# CRP and fibrinogen imply clinical outcome of patients with type-2 diabetes and coronary artery disease

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**List of abbreviations**: ABI, ankle-brachial index; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; HbA1c, hemaglobin A1c levels; HDL, high density lipoprotein; IL, interleukin; IMT, intima media thickness; LDL, low density lipoprotein; PAD, peripheral artery disease; ROC, receiver operating characteristics; SEM, standard error of the mean; TNF, tumor necrosis factor

Patients with type-2 diabetes have accelerated atherosclerosis and vascular disease, which is a result of endothelial injury leading to accumulation of platelets at the site of injury [1]. Further, abnormalities in smooth muscle cell proliferation, elevated low density lipoprotein (LDL), and changes in coagulation all contribute to accelerated atherosclerosis in type-2 diabetic patients. Other risk factors such as, hyperglycemia, glucose intolerance, obesity and hypertension are well established risk factors for diabetic vascular disease [2]. Physical inactivity and sedentary lifestyles should not be discounted [3, 4]. Furthermore, in the INVADE study (Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg, Bavaria), it was noted that the combination of hyperglycemia measured as hemaglobin A1c levels (HbA1c) and overall inflammatory state as measured by C-reactive protein (CRP), is associated with progression of atherosclerosis and increased risk of vascular disease in type-2 diabetic patients [2]. Interestingly, the combination of HbA1c and CRP in non-diabetic subjects also demonstrated increased atherosclerosis progression [2]. Despite this information, it is still not clear why some type-2 diabetic patients with the same duration of diabetic disease and the same metabolic control, have different clinical outcome. Chronic inflammation involving pro-inflammatory cytokines (primarily tumor necrosis factor (TNF)-alpha and interleukin (IL)-6) are highly prevalent in chronic conditions

including, atherosclerosis, type-2 diabetes and obesity [5]. The combination of TNF-alpha and IL-6 contribute to high blood glucose levels and endothelial dysfunction. In addition, high IL-6 levels are associated with high coronary artery calcium scores as noted in a cross sectional study involving 306 diabetic patients. More recently, Th22 cells and IL-22 have been found to be highly prevalent in type-2 diabetes and coronary heart disease, however, their role as being useful markers for coronary artery (CAD) disease and type-2 diabetes is not yet clear. Furthermore, CRP and fibrinogen, proteins found in blood plasma, play a role in atherosclerosis development in diabetic patients. There is a clear link between the proccess of plaque formation and future cardiovascular events with inflammatory markers, including CRP and fibrinogen. Indeed, high levels of CRP and fibrinogen relates to a relatively increased risk of 1.5-2.5 fold for fatal events in type-2 diabetic patients. In addition, in the ADOPT (a diabetes outcome progression trial) study, obesity, was the major determinant associated with high CRP and fibrinogen levels in a population with metabolic syndrome or type-2 diabetes [6]. However, better glycometabolic control is most likely the key for inflammatory status improvement in type- 2 diabetes population.

Here we determined the inflammatory markers, CRP and fibrinogen in patients with diabetic vascular disease and estalished its influence to the clinical outcome of patients with CAD and type-2 diabetes. This prospective non-randomized cohort study included 62 patients with type-2 diabetes and CAD. Patients were followed-up for 36 months. The study was conducted at University Cardiology Clinic Skopje. The study was carried out according to the Helsinki declaration and was approved by the University Clinic Ethics Committee, Skopje. All patients signed an informed consent. Type-2 diabetes was defined based on the criteria of the International Diabetes Federation. CAD was defined as asymptomatic one, confirmed with coronary angiography. Carotid stenosis were determine as significant, when 60 % or more severe stenosis was detected by Echo Color Doppler sonography (by hemodinamic criteria of Bluth). Peripheral artery disease (PAD) was determinated by Doppler sonography measuring ankle-brachial index (ABI), at the beggining of the study. ABI values < 0.9 and > 1.3 determined the presence of PAD. Fibrinogen, CRP, total cholesterol, triglycerides, high density lipoprotein (HDL), LDL, plasma glucose concentrations and body mass index (BMI) were measured at baseline (Table 1). In the evaluated population we determined CRP values of 5.69 + 6.92 mmol/L and fibrinogen values of 4.12 + 0.85 g/L. Study population was with mean diabetes duration of 7.8 years. 50 pts did have hypertension (80.6 %), 60 patients were on antiplatelet drugs (96.8 %), 58 patients (93.5 %) on lipid lowering agents. 56.4 % of patients were taking insulin (35 patients) and 43.5 % were on oral antidiabetic agents (27 patients).

All patients were followed up for new angina onset (defined as chest pain or discomfort due to CAD) for a period of 36 months. Multivariate logistic analysis was performed to define predictors for new angina, when basic characteristics and Fibrinogen, CRP, total cholesterol, triglycerides, high density lipoprotein (HDL), LDL, plasma glucose concentrations and body mass index (BMI) were incorporated in the model. Analysis was adjusted for age.

CRP was determinated by diabetes duration, BMI and minimal value of ABI. Fibrinogen was determinated by non-HDL cholesterol (Table 2). C - reactive protein is associated with a new angina onset in type-2 diabetic patients. This parameter when increased has a hazard ratio of 9.6, and prediction of a new angina for a period of 36 months (Table 3). Increased fibrinogen is only correlated by new angina by univariate analysis (score= 3.6, p= 0.05).

Inflammation links metabolic syndrome / insulin resistance and atherosclerosis. Inflammation influences development of pre-diabetic phase to type-2 diabetes [7]. In summary, we demonstrated that CRP values, as a measure of inflammation, were correlated to BMI and diabetes duration, confirming its connection with early stages of atherosclerosis and stenosis. In fact, obesity is a major risk factor, connected to CRP in populations with metabolic syndrome and/or type-2 diabetes [8]. Furthermore, advanced atherosclerosis in type-2 diabetic patients, correlates with increased serum CRP concentrations, when there is increased HbA1c and advanced glycation end products [9]. These studies are shown through follow up of coronary and carotid atherosclerosis. Moreover, inflammation is connected with the pathophysiological process of plaque rupture, and CRP and fibrinogen are tightly connected with future cardiac events in type-2 diabetic subjects, increasing the relative risk by 1.5-2.5 fold, independent of blood lipids and glycemic control. CRP has an incremental value between other biomarkers in patients with stable CAD and type-2 diabetes, according to the ARTEMIS study [9]. Our results show that augmented CRP increases the risk for new angina. Although numerous studies address the question of typical risk factors of vascular disease in type-2 diabetic patients, so far there has not been an established definitive opinion regarding “novel” risk factors [10]. Our data supports previous studies that indicate inflammatory biomarkers, CRP and fibrinogen, as risk factors in prognostic models for patients with type-2 diabetes and diabetic vascular disease.

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**Table 1.** Basic characteristics of study population

| Variables | Mean values | Std deviation |
|---|---|---|
| Systolic pressure (mmHg) | 143.9 | 19.6 |
| Diastolic pressure | 86.1 | 9.2 |
| Waist | 96.9 | 8.0 |
| BMI ($kg/m^2$) | 28.7 | 4.0 |
| Fibrinogen g/L | 4.12 | 0.85 |
| CRP (mmol/L) | 5.69 | 6.92 |
| Glycemia | 8.5 | 2.4 |
| Total cholesterol | 5.4 | 1.4 |
| HDL-cholesterol | 1.0 | 0.4 |
| Non HDL-cholesterol | 4.3 | 1.4 |
| LDL-cholesterol | 3.3 | 0.9 |
| Triglycerides | 2.0 | 1.0 |

**Table 2.** Determinants of CRP and fibrinogen by mutlivariate analysis

| Model | | B | SEM | Beta | t | *p* value |
|---|---|---|---|---|---|---|
| CRP | | | | | | |
| | Diabetes duration | -0.652 | 0.226 | -0.696 | -2.881 | 0.024 |
| | BMI | -1.134 | 0.476 | -0.565 | -.2.381 | 0.049 |
| | ABI minimum | 54.120 | 22.970 | 3.477 | 2.356 | 0.050 |
| Fibrinogen | | | | | | |
| | Non-HDL | 0.706 | 0.277 | 1.093 | 2.548 | 0.027 |

ABI, ankle brachial index; BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; SEM, standard error of the mean

**Table 3.** Predictors for new angina

| | B | S.E. | Wald | df | Sig. | Exp(B) | 95 % CI ExpB | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| > CRP | 2.270 | 0.870 | 6.807 | 1 | 0.009 | 9.679 | 1.759 | 53.262 |
| Carotid Stenosis | -2.219 | 0.931 | 5.679 | 1 | 0.017 | 0.109 | 0.018 | 0.674 |