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EVALUATION OF PLASMIN SYSTEM FACTORS IN COVID-19 PATIENTS WITH ISCHEMIC HEART DISEASE

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ABSTRACT

Evaluation of the activity of plasmin system's factor type 1 plasminogen activator inhibitor (PAI-1). PAI-1 is important for early prediction of disease progression and possible thrombogenic complications in patients with CAD and COVID-19. The study included 32 patients with coronary CAD receiving inpatient treatment with a diagnosis of COVID-19 at the "ATLAS" distribution center and 28 currently healthy people. In the main group, 71.8% (23 out of 32) of patients had an increased level of PAI-1 in the blood plasma and a significantly reduced level of plasminogen in the same patients. Risk factors such as obesity, anxiety and depression syndrome, and hypercholesterolemia have been identified in patients with high PAI-1 levels. In practically healthy subjects, adverse changes in PAI-1 and plasminogen were not observed. Evaluation of systemic plasmin factors in patients infected with COVID-19 and suffering from coronary artery disease may be an important link in the selection of adequate anticoagulants for the prevention of thrombogenic complications.

KEYWORDS: *Ischemic heart disease, type 1 plasminogen activator inhibitor (PAI-1), plasminogen, COVID-19, risk factors.*

Relevance

Noncommunicable diseases now make up 7 of the world's top 10 causes of death. Heart disease has remained the leading cause of death at the global level for the last 20 years. However, it is now killing more people than ever before. The number of deaths from heart disease increased by more than 2 million since 2000, to nearly 9 million in 2019. Heart disease now represents 16% of total deaths from all causes.[1] Patients infected with the virus SARS-CoV-2 and its clinical disease COVID-19 are often minimally symptomatic or asymptomatic. More severe presentations include pneumonia and acute respiratory distress syndrome. In some patients, the heart may be affected, and this can occur in individuals with or without a prior cardiovascular diagnosis. Patients with cardiovascular disease, hypertension, obesity, and diabetes are at increased risk of a poor prognosis.[2]

In some cases of severe COVID-19, fibrinolysis may be markedly enhanced within a few days, resulting in fatal bleeding. In the treatment of COVID-19, attention should be paid to both coagulation activation and fibrinolytic activation.[3] The pathology of coronavirus disease 2019 (COVID-19) is exacerbated by the progression of thrombosis, and disseminated intravascular coagulation (DIC). he most frequently reported coagulation/fibrinolytic abnormality in COVID-19 is the increase in D-dimer, and its relationship with prognosis has been discussed. However, limits exist to the utility of evaluation by D-dimer alone. In addition, since the coagulation/fibrinolytic condition sometimes fluctuates within a short period of time, regular examinations in recognition of the significance of the examination are desirable. The pathophysiology of disseminated intravascular coagulation (DIC) associated with COVID-19 is very different from that of septic DIC, and both thrombotic and hemorrhagic pathologies should be noted. COVID-19 thrombosis includes macro- and microthrombosis, with diagnosis of the latter depending on markers of coagulation and fibrinolysis.[4]

While coronary artery disease (CAD) is associated with disturbances of the plasma fibrinolytic system, the nature of these disturbances is not fully defined. Fibrinolysis is regulated by plasmin, whose production is mediated by plasminogen activator conversion of plasminogen (Plg) to plasmin. The cascade is modulated by feedback loops that include Plg activator inhibitor 1 (PAI-1). Molecular interactions with Plg kringle domains play an important role in regulating plasmin production and its modulation of fibrinolysis.[5]

Plasminogen, a zymogen that is usually present in plasma,[6] is a single-chain glycoprotein synthesized in the liver; it is considered an inactive proenzyme that is converted to plasmin,[7] It is still unclear in the literature whether the quantity ofplasminogen that is transformed into plasmin is linearly correlatedto plasminogen levels. Plasminogen plasma concentration does notvary significantly in normal blood coagulation.[8] Some researchers have shown an independent and unexpected association between high plasminogen levels and the risk of coronary artery disease.[9] Decreased plasminogen levels suggest the generation of less plasmin and signal impaired fibrinolytic activity, which favors thedeposit of fibrin and contributes to atherothrombosis. However,plasminogen has several non-fibrinolytic roles the most importantof which is related to the inflammatory process.[8] Clinical studies have demonstrated elevated plasma levels of PAI-1 in patients with coronary artery disease[10] and in individuals at high risk of future myocardial infarction.[11]

Patients with coronavirus disease 19 (COVID-19) are at high risk for thrombotic arterial and venous occlusions.[12] The close relationship between COVID-19 and thrombosis is of significant clinical importance. There are increasing reports of venous thromboembolism in COVID-19 patients.[13] and arterial thrombosis including strokes and myocardial infarctions have been described.[14]

According to Yu Zuo, Mark Warnock and co-author (2020, september) markedly elevated levels of both PAI-1 and tPA were detected in patients with COVID-19 as compared with healthy controls, which included a significant correlation between levels of PAI-1 and tPA among COVID-19 patients.

In view of the above, we set out to determine the activity of plasminogen activator inhibitor type 1 and plasminogen activator in patients with COVID-19.
The aim of the study: To assess plasminogen and plasminogen activator inhibitor-1 in Covid-19 with ischemic heart disease

MATERIAL AND METHODS OF RESEARCH

The study involved 32 patients who were hospitalized at the ATLAS distribution center with a diagnosis of COVID-19, virus identified (code U07.1 according to ICD-10), the diagnosis was made according to version 6 of the temporary guidelines of the Ministry of Health of the Republic of Uzbekistan). Patients at the time of the diagnosis of COVID-19 suffered from coronary artery disease: stable angina pectoris II -IV functional class (FC). All patients gave informed consent to participate in the study. The exclusion criteria were patients who were in intensive care wards in another part of the ATLAS distribution center.

Analysis of the data obtained from patients with COVID-19 showed that 1 comorbid pathology was found in 5 patients (15, 6%), 2 and 3 comorbid pathologies in 23 patients (71.8%). In particular, the most frequently noted comorbid pathologies: obesity, diabetes mellitus, bronchial asthma, gout, chronic non-calculous cholecystitis.

Average age of included patients was 66, 5±1,8 years, of them women were 18/32 (56,2%) and men 14/32 (43,7%). Besides of patients we had a controle group, wich consist of 28 practical healthy people. They were women 16/28 (57, 1%) and men 12/28 (42,8%), avarege age was 59,4 ±2,4, comparable with the main group.

Determination of the activity of the plasminogen and plasminogen activator inhibitor 1-type (PAI-1) in patients with COVID-19 by taking blood at the ATLAS distribution center with its further delivery to the laboratory of Genotexnology LLC.

THE RESULTS AND DISCUSSION

The data obtained in the study reflected the total content of the biomarker in the blood, its relationship with risk factors for coronary heart disease against the background of coronavirus infection. In the main group's patients 71, 8% (23/32) had appreciable high level of PAI-1. Average index was 73, 5±7, 6 ng/ml. This index in control group didn't increased and equaled 40, 2 ±2, 1 ng/ml. Once a thrombus resulting from a hypercoagulability condition is formed it is dissolved by the fibrinolytic system. So, researchers have hypothesized that a decrease in fibrinolytic activity could be a risk factor for ischemic events.[15] In our investigation we didin't find increasing level of plasminogen, vice versa this marker was a little bit decreased. In the main group average index of plasminogen was 141,3±4,2 ng/ml, in control group was 150-250±1,9ng/ml (table 1).

Table 1: Level of plasminogen activator inhibitor -1 and plasminogen level in healthy people and COVID-19.

Index	Healthy people, n=28	Patients with COVID-19, n=32
PAI -1 (ng/ml)	40,2 ±2,1	73,5±7,6*
Plasminogen (%)	112,4±1,9	72,3±4,2*

Note: * - $p < 0,05$

We found markedly elevated levels of PAI-1 among patients hospitalized with COVID-19. The PAI -1 level in patients was authentically increased by 33.3 ng / ml in COVID-19 patients compared to healthy individuals. Level of plasminogen decreased with 1,7 in the main group.

Table 2: Coagulogram indicators of patients with COVID-19 and healthy individuals.

Index	Healthy people, n=28	Patients with COVID-19, n=32
Platelets (10^9/l)	188±15,2	242±21,3*
Clotting time (min.)	3^2±0,1 3^4±0,1	3^7±0,1 3^9±0,1
PTI (%)	70,8±3,1	91,9±5,3
Activated partial thromboplastin time (sec.)	30,8±0,2	28,1±0,9
International normalized ratio	0,81±0,05	0,99±0,03
Fibrinogen (mg/l)	2,9±0,2	3,7±0,1
Hematocrit (%)	32,3±1,2	37,1±1,2

Note: * - $p < 0,05$

The results authentically showed that there was a significant predominance of the number of platelets by 54±6.1x10^9/l, PTI by 21.1% compared to the rest of the indicators in relation to the comparison group.

It has previously been indicated that an increase in plasma PAI-1 levels can induce a hypercoagulable state. Our clinical study has demonstrated increased levels of PAI-1 in plasma in patients with coronary artery disease and Covid-19 in persons with high cardiovascular risk. Numerous COVID-19 patients showed levels of fibrinogen, t-PA and PAI-1 that were above the consensus normal range. Observed that a positive correlation between fibrinogen and plasminogen levels and a negative correlation of D-dimer with both fibrinogen (and plasminogen. Plasma levels of PAI-1 and t-PA were somewhat correlated.[16,17,18]

Limited data suggest a high incidence of deep vein thrombosis and pulmonary embolism in up to 40% of patients, despite the use of a standard dose of low-molecular-weight heparin (LMWH) in most cases. Prophylactic LMWH has been recommended by the International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH), but the best effective dosage is uncertain.[19]

CONCLUSION

Plasma level of plasminogen activator inhibitor-1, but not plasminogen levels were higher in patients with CAD compared to healthy people. This dates give to continue to investigate plasminogen system with coronary artery disease especially in Covid-19.

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