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Evaluation of Thrombin- Antithrombin Complex in Patients with Type-II Diabetic Coronary Artery Disease

Enver Ciraci[1]* Koray Ak[2] Sermin Tetik[3]

1 Biruni University, Faculty of Pharmacy, Department of Biochemistry, Zeytinburnu, Istanbul, Turkey
2 Marmara University, Faculty of Medicine, Department of Cardiovascular Surgery, Basibuyuk, Istanbul, Turkey
3 Marmara University, Faculty of Pharmacy, Department of Biochemistry, Basibuyuk, Istanbul, Turkey

Abstract

The aim of the study was to determine whether plasma levels of thrombin-formation antithrombin III (TAT) complex and oxidized LDL (ox-LDL) levels as a biomarkers in patient with diabetic coronary arter diseases differed from that in coronary artery patients.

Patients were included in this study and were divided into two groups- just patient with coronary artery diseases as group 1 and the diabetic coronary artery disease as group 2. Demographic data were collected all patients. Blood samples were taken from all groups after the exmanination according to the protocol. Serum TAT and ox-LDL were assayed using enzyme-linked immunoabsorbent assay. Regular biochemical data were measured using conventional methods.

Of the 39 participants in this study, 19 had diabetic coronary artery diseases. TAT complex levels in the plasma of 20 control grup (Group 1) and 19 patients (Group 2) were assessed by ELISA method. C-reactif protein (CRP) and fibrinogen levels were assed in plasma of group 1 and and group 2 in Marmara University Pendik Education and Research Hospital, Cardiovascular Surgery department. CRP and fibrinogen levels in group 2 plasmas were found high in significant level ($p=0.001$). HbA1c ($p<0.001$) levels and in terms of diabetes duration in both groups were observed meaningful difference ($p<0.001$). A significant difference was not detected between groups in terms of platelet levels ($p>0.05$). A significant difference has been detected between plasma LDL levels of group 1 and and group 2 ($p<0.001$). The levels of TAT complex in the plasma collected from group 1 (29,27±24.14 ng/mL) was found higher than the group 2 (10.12±3.62 ng/mL) ($p<0.001$). In addition to this, a significant difference has not been detected between the oxidized LDL values of group 1 (123.26±17.18 pg/mL) and group 2 (122.87±27.13 pg/mL) ($p>0.05$).

The present study showed that serum TAT levels were significantly higher in patient with coronary artery diseases group than just coronary artery diseases group. We concluded that serum TAT complex may be used as a coagulation risk biomarker in this group.

MAR-YÇ-2009-0006 (Marmara University Faculty of Medicine,
Research Ethics Committee

Key words: coagulation abnormalities, type 2 diabetes, coronary artery disease, thrombin-antithrombin complex

*Correspondance to:
Enver Ciraci, Ph.D. Biruni University, Faculty of Pharmacy, Department of Biochemistry, Zeytinburnu, Istanbul, Turkey GSM:05520005135 ORCID: 0000-0001-9222-8464 Email: eciraci@biruni.edu.tr

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Introduction

Diabetes mellitus has become one the most pressing and prevalent issue in the last few decades, hand-in-hand with the rising obesity crisis, and is now the seventh leading cause of death in the USA as well as worldwide, with 5.2 million deaths globally attributed to diabetes, a mortality rate of 82.4 per 100,000 (1). Insulin is an essential hormone produced in the pancreas. It allows glucose from the bloodstream to enter the body's cells where that glucose is converted into energy. Insulin is also essential for the metabolism of protein and fat. A lack of insulin, or the inability of cells to respond to it, leads to high levels of blood glucose (hyperglycaemia), which is the clinical indicator of diabetes. DM poses as a major risk factor for the development of cardiovascular disease (CVD), which ultimately results as the most common cause of death in those with DM (2). In addition to microvascular complications of DM, including nephropathy, retinopathy, and neuropathy; macrovascular complications also become more prevalent in the form of coronary artery disease, peripheral vascular disease, and carotid artery disease with the increasing duration of diabetes (3).

The prevalence of diabetes is increasing rapidly worldwide (4,5). In 2016, the World Health Organization (WHO) reported that nearly 422 million adults live with diabetes; this is an increase in global prevalence from 4.7% in 1980 to 8.5% in 2014 Diabetes mellitus (DM) doubles the risk of cardiovascular disease (6) and about 75% of deaths in diabetic patients are due to coronary artery disease (7).

In 2017, combined occurrences of type-1 diabetes mellitus (T1DM) and type-2 diabetes mellitus (T2DM) were estimated at 425 million individuals worldwide. The number is predicted to rise to 629 million by 2045 (8). T2DM have wide-ranging consequences for the body as glucose levels are associated with many physiological processes. These include lipid metabolism and the regulation of inflammation, vasodilatation, basic cell growth and replication. Unmanaged diabetes and hyperglycaemia can worsen these physiological changes, potentially leading to diabetes-associated complications. In particular, individuals with diabetes are two to three times more likely to develop cardiovascular diseases than those without diabetes (8).

Additionally, in individuals with diabetes, platelets are hyper-reactive, giving rise to increased activation of prothrombotic factors and decreased fibrinolysis which results in an increased risk of thrombosis (9,10). What is more, the altered lipid profile found in individuals with diabetes affects cardiac function and can cause lipotoxicity in the heart (11).

The prognosis following a cardiovascular event remains poor for individuals with diabetes despite intensive research on the subject and the development of new therapies . Thus, it is important to better understand the underlying mechanisms that drive the haemostatic changes observed in T2DM .T2DM are associated with changes in blood coagulability, including alterations in clot structure and in the kinetics of clot formation and lysis. The factors responsible for these alterations include changes in the concentration and activity of numerous coagulatory proteins, resulting in defective thrombin generation and changes in the molecular make-up of fibrin clots. Proteins with elevated concentrations in Type II diabetes include von Willebrand factor (vWF) (pre) kallikrein, factor V, (activated) factor VII, factor VIII, factor X,

factor XI, prothrombin and fibrinogen. Proteins only elevated in T2DM include: kininogen, soluble tissue factor, factor IX, (activated) factor XII, and factor XIII (12,13). A number of reports have examined antithrombin concentration in T2DM. One such study found reduced concentrations (14), whilst two other studies reported elevated concentrations of this protein associated with the disease (15). The cause of this difference is not known; it may be due to a difference in methodology or to the individuals studied being at a different stage of progression of the disease.

Hereby, the thrombin-antithrombin (TAT) complex provides thrombin neutralization. The high plasma levels of the TAT complex vary in some diseases due to the increased hemostatic activation. The TAT complex is an alternative indicator used to monitor morphological changes in chronic aortic diseases. In order to evaluate the role of coagulation abnormalities, plasma levels of thrombin-antithrombin III (TAT) complex and oxidized-LDL, which are indicators of thrombin formation, were evaluated in diabetic coronary cardiac patients in terms of the results of pathogenesis and therapeutic approach.

Materials and Methods

Study Population and design

The study was conducted at Marmara University Pendik Training Research Hospital, Istanbul-Turkey, and approved by Marmara University Ethics Commitee (MAR-YÇ-2009-0006). All procedures were conducted in accordance with the Declaration of Helsinki, and all participants gave their informed consent before participating in the study.

Our study comprised covered of the other group-just patients with coronary artery diseases as group 1 (n:20) and patients with diabetic coronary artery diseases as group 2 (n:19).

The exclusion criteria were as follows:

1) Use of antiplatelet agent
2) Type 1 Diabetes
3) Malignancy
4) Alcohol and/or smoking

Diabetic coronary artery is defined after examination and several tests. In addition, included measuring levels of HbA1c and CRP levels as rutine biochemical tests and gave at below furthermore tests to follow-up.

Collection of plasma and data collection

Blood samples of 20 just patient with coronary artery diseases as group 1 and 19 patients who were admitted to the Cardiovascular Surgery Department in Marmara University Pendik Education and Research Hospital and diagnosed with diabetes-related coronary artery as group 2 were taken into vacutainer serum separator tubes containing citrate (1:9) as an anticoagulant. In these patients, diabetes diagnosis and follow-up are performed with coronary artery disease

and fasting blood sugar> 104 mg / dL and satiety blood sugar> 160 mg /dL, characterized by the presence of plasma LDL cholesterol> 100 mg / dL. It was paid attention that the controls did not use an anticoagulant agent such as aspirin for 10 days and that they were not smokers. The tubes were kept at room temperature and centrifuged for 10 minutes at 1,000xg within the first hour of blood collection. The obtained plasmas were stored at -20°C until the day of study. When the study was planned, Marmara University Ethics committee approval was obtained by applying to the Ethics Committee Presidency.

Plasma TAT Quantification

AssayMax Human Thrombin-antithrombin TAT ELISA kit (cat. No: ET1020-1) was used to reveal the TAT complex in plasma. In this experiment measuring the TAT complex within 4 hours, the quantitative sandwich enzyme immunoassay technique was used.

Calculation of TAT complex standard

With the help of the obtained standard curve graph (Figure 5.1), the TAT complex concentrations of the samples were determined in ng / mL.

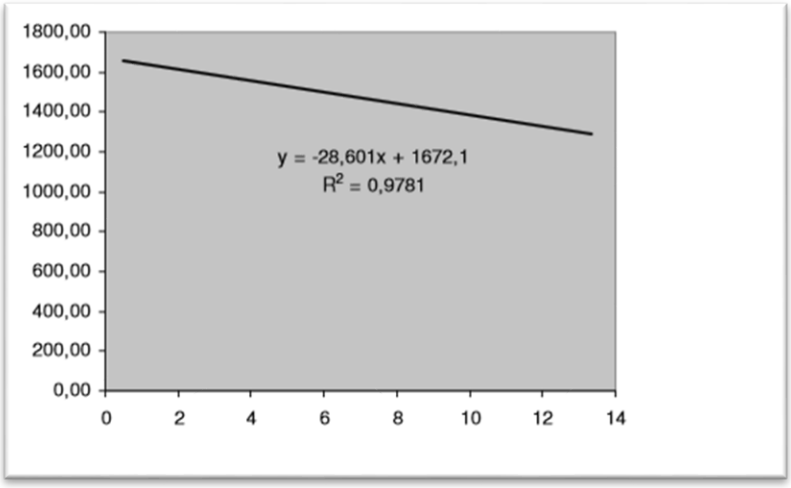

Figure 1. TAT Complex Standard Curve Graph

Determination of Oxidized LDL Levels in Plasma

Amount Ox-LDL determination in blood plasma was done using ELISA commercial kits (Immundiagnostic AG Bensheim, Cat. No. BI-20042).

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Calculation of Ox-LDL Standard

Ox-LDL concentrations of plasma samples were determined in ng / mL from the standard curve graph obtained (Figure 2).

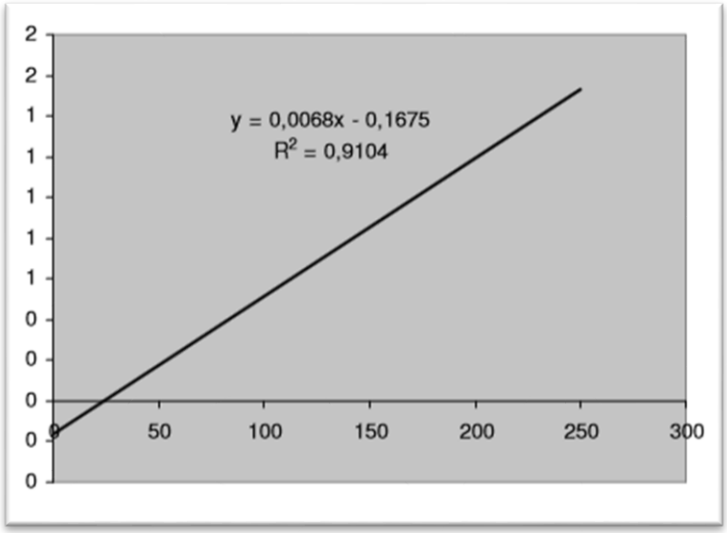

Figure 2. Oxidized LDL Standard Curve Graph

Statistical Analysis

For the difference between group I and group II, 'Mann-Whitney Test', which is a non-parametric method, was used. Statistical significance was tested at 95% confidence interval. Statistical significance was expressed as $p < 0.05$. SPSS 11.0 programs were used in all statistical analyses.

Results

Of the 39 participants in this study, 19 had diabetic coronary artery diseases. This study was planned to investigate the relationship between atheroschlerosis and anticoagulation factor antithrombin III (AT-III) and oxide LDL levels in the diabetic coroneray artery diseases. In this study, to evaluate the role of the coagulation abnormalities, TAT complex levels were evaluated in diabetic coronary artery diseases (Group 2). TAT complex levels in the plasma of 20 control grup (Group 1) and 19 patients (Group 2) were assessed by ELISA method. C-reactif protein (CRP) and fibrinogen levels were assed in plasma of group 1 and and group 2 in Marmara University Cardiovascular Surgery department as conventional methods. CRP level was found higher in group 2 (6.18±0.56) than group 1(1.78±0.34) ($p<0.001$). Moreover, fibrinogen level was found higher significantly in group 2 (347.25±57 mg/dl) than group 1(289.71±63 mg/dl)

(p<.0.01). HbA1c level was detected higher in group 2 (7. 82±0.73 %) than group 1 5.35±0.42 %) (p<0.01) .A significant difference was not detected between groups in terms of platelet levels (p>0.05). A significant difference between the group (123.10±0.12) and group 2 (25.47±1.21) in terms of BMI (Table 1).

Table 1. Clinical and biological parameters of controls (Group 1) and patients with Type 2 Diabetic Coronary Artery Disease Individuals (Group 2)

Characteristic	**Group 1 (n=20)**	**Group 2 (n=19)**	**p value**
Age	25±5	58.5±6	ns
Gender	3/7	4/15	ns
TAT (ng/mL)	29.27±24.14	10.12±3.62	p<0.001
CRP (mg/dl)	1.78±0.34	6.18±0.56	p<0.01
Fibrinogen (mg/dl)	289.71±63	347.25±57	p<0.01
Platelet number (mm3)	272.63±32.26	294.27±46.51	p>0.05
HbA1c (%)	5.35±0.42	7. 82±0.73	p<0.01
Duration of Type 2 Diabetes (year)	-	12.64±5.43	p<0.01
LDL (mg/dl)	76.12±10.63	164.26±27.74	p<0.01
Ox-LDL (mg/dl	123.26±17.18	122.87±27.13	p>0.05
BMI (kg/m^2)	23.10±0.12*	25.47±1.21	p<0.01

The levels of TAT complex in the plasma collected from group 1 (29.27±24.14 ng/mL) was found higher than the group 2 (10.12±3.62 ng/mL) (p<0.001).

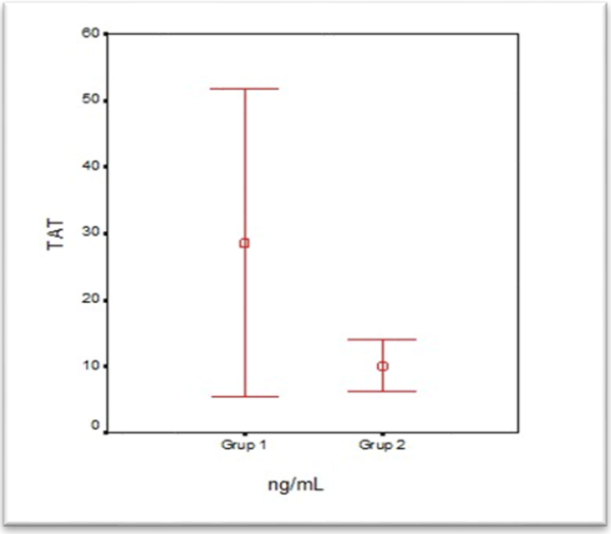

Figure 1. TAT complex levels in the plasma of group 1and group 2.

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Group 1: control group (n: 20) , Group 2: Diabetic coronary artery patients (n:19)
In addition to this, a significant difference has not been detected between the oxidized LDL values of group 1 (123.26±17.18 pg/mL) and group 2 (122.87±27.13 pg/mL) (p>0.05).

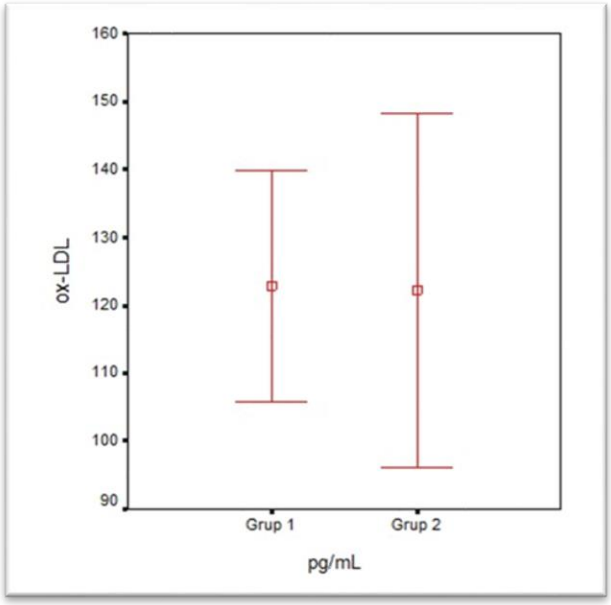

Figure 2 Ox-LDL levels in the plasma of group 1and group 2.

Discussion

Coronary artery disease is the leading global cause of mortality . Studies in recent years have shown that atherosclerosis has started in childhood or the findings of advanced age. Obesity, lipoprotein metabolism disorders, hypertension, smoking, diabetes, sedentary life, stress, and genetic predisposition are risk factors for atherosclerosis. The role of diabetes in the pathogenesis of CVD was unclear until 1979 when Kannel et al. used data from the Framingham heart study to identify diabetes as a major cardiovascular risk factor. Based on 20 years of surveillance of the Framingham cohort, a two-fold to threefold increased risk of clinical atherosclerotic disease was reported. It was also one of the first studies to demonstrate the higher risk of CVD in women with diabetes compared to men with diabetes (15). These results have been duplicated by multiple studies. The Kannel article changed the way the medical community thought about diabetes. It is now accepted as a major cardiovascular risk factor (16). DM is commonly associated with micro- and macrovascular complications. Dysfunction of the vascular endothelium is regarded as an important factor in the pathogenesis of vascular complications in patients with DM (19). Diabetes does not only increase the risk of myocardial infarction, but also increases mortality associated with acute events. Acang and Jalil reported that prothrombin time (PTs) and activated partial thromboplastin time (aPTTs) were shorter in

patients with diabetes. A different group of researchers found that PTs time was normal in patients with Type 2 diabetes, whereas platelet-dependent thrombin formation was increased in diabetics (17). The thrombus, which is formed by the activation of the coagulation system, grows, decreases the coronary blood flow and can even stop the flow completely. On the other hand, with the activation of the fibrinolytic system, thrombus undergoes fibrinolysis and coronary flow is provided again (18-21).

In the study of Hoffmeister et al., 31 patients with unstable angina were found to have a higher TAT level than the control group (7.6 ± 1.9 ng / ml to 4.0 ± 0.5 ng / ml). However, the relationship between TAT level and coronary lesion morphology cannot be shown (22). In another study, while TAT level was found to be approximately two times higher in patients with unstable angina compared to the control group, the TAT levels of stable angina and control group were similar (23).

Our patient portfolio, which constitutes the study group, is the group with Type 2 Diabetes, which has an average of 12 years. When the biochemical values between the patient population and the controls were examined, CRP and fibrinogen levels were found to be significantly higher in patient plasma compared to the controls, whereas HbA1c levels and duration of diabetes were significantly different between each group. When the platelet count was evaluated, there was no significant difference between the groups, while plasma LDL cholesterol levels of the patient group and controls were found to be significantly different.

Fibrinogen is a plasma protein with a long half-life. In uncontrolled diabetes with high blood glucose, fibrinogen may become hyperglycosylated (24). Fibrin structures are formed in the coagulation that fibrinogen joins, which have been shown to be resistant to degradation by plasmin. The high concentration of hyperglycosylated fibrinogen requires a long time to dissolve. These results report that increased resistance to fibrinolysis in a poorly controlled diabetes is characterized by abnormal fibrin structures in the clinic (25).

Disruption of lipid metabolism is one of the primary cases in Type 2 diabetes (26). This is the typical dyslipidemic picture seen in diabetics. Lipoprotein abnormalities in diabetics include high plasma triglyceride, low HDL, and atherogenic small-dense LDL particles that are highly elevated and susceptible to glyco-oxidation (27). In addition, in ox-LDL diabetic endothelial cells, ICAM-1 stimulates the biosynthesis of cell adhesion molecules such as E-selectin, and leukocyte and macrophage associations occur depending on this. LDL particles accumulate as foam cells in macrophages and the onset of the atherosclerotic process is induced (28).

In our study, the patient population consists of patients who received oral antidibetic (1000 mg / day), antilipidemic (40 mg / day) and antithrombotic (100 mg / day) therapy. When the ox-LDL values of the control group plasma and the ox-LDL values of the patient group were compared, it was found that the plasma ox-LDL concentrations of the control group were similar to the patient group. This similarity is thought to come from the anti-oxidizing effects of anti-lipidemic drugs. In many studies and in a study we performed in our laboratories, Statin group agents have been reported to control inflammation while preventing oxidation (29).

The high plasma level of TAT complex argentine hemorrhagic fever, chronic dialysis patients give an idea to change hemostatic activation in pregnancy toxemia (30). Low plasma levels of TAT complex have been found in type 1 diabetes, neonatal respiratory distress syndrome and

cancer without primary treatment (32). TAT complex chronic aortic and it is the major inhibitor of AT III plasma thrombin and factor Xa. AT III deficiency leads to increase in thrombin formation and hypercoagulation. They showed that moderate reduction in plasma AT III level increased fibrin formation and shortened clotting time (31).

Consequently, diabetes is a complex disease that strongly impacts on haemostasis and the risk of developing cardiovascular disease in multiple ways. It is important to understand and these mechanisms in order to appropriately treat these diseases and to reduce thrombotic risk in these individuals. TAT complex levels are important to follow cardiovascular risk as a biomarker. Also Ox-LDL and TAT complex levels are contributed to evaluate risk factors of haemostasis and the risk of developing cardiovascular disease as a new biomarkers. New approaches to be developed in the diagnosis and treatment of diabetes and coronary artery diseases associated with it are important in terms of controlling the morbidity and mortality of these patients based on the coronary cardiovascular disease.

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