ORIGINAL ARTICLE

UDC: 616.379-008.64:616.12
DOI: https://doi.org/10.2298/VSP201012010M

# Inflammatory cardiovascular risk markers and silent myocardial ischemia in type 2 diabetic patients

## Markeri rizika od kardiovaskularne inflamacije i „tiha" ishemija miokarda kod bolesnika sa dijabetesom melitusom tipa 2

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**Abstract**

**Background/Aim.** A special feature of coronary heart disease (CHD) in patients with type 2 diabetes mellitus (T2DM) is that it is often asymptomatic and occurs as a consequence of cardiovascular autonomic neuropathy. Dysregulation of the autonomic nervous system is associated with elevated values of inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6), which accelerate atherosclerosis and the occurrence of cardiovascular complications in patients with T2DM. The aim of the study was to evaluate the importance of determining inflammatory cardiovascular risk markers IL-6 and hs-CRP in screening for the presence of CHD in asymptomatic patients with T2DM. **Methods.** The study included 169 patients with T2DM without any symptoms and signs of CHD. Ergometric testing proved or ruled out the presence of silent CHD. The levels of hs-CRP and IL-6 were determined by ELISA. **Results.** IL-6 values were significantly higher in patients with a positive ergometric test (6.83 ± 1.99 pg/mL) compared to patients with a negative ergometric test (3.04 ± 1.39 pg/mL) ($p < 0.001$). We also found that hs-CRP values in patients with a positive ergometric test were significantly higher compared to patients with a negative ergometric test (6.37 ± 2.25 *vs* 1.67 ± 1.41 mg/L; $p < 0.001$). Combinations of IL-6 and hs-CRP with age, HbA1c values, and duration of diabetes, presented through three binary logistic regression models, are significant predictors of silent CHD proven by ergometric testing, *ie*, with their increase, the probability of a positive ergometric test also increases ($p < 0.01$). The sensitivity of the associated finding of elevated IL-6 and hs-CRP values in the detection of silent CHD by ergometric testing was 90%, and the specificity was 86%. **Conclusion.** Hs-CRP and IL-6 are significant predictors of silent CHD, and their determination could be recommended for improving cardiovascular risk stratification in asymptomatic patients with T2DM.

**Key words:**
**biomarkers; c-reactive protein; coronary disease; diabetes mellitus, type 2; interleukin-6; prognosis.**

**Apstrakt**

**Uvod/Cilj.** Posebna osobina koronarne bolesti srca (KBS) kod bolesnika sa dijabetesom melitusom tipa 2 (T2DM) je ta da je često asimptomatska i javlja se kao posledica autonomne neuropatije kardiovaskularnog sistema. Disregulacija autonomnog nervnog sistema povezana je sa povišenim vrednostima markera inflamacije, kao što su visoko senzitivni C-reaktivni protein (hs-CRP) i interleukin-6 (IL-6), koji ubrzavaju aterosklerozu i pojavu kardiovaskularnih komplikacija kod bolesnika sa T2DM. Cilj studije bio je da se proceni značaj određivanja markera rizika od kardiovaskularne inflamacije IL-6 i hs-CRP u „skriningu" na prisustvo KBS kod asimptomatskih bolesnika sa T2DM. **Metode.** Studijom je bilo obuhvaćeno 169 bolesnika sa T2DM, bez simptoma i znakova KBS. Ergometrijskim testiranjem dokazano je ili isključeno prisustvo „tihe" KBS. Nivoi hs-CRP i IL-6 određeni su ELISA metodom. **Rezultati.** Vrednosti IL-6 bile su statistički značajno više kod bolesnika sa pozitivnim ergometrijskim testom u odnosu na bolesnike sa negativnim ergometrijskim testom (6,83 ± 1,99 pg/mL prema 3,04 ± 1,39 pg/mL, redom; $p < 0,001$). Utvrđene su statistički značajno više vrednosti CRP kod bolesnika sa pozitivnim ergometrijskim testom u odnosu na bolesnike sa negativnim ergometrijskim testom (6,37 ± 2,25 prema 1,67 ± 1,41

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mg/L, redom; $p < 0{,}001$). Kombinacije IL-6 i hs-CRP sa godinama starosti, vrednostima HbA1c i trajanjem T2D, predstavljene kroz tri binarna logistička regresiona modela, značajni su prediktori „tihe" KBS dokazane ergometrijskim testom, tj. sa njihovim povećanjem verovatnoća pozitivnog ergometrijskog testa takođe se povećava ($p < 0{,}01$). Senzitivnost udruženog nalaza povišenih vrednosti IL-6 i hs-CRP u detekciji „tihe" KBS ergometrijskim testiranjem bila je 90%, a specifičnost 86%. **Zaključak.** Hs-CRP i IL-6 su značajni prediktori „tihe" KBS i njihovo određivanje bilo bi značajno u poboljšanju stratifikacije kardiovaskularnog rizika kod asimptomatskih bolesnika sa T2DM.

**Ključne reči:**
**biomarkeri; c-reaktivni protein; koronarna bolest; dijabetes melitus, tip 2; interleukin-6; prognoza.**

## Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in three out of four type 2 diabetes mellitus (T2DM) patients. A special feature of CVD in patients with diabetes is that it is often asymptomatic and occurs as a consequence of cardiovascular autonomic neuropathy. The absence of pain during ischemic myocardial episodes and atypical and mild symptoms of acute myocardial infarction delay the start of treatment, causing increased morbidity and mortality in patients. It is believed that autonomic dysfunction leads to the development of silent episodes of ischemia and silent infarction in patients with T2DM [1, 2].

Recent studies have shown that autonomic nervous system dysregulation is associated with elevated inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6), and their determination could reflect the severity of atherosclerosis as well as the risk of developing future cardiovascular events in T2DM patients [3, 4].

In order to identify the presence of coronary heart disease (CHD) in asymptomatic patients with diabetes, only an approach based on a detailed assessment of traditional cardiovascular risk factors has been recommended for the time being. Predicting the risk of cardiovascular events occurrence and progression of atherosclerosis and the correlation of inflammatory agents in its progression has increasingly been the focus of research [5, 6]. Traditional risk factors for CVD, such as high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, hypertension, and smoking, explain only a part of cardiovascular risk in T2DM patients [7, 8].

At present, atherosclerosis is considered an inflammatory disease, given the key role of inflammation in all stages of the occurrence and development of the atherosclerotic process, and the inflammatory nature of atherosclerosis is manifested by the correlation of inflammatory marker levels in blood with its occurrence and progression [3, 9]. Vascular complications arise primarily as a consequence of endothelial dysfunction and inflammatory processes that play a role not only in initiation but also in the progression of atherosclerosis. Therefore, it is crucial to determine other risk factors for CVD occurrence, such as progressive inflammatory tissue response to continuous deposition and modification of lipoproteins in the vascular wall [10, 11].

The aim of the study was to evaluate the significance of determining inflammatory markers IL-6 and hs-CRP as atherosclerosis markers during screening for the presence of CHD in asymptomatic patients with T2DM.

## Methods

The study was conducted at the University Clinical Center of the Republic of Srpska as a cross-sectional study, and it included 169 T2DM patients, men (n = 71) and women (n = 98). All subjects underwent ergometric testing and based on the obtained results, they were divided into two groups. The first group consisted of 117 T2DM diabetic patients without the presence of CHD, proven by the absence of symptoms and a negative ergometric test. The second group consisted of 52 T2DM patients with silent ischemic heart disease, proven by a positive stress test.

All subjects underwent an anamnestic interview after which they all gave their written consent to participate in the study. Afterward, a physical examination was performed to define the anthropometric measures. Calculation of body mass index (BMI) for the assessment and monitoring of nutritional status was performed according to Quetelet's formula: BMI = body weight in kg/square of body height in meters ($kg/m^2$). Subjects with T2DM and CHD, with a history of cerebrovascular, peripheral vascular, and malignant diseases were excluded from the study. Moreover, all the subjects who had an acute or chronic infection or who had been receiving corticosteroids or immunosuppressants within their therapy were excluded from our study.

The study was conducted in compliance with the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Ethics Committee of the Republic of Srpska University Clinical Center in Banja Luka gave their consent for approval of the research protocol.

### *CHD diagnosis*

Ergometric testing was performed on a general electric treadmill type T-2100. Testing was performed according to the standard Bruce protocol. The test was evaluated as positive in subjects with horizontal or descending ST-segment depression equal to or > 1 mm for 60–80 ms after the J-point, at least in three successive QRS complexes, as well as in patients who experienced ST-segment elevation during the stress test that was characterized as pathological if it occurred with the same characteristics, as well as ST-

segment depression (> 1 mm, lasts longer than 60–80 ms). The test was defined as positive and negative, and the patients in whom it was described as inconclusive were not considered [12].

*Laboratory analysis*

Biochemical blood tests for laboratory processing were taken in the morning after 12-hour overnight fasting. The total cholesterol, HDL cholesterol, LDL cholesterol, and serum triglycerides were measured directly by homogeneous enzymatic procedure on INTEGRA® 400 plus analyzer manufactured by Roche, and glycosylated haemoglobin (HbA1c) and urine albumin concentration in 24-hour urine by a turbidimetric assay method. Determination of the levels of inflammatory markers hs-CRP and IL-6 was performed using ELISA (R&D Systems, Inc., Minneapolis, USA). It is a quantitative sandwich enzyme-linked immunosorbent assay technique. Blood serum was used for this test. The blood was centrifuged at 3,000 rpm at 4 °C for 15 min and aliquots were stored at -70 °C. A commercial calibrator was used for calibration. Subjects with hs-CRP values above 10 mg/L were excluded from the study because such hs-CRP values indicate the presence of acute inflammatory disease. An hs-CRP value of 1 mg/L indicates low risk for CVD; from 1 to 3 mg/L, moderate risk; from 3 to 10 mg/L, high risk [13]. The lowest level of IL-6 detectability in the serum was 1.5 pg/mL [14]. The coefficients of variation of the test were 5%. Calibrations of the testing instrument were performed as recommended by the manufacturer within the given specifications.

*Statistical analysis*

The data were analyzed using a commercially available statistical program (SPSS 17.0 for Windows; SPSS, Chicago, IL, USA). Continuous variables are summarized as mean ± standard deviation (SD) or as a percentage of frequency. Categorical variables are expressed as proportions (percentage). Student's *t*-test (for continuous variables) and $\chi^2$ proportion test (for categorical variables) were used. Appropriate descriptive and analytical methods (absolute and relative numbers, *t*-test, Wilcoxon test, Mann-Whitney *U* test) were also used. Multiple logistic regression was applied to predict and evaluate one variable based on the value of the other variable or multiple variables. The significance level was less than 0.05.

## Results

A screening test for the presence of CHD was performed in 169 asymptomatic patients with a mean age of 58.71 ± 6.76, ranging from 40 to 70 years, with T2DM without a history of any CVD. The presence of silent CHD was proven in 52 subjects using ergometric testing, while 117 subjects were without CHD. We examined whether there were differences in cardiovascular risk factors between the study groups.

Table 1 shows a comparison of demographic and risk factors between subjects with a positive or negative ergometric test result. The patients with positive ergometric test (silent CHD) were older with a longer duration of diabetes and a higher incidence of smokers compared to the patients with a negative ergometric test result ($p < 0.05$). Prevalence of hypertension, as well as HbA1c values, were statistically significantly higher in subjects with a positive ergometric test compared to the patients with a negative ergometric test ($p < 0.05$). Regarding the lipid parameters, total cholesterol, LDL cholesterol, as well as triglycerides, were significantly higher in the group of subjects with a positive ergometric test ($p < 0.05$), whereas the values of HDL cholesterol did not differ significantly between the study groups. Microalbuminuria was a statistically significantly different characteristic ($p < 0.001$).

**Table 1**

**Demographic and anthropometric characteristics of the type 2 diabetes mellitus patients with positive or negative ergometric test**

| Characteristics | Patients | | *p* |
|---|---|---|---|
| | positive ergometric test (n = 52) | negative ergometric test (n = 117) | |
| Gender (male/female), n | 24/28 | 47/70 | ns |
| Smoking, n (%) | 32 (38.5) | 16 (13.7) | < 0.05 |
| Age (years), mean ± SD | 58.71 ± 6.76 | 54.98 ± 6.69 | < 0.05 |
| Duration of DM (years), mean ± SD | 10.52 ± 4.60 | 7.08 ± 3.19 | < 0.05 |
| BMI (kg/m$^2$), mean ± SD | 27.6 ± 1.58 | 27.2 ± 1.46 | ns |
| Systolic BP (mm Hg), mean ± SD | 139.90 ± 11.7 | 128.16 ± 10.72 | < 0.05 |
| Diastolic BP (mm Hg), mean ± SD | 88.56 ± 9.3 | 81.03 ± 7.27 | < 0.05 |
| HbA1c (%), mean ± SD | 9.16 ± 1.91 | 7.43 ± 1.08 | < 0.05 |
| Total cholesterol (mmol/L), mean ± SD | 6.07 ± 1.33 | 5.37 ± 1.11 | < 0.05 |
| LDL cholesterol (mmol/L), mean ± SD | 3.97 ± 1.11 | 3.33 ± 0.86 | < 0.05 |
| HDL cholesterol (mmol/L), mean ± SD | 1.17 ± 0.2 | 1.14 ± 0.37 | ns |
| Triglyceride (mmol/L), mean ± SD | 2.35 ± 1.1 | 2.06 ± 1.37 | < 0.05 |
| Microalbuminuria, n (%) | 47 (90.4) | 20 (17.1) | < 0.001 |
| IL-6 (pg/mL), mean ± SD | 6.83 ± 1.99 | 3.04 ± 1.39 | < 0.001 |
| hs-CRP (mg/L), mean ± SD | 6.37 ± 2.25 | 1.67 ±1.41 | < 0.001 |

**DM – diabetes mellitus; BMI – body mass index; BP – blood pressure; HbA1c – glycosylated haemoglobin; LDL – low-density lipoprotein; HDL – high-density lipoprotein; IL-6 – interleukin-6; hs-CRP – high-sensitivity C-reactive protein; SD – standard deviation.**

When we analyzed inflammatory markers (IL-6 and hs-CRP), we found that IL-6 values were significantly higher in patients with a positive ergometric test ($p < 0.001$) (Table 1). Similarly, we also found that hs-CRP values in patients with a positive ergometric test were significantly higher compared to patients with a negative ergometric test (Table 1).

The results of combinations of IL-6 and hs-CRP with age show the following: increasing the value of IL-6 by one unit increased the possibility of a positive ergometric test by 1.439 times, increasing the value of hs-CRP by one unit increased the possibility of a positive ergometric test by 1.830 times, while increasing the patient's age by one year increased the possibility of a positive ergometric test by 1.160 times (Table 2).

The results of combining IL-6 and hs-CRP with HbA1c in our study showed that an increase in IL-6 by one unit increased the possibility of a positive ergometric test by 1.495 times, increasing the value of hs-CRP by one unit increased the possibility of a positive ergometric test by 1.565 times, while an increase in HbA1c by one unit increased the possibility of a positive test by 1.471 times (Table 2).

The results of combinations of independent variables IL-6 and hs-CRP with T2DM duration show that increasing the value of IL-6 by one unit increased the possibility of a positive ergometric test by 1.581 times, increasing the value of hs-CRP by one unit increases the possibility of a positive ergometric test for 1.663 times while increasing the duration of T2DM by one unit increases the possibility of a positive test 1.293 times (Table 2).

Within all three analyzed binary logistic regression models, combinations of IL-6 and hs-CRP with age, HbA1c values, and duration of diabetes showed that these values, are significant predictors of silent CHD proven by ergometric test, i.e., with their increase, the probability of a positive ergometric test also increases ($p < 0.01$) (Table 2).

A receiver operating characteristic curve (ROC) analysis was used to test the predictive powers of IL-6 with a positive ergometric test. Using the multivariate logistic regression model in ROC analysis, the clinical accuracy of the diagnostic procedure was good with the area under the curve (AUC) of 0.925 confidence interval (CI): 0.882 to 0.969). IL-6 had a sensitivity of 90.4% and a specificity of 82.9% (Figure 1).

**Table 2**

**Binominal logistic regression analysis of risk factors for prediction of ergometric test amongst the study population**

| Variables | B | S.E. | *p* | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|
| | | | | | lower | upper |
| Model 1: IL-6 + hs-CRP + Age | | | | | | |
| IL-6 | 0.364 | 0.219 | 0.97 | 1.439 | 0.937 | 2.210 |
| hs-CRP | 0.604 | 0.194 | 0.002 | 1.830 | 1.250 | 2.678 |
| Age | 0.148 | 0.056 | 0.008 | 1.160 | 1.039 | 1.294 |
| Constant | -7.454 | 1.956 | 0.000 | 0.001 | | |
| Model 2: IL-6 + hs-CRP + HbA1c | | | | | | |
| IL-6 | 0.402 | 0.209 | 0.054 | 1.495 | 0.993 | 2.249 |
| hs-CRP | 0.448 | 0.174 | 0.010 | 1.565 | 1.112 | 2.202 |
| HbA1c | 0.386 | 0.238 | 0.106 | 1.471 | 0.922 | 2.348 |
| Constant | -7.454 | 1.95 | 0.000 | 0.001 | | |
| Model 3: IL-6 + hs-CRP + diabetes duration | | | | | | |
| IL-6 | 0.458 | 0.219 | 0.037 | 1.581 | 1.029 | 2.429 |
| hs-CRP | 0.509 | 0.184 | 0.006 | 1.663 | 1.160 | 2.384 |
| Diabetes duration | 0.257 | 0.081 | 0.001 | 1.293 | 1.105 | 1.514 |
| Constant | -7.092 | 1.202 | 0.000 | 0.001 | | |

**IL-6 – interleukin-6; hs-CRP – high-sensitivity C-reactive protein; HbA1c – glycosylated haemoglobin; OR – odds ratio; CI – confidence interval.**

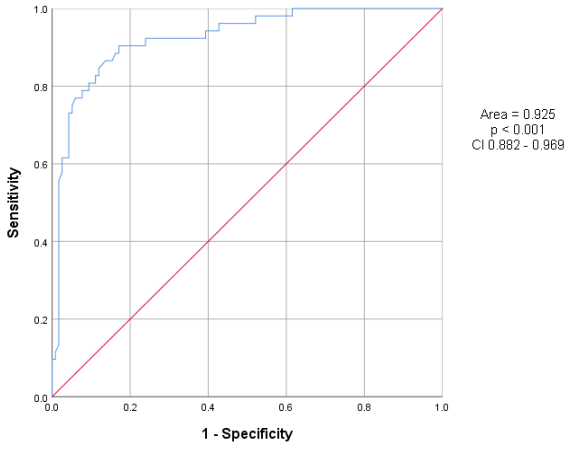


**Fig. 1 – A receiver operating characteristic curve (ROC) predictive power of interleukin-6 with positive ergometric test. CI – confidence interval.**

ROC analysis was also used in testing the predictive power of hs-CRP with a positive ergometric test. Using the multivariate logistic regression model used in the ROC analysis, the clinical accuracy of the diagnostic procedure was good with the AUC of 0.934 (CI: 0.895 to 0.972). Hs-CRP had a sensitivity of 88.5% and a specificity of 80% (Figure 2).

We examined the significance of the associated risk of increased hs-CRP and IL-6 values in the detection of silent CHD proven by ergometric testing. In patients with T2DM in whom silent CHD was detected, 47 (90%) subjects had a finding of associated risk, while 5 (10%) had no associated risk. In patients with T2D without CHD, there was an associated risk in 16 (14%), while in 101 (86%) subjects, it did not exist. This difference in a frequency distribution is statistically significant ($p < 0.001$) (Figure 3).

**Discussion**

Our study demonstrated that a large percentage of patients with T2DM have silent CHD and that elevated levels of inflammatory markers (IL-6 and hs-CRP) represent a strong markers for the presence of silent CHD.

Previous research has shown that silent CHD in people with diabetes varied and that there was a need to define the degree of cardiovascular risk in people with silent CHD who could benefit from screening [15]. In detecting ischemia in asymptomatic diabetics, the study was randomly assigned to either stress testing and a 5-year clinical follow-up or to follow-up only. A total of 22% of patients had silent ischemia [16]. The prevalence of silent myocardial ischemia in our study was 29%, which is mostly consistent with previously published literature. Due to all the above, coronary artery disease in patients with diabetes is a diagnostic and therapeutic challenge.

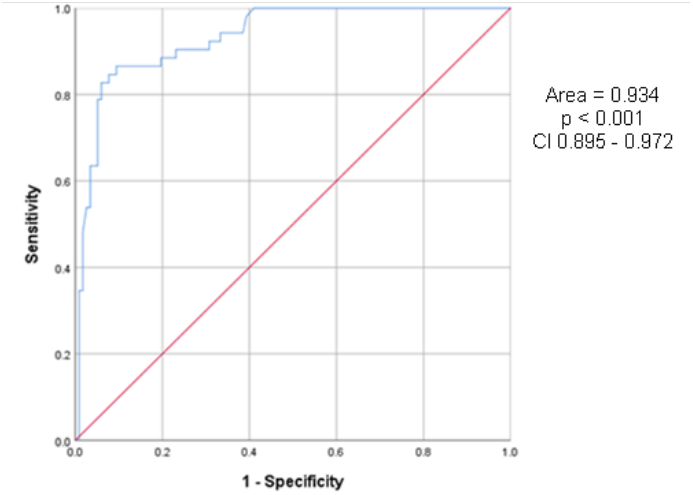


**Fig. 2 – A receiver operating characteristic curve predictive power of high sensitivity C-reactive protein with a positive ergometric test.**
**CI – confidence interval.**

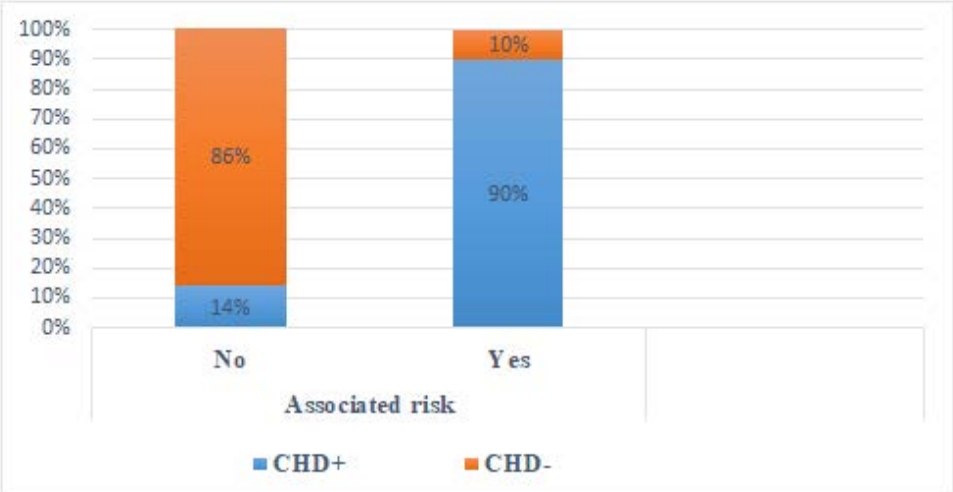


**Fig. 3 – Significance of the associated risk of increased hs-CRP and IL-6 values in the detection of silent CHD proven by ergometric testing.**
**CHD – coronary heart disease.**
**hs-CRP – high sensitivity C-reactive protein; IL – interleukin.**

Although T2DM alone is a large and independent risk factor for the occurrence of CVD, the coexistence of traditional cardiovascular risk factors significantly increases the risk of silent CHD occurring in T2DM patients. The Multiple Risk Factor Intervention Trial showed that multiple risk factors in the same patient significantly increased the overall cardiovascular risk [17]. Gaede et al. [18] reported that an intervention directed at multiple risk factors significantly improves cardiovascular prognosis. This is supported by the results of our study, which showed that the patients with silent CHD were older, with a longer duration of diabetes, higher prevalence of hypertension, poorer glucose regulation, higher values of total cholesterol, LDL cholesterol, and triglycerides as well as a higher prevalence of albuminuria compared to subjects who did not have CHD, while HDL cholesterol levels and BMI had no statistically significant difference between the study groups.

Since the inflammatory process is an integral part of the evolution of atherosclerosis, the use of CRP as a biomarker becomes very useful in combination with the control of classic risk factors such as lipid levels, changes in eating habits, weight loss, regular physical activity, glycemic control, and smoking cessation. The interrelation of these risk factors for CVD are strategies to reduce cardiovascular events in primary and secondary prevention [19]. Due to the relationship between high CRP plasma levels and cardiovascular mortality and morbidity risk, it is important to establish a primary care line to decrease CVD. For this, the evaluation of cardiovascular risk factors is essential for stopping their progression. Several prospective studies having CRP as a central target have shown the benefits of primary prevention. In 1999, the MONICA-Augsburg study, performed on a sample of 936 asymptomatic men, concluded that the increase in hs-CRP leads to a 19% increased risk of fatal and non-fatal coronary events [20]. In the same way, the PREVEND study in 8,139 asymptomatic men and women observed a relationship between hs-CRP and angiographic characteristics and consequently clinical instability of the atherosclerotic plaque [21].

A six-year follow-up study of healthy middle-aged men showed that baseline IL-6 levels greater than 2.28 pg/mL were associated with a 2.3-fold higher risk of future myocardial infarction, which is why IL-6 was also identified as a significant risk predictor of cardiovascular events [22]. Recent research has reported the importance of inflammation in the development and progression of atherosclerosis, as well as the possibility of using inflammatory markers to assess cardiovascular risk. Among the several biomarkers proposed in cardiovascular risk stratification is CRP, which would be used in identifying individuals at risk for developing CVD, but this is not yet recommended in the guidelines [23–25]. Prospective clinical case-control studies, Physicians' Health Study, and Women's Health Study have identified CRP as a strong, independent risk factor for CHD [26, 27]. Previous research has shown that hs-CRP was a predictor of CVD, even after adjusting to traditional risk factors indicating that hs-CRP may provide additional significant prognostic information in cardiovascular risk assessment [28]. Furthermore, elevated levels of IL-6 in serum are correlated with the development of coronary artery disease, which is why IL-6 has become an important cytokine in the assessment of atherosclerosis in people with T2DM, as evidenced by two large genetic studies reporting a correlation between IL-6 receptor signaling and CVD [29–31]. It has been also suggested that elevated IL-6 values were correlated with an increased risk of future myocardial infarction even after adjustment in initial differences in total cholesterol, HDL-cholesterol, BMI, blood pressure, diabetes mellitus, family medical history, alcohol consumption, and doing physical activity [32, 33]. Moreover, elevated levels of IL-6 can play a predictive role in the occurrence of CVD, thus providing a potential prognostic means in the detection of CVD [22].

The results of our research also support these studies. We concluded that the combined finding of increased values of IL-6 and hs-CRP posed a high risk of the presence of silent CHD in T2DM patients.

In this study, we also analyzed the significance of inflammatory cardiovascular risk markers (CRP, IL-6) for the appearance of silent CHD in patients with T2DM. In subjects with silent CHD, there was a direct correlation with IL-6 and hs-CRP values that were significantly higher compared to the subjects without CHD. The results of our study showed that IL-6 and hs-CRP are significant predictors of silent CHD and showed that the association of IL-6 and hs-CRP with age, HbA1c values, and duration of diabetes is significant predictor of silent CHD proven by ergometric testing.

There are some limitations of our study. First, the study was a single-center trial with a relatively small number of subjects. Second, this study was cross-sectional, without appropriate follow-up, so our study could not demonstrate, in the long term, the incidence of silent CHD or the influence of investigated markers on the future appearance of CHD. This could be the main reason to extend the investigation to a larger number of subjects and a longer follow-up in the future in order to get stronger results.

## Conclusion

Our study showed that a large percentage of T2DM patients had silent CHD. Elevated levels of inflammatory cardiovascular risk markers, hs-CRP and IL-6, are strong markers of the presence of silent CHD in asymptomatic T2DM patients. Given that traditional risk factors for CVD explain only a part of cardiovascular risk in T2DM patients, and current screening recommendations are based on their use, it would be important to include the determination of inflammatory cardiovascular risk markers in order to improve cardiovascular risk stratification in asymptomatic patients with T2DM. By doing so, we would be able to reduce the incidence of cardiovascular complications occurrence and apply appropriate treatment modalities in a timely manner, whether it was a conservative or invasive treatment.

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Received on October 12, 2020
Revised on January 24, 2021
Accepted on January 27, 2021
Online First February 2021