (hsCRP), and albumin in a 24-hour urine.

The study was approved by the Ethics Committee of the Cantonal Hospital in Zenica.

### Methods

Biochemical analyses (creatinine, urea, hsCRP, albumin in 24-hour urine) were performed at central laboratory CHZ. Jaffé kinetic reaction without deproteinization for creatinine measurement, kinetic method with urease and glutama-

te dehydrogenase for the urea measurement, and the hexokinase enzymatic method for blood glucose measurement were performed using Cobas Integra 400 plus (Roche Ltd., France) analyzer. Immunonephelometry measurement of hsCRP was performed on the Nephelometer Analyzer BN II (Siemens, Germany). HbA1c was measured by turbidimetric inhibition immunoassay (TINIA) using Dimension Clinical Chemistry System analyzer (Siemens, Germany). The 24 urinary albumin measurement was performed using immunoturbidimetric method (PETINIA), and an analysis was performed using the Dimension Clinical Chemistry System analyzer (Siemens, Germany). Albumin concentrations in 24-hour urine (UA, urinary albumin) were calculated according to the formula (16): UA = albumin (mg/L) x volume of 24-hour urine. Albuminuria was defined as following: normal albuminuria with albumin level of <30 mg/24-hour urine, microalbuminuria with 30-300 mg/24-hour urine, macroalbuminuria with >300 mg/24-hour urine.

### Statistical analysis

The following statistical tests were used: the parametric t test for independent sample or non-parametric Mann Whitney U test, Yates' corrected version of Pearson's chi-squared test, Spearman's test, multiple linear regression analysis, binary regression analysis. Significance level of $p<0.05$ was used.

## RESULTS

Patients in T2DM-MA group were older than patients in T2DM-NA group, but the difference was not significant ($p>0.05$). Both glycated hemoglobin (HbA1c) value and average value of blood glucose (random sample) were significantly higher in patients assigned to T2DM-NA group versus patients in T2DM-MA group ($p<0.05$). There was a statistically significant difference between the two groups according to the type of therapy for diabetes $p<0.05$ (Table 1).

The average urea level was significantly lower in T2DM-NA group, with value of 6.35 (5.10 to 7.35) mmol/L compared to those with microalbuminuria (T2DM-MA) group with value of 7.50 (5.45-14.1) mmol/L ($p=0.009$). The average creatinine level was significantly lower in T2DM-NA group, with value of 90 (83.25 - 105.50) μmol/L compared to those with T2DM-MA group with value of 101 (91.50 - 120) μmol/L ($p=0.011$) (Figure 1).

**Table 1. Baseline characteristics of the diabetes mellitus type 2 (T2DM) patients**

| Variables | Patients | | p |
|---|---|---|---|
| | T2DM-NA (N=40) | T2DM-MA (N=29) | |
| **Age (years)** | 61.80±12.37 | 66.79±8.30 | 0.064 |
| **Gender** | | | |
| **Females No (%)** | 23 (57.5) | 22 (75.9) | 0.185 |
| **Males No (%)** | 17 (42.5) | 7 (24.1) | |
| **UA (mg/dU)** | 9 (5.32-14,9) | 113 (61.35-200.35) | < 0.0005 |
| **Illness duration (years)** | 7±5.39 | 11.72±6.14 | 0.001 |
| **Blood glucose (mmol/L)** | 15.35 (11.55-23.78) | 11.40 (9.35-14.50) | 0.008 |
| **HbA1c (%)-** | 10.32 ± 2.42 | 9.22 ± 1.90 | 0.047 |
| **T2DM therapy** | | | |
| **Oral (hypoglycemic drugs) No (%)** | 21 (52.5) | 7 (24.1) | 0.034 |
| **Insulin No (%)** | 19 (47.5) | 22 (75.9) | |

T2DM-NA, patients with type 2 diabetes mellitus and normal albuminuria; T2DM-MA, patients with type 2 diabetes mellitus and microalbuminuria; UA, urinary albumin concentration in milligram per 24-hour (daily) urine

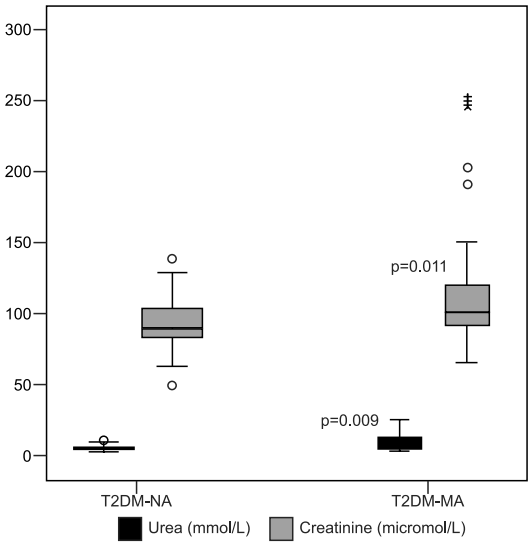


**Figure 1. The difference in serum urea and creatinine level in patients with type 2 diabetes mellitus, depending on the type of albuminuria**

Urea levels (mmol/L) and serum creatinine levels (mmol/L) are presented as median range of 25-75 percentile. The vertical lines represent the range of minimum and maximum values. Star rating and circles designate extreme values in the group.
T2DM-NA, patients with type 2 diabetes mellitus and normal albuminuria; T2DM-MA, patients with type 2 diabetes mellitus and microalbuminuria;

In the patients with type 2 diabetes mellitus urinary albumin had a positive significant correlation with urea level (Rho = 0.503; $p<0.0005$) and creatinine (Rho = 0.438; $p<0.0005$).

The average serum hsCRP was significantly lower in T2DM-NA group, with the value of 3.45 (3.45 - 4.53) mg/L compared to those with microalbuminuria (T2DM-MA group) with the value of 4.93 (3.45 - 11.15) mg/L (p=0.005). The minimum value of hsCRP in T2DM patients with normal albuminuria was 3 mg/L, and a maximum value was 34 mg/L. In patients with microalbuminuria minimum hsCRP value was 3.45 mg/L, and the maximum value was 29.20 mg/L (Figure 2).

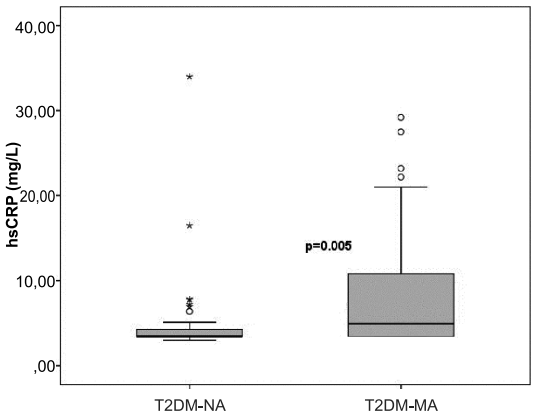


**Figure 2. Serum levels of C-reactive protein in patients with diabetes mellitus type 2 depending on type of albuminuria**
Serum hsCRP levels (mg/L) are presented as median range of 25-75 percentile. The vertical lines represent the range of minimum and maximum values. Star rating and circles designate extreme values in the group.
hsCRP, high sensibility C-reactive protein; T2DM-NA, patients with type 2 diabetes mellitus and normal albuminuria; T2DM-MA, patients with type 2 diabetes mellitus and microalbuminuria;

Examination of serum hsCRP to urinary albumin concentration ratio revealed a weak, positive correlation as Rho = 0.286; p=0.017 (Figure 3).

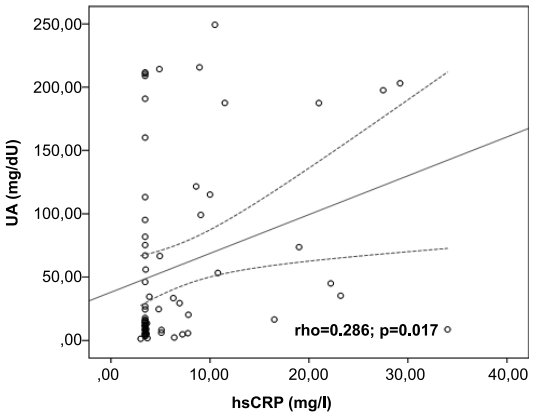


**Figure 3. Association of high sensitivity C-reactive protein and urinary albumin in type 2 diabetes mellitus patients**
The solid line represents a regression line. Dashed line represents 95% confidence interval for the regression line;
Rho, Spearman's rank correlation coefficient; hsCRP, high sensitivity C-reactive protein; mg/dU, milligram per 24-hour urine;

Binary regression analysis showed that increasing CRP level in T2DM patients significantly increased likelihood of microalbuminuria occurrence (p=0.025). Odds ratio indicated that any increase of CRP by 1 mg/L would increase the risk for microalbuminuria by 11.5%, with 95% confidence interval (95%CI: 1.014 - 1.225).

## DISCUSSION

Diabetes mellitus is a very complex condition with disturbed metabolism of carbohydrates, lipids and proteins, and thus with altered expression of certain biomarkers that interact with each other (17,18). In our study we found a relation between low-grade inflammation, reflected through CRP values and microalbuminuria in diabetic patients.

Average random blood glucose levels and HbA1c values were significantly higher in T2DM-NA group compared to the patients with microalbuminuria. In studies conducted by Sheikh et al. (19), as well as by Kassab et al. (20), a statistically significant positive correlation between HbA1c and microalbuminuria was shown. On the other side, Patil et al. (21) found no statistically significant difference in blood glucose level in patients with normal albuminuria versus microalbuminuria neither in patients with normal albuminuria versus macroalbuminuria, nor in those with microalbuminuria versus macroalbuminuria. One possible reason for poorer glycemic control in the patients with normal albuminuria in our study is the difference in the illness duration between T2DM-NA and T2DM-MA group.

In our study, patients with microalbuminuria had significantly higher urea level and creatinine compared to patients with normal albuminuria, and urinary albumin was positively correlated with the urea level and creatinine. Studies conducted by Stehouwer et al. (7), as well as by Meisinger et al. (22), showed that creatinine was one of the independent risk factors for urinary excretion of albumin. Significantly higher value of urea and creatinine is expected in patients with microalbuminuria, considering that urea/creatinine are markers of kidney injury, as well as of microalbuminuria (2,22). Measurement of serum creatinine, affected by age, sex, and weight, is widely used as an index of renal function (23). Constantly elevated serum creatinine indicates chronic kidney disease, but the screening test has

low sensitivity for early renal disease, because although in some patients there is a significant reduction in glomerular filtration rate (GFR), serum creatinine remains in the normal range (19).

High sensitive CRP values in our study were significantly higher in patients with microalbuminuria compared to T2DM patients with normal albuminuria indicating more intense systemic inflammation in T2DM-MA patients compared to T2DM-NA patients. Also, poor statistically positive correlation between serum hsCRP and urinary albumin concentration was shown. Our results indicate the role of inflammation in the pathogenesis of microalbuminuria and complementary role of CRP. Insulin Resistance - Atherosclerosis Study conducted by Festa et al. (13) showed an association between chronic inflammation and microalbuminuria in diabetics as well as in patients without diabetes. Authors have explained that elevated level of inflammatory markers may be the result of underlying atherosclerosis in patients with microalbuminuria (which is in diabetic patients) as well as in the general population, associated with increased cardiovascular morbidity and mortality; the increase of acute phase proteins and inflammatory cytokines can directly change glomerular function and thus influence the development of microalbuminuria. Finally, it is possible that microalbuminuria and increase of inflammatory proteins have the same cause such as increased production of inflammatory cytokines (13).

Our study showed that increasing CRP levels in T2DM patients significantly increased likelihood of microalbuminuria occurrence. Odds ratio indicated that any increase of CRP by 1 mg/L would increase the risk for microalbuminuria by 11.5%. A study conducted by Kshirsagar et al. (24) showed that the increase of CRP by 1 mg/L has increased the likelihood of the occurrence of microalbuminuria by 2%, and Wang et al. study (25) showed that any increase of CRP by 1 mg/L significantly increased the risk for microalbuminuria by 1.29%.

The presented study confirmed the importance of inflammatory marker CRP, i. e. the existence of a positive relationship between serum CRP with albuminuria severity. Several studies have shown that inflammatory biomarker CRP is an initial factor in atherosclerosis development in DM and that CRP plays role in atherosclerosis progression in DM. It is associated with metabolic syndrome and insulin resistance and may have an impact on the development of potential cardiovascular events (26). There are several mechanisms of chronic inflammation in the DM. One possible mechanism is that hyperglycemia stimulates synthesis of advanced glycation end products (AGEs), which activate macrophages, enhance oxidative stress, and affect the synthesis of inflammatory markers (27). High CRP levels were found in advanced atherosclerosis in diabetic patients, and studies have shown that CRP had likely a pathogenic role on the vascular endothelium (25,28). CRP is a predictor of changes in the albuminuria severity over time (29).

This study was limited by a small sample size as well as inclusion of patients from only one hospital. Potential weakness is the measurement of urinary albumin excretion based on a single-spot urine sample.

The conducted study has confirmed the importance of the observed marker values (CRP) on the occurrence of microalbuminuria in T2DM patients. Also, we found poorer glycemic control in normoalbuminuric patients compared to those with microalbuminuria, which is not in concordance with similar studies (19,20). Uncontrolled glycaemia in T2DM patients is linked with unhealthy eating habits, physical inactivity, nonadherence to medication, and lack of regular blood glucose monitoring (30). However, due to the limited data, this study did not perform subgroup studies for these factors. Thus, these relationships need further investigations by more studies.

The significance of obtained results is reflected in the fact that simple and affordable tests such as the CRP measurement could be used for monitoring of subclinical inflammation intensity in patients with diabetes as an indicator of possible development of DN. It would be ultimately a signal for preventive action and a possible change of therapy to achieve adequate glycemic control to prevent the occurrence of DN and reduce the number of patients with end-stage renal disease (ESRD) treated with chronic hemodialysis.

## FUNDING

No specific funding was received for this study.

## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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