ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Association Between Soluble Urokinase Plasminogen Activator Receptor And Interleukin 6 In The Diagnosis Of Coronary Artery Disease Patients.

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ABSTRACT

Coronary artery diseases CAD considered one of a major cause of morbidity and mortality worldwide. suPAR plays a crucial role in the complex pathophysiology of the CAD . IL-6 is a pro-inflammatory cytokine which is generated in CAD. Therefore, we investigate the diagnostic role and differential value of suPAR and IL-6 in ST myocardial infarction elevation and stable angina.The serum levels of suPAR and IL-6 were measured in 30 patients with myocardial infarction, 30 patients with stable angina and 30 healthy volunteers which are differentiated by (ECG) at baseline .We also examined the cardiac biomarkers troponin I and CK-MB by immunoassay and spectrophotometric methods, respectively and Lipid profile .We observed that suPAR and IL-6 level was significantly different between the myocardial infarction group and the control group ($p<0.001$) and between the stable angina group and the control group ($p<0.001$).. Furthermore, this result showed a correlation with the traditional cardiac biomarkers troponin I (+ve r = .725) and CK-MB (+ve r = .421) in myocardial group patient. We concluded that suPAR and IL-6 are stable biomarkers and have a positive correlation with cardiac biomarkers in ST-segment elevation MI patients and patients with stable angina that may aid in the diagnosis of CAD.

Keywords: Coronary artery diseases, biomarkers, suPAR, IL-6, diagnosis, lipid profile

https://doi.org/10.33887/rjpbcs/2019.10.3.35

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ISSN: 0975-8585

INTRODUCTION

Atherosclerosis considered one of the major reason for mortality in developed countries it is a progressive inflammatory disease **[1].** Early atherosclerosis is recognized by the attachment of monocytes to the endothelium of the blood vessel and their stealth into the subendothelial space in the intima of the vessel which separated into macrophages **[2and3].** Macrophages in the atheroma might have pro-inflammatory proprieties of M1 macrophages, which produce high levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNFα), or characteristics of M2 macrophages, which are more prominent producers of the anti-inflammatory cytokines IL-10) **[4]**.

ST-segment elevation myocardial infarction (STEMI) defined by presence of increased cardiac biomarkers of necrosis (usually troponin I) with at least 1 value above the 99th percentile along with occurrence of myocardial ischemia with at least 1 of the following: imaging evidence of new loss of myocardium, or new wall motion abnormality, electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block **[5],** Stable angina is a major debilitating health condition with common chronic symptoms of intermittent, reversible chest pain or discomfort. It has a major negative impact on health-related quality of life (HRQoL), including poor general health status, pain, impaired role functioning, activity restriction, inability to self-manage, and psychological distress **[6].**

There are many cardiac biomarkers for coronary artery diseases, one of which is troponin. Troponin is a complex comprised of troponin isoforms I/T expressed selectively in the heart and expressed in both skeletal and cardiac muscles. **[7]** Cardiac troponin I (cTnI) is considered to be specific to myocardial tissue. Serum levels elevate within 3-12 hours, reach a peak at 24-48 hours from the onset of chest pain, and return to baseline over 5-14 days **[8]**.

Creatine kinase (CK) is an enzyme that is found primarily in the cardiac muscle and skeletal muscle. This enzyme has 3 isoenzymes on of them is CK-MB which is the specific cardiac muscle fraction **[9]**.

Soluble urokinase plasminogen activator receptor (suPAR) has been identified as an inflammatory biomarker that is released into the circulation by cleavage of the membrane-bound uPAR from various cells, including inflammatory and endothelial cells **[10].** High suPAR levels have been reported in ruptured atherosclerotic plaque or segments with severe atherosclerosis due to its role in migration, orchestrating cellular adhesion and proliferation during tissue remodeling in the atherosclerotic plaque **[11]**.

SuPAR is an emerging biomarker that represents activation of both immunity and inflammation. It accumulates in the atherosclerotic lesion, and plasma levels of suPAR have been associated with increased incidence of cardiovascular events **[12],** These findings together with the knowledge that suPAR is a stable protein; make it interesting as a future biomarker for the diagnosis of coronary artery diseases (CAD) **[13].**

Interleukin 6 (IL-6) is anti-inflammatory myokine and a pro-inflammatory cytokine. Recent studies have demonstrated that elevated levels of serum IL-6 provide precious information for the risk evaluation of long-term cardiovascular mortality in patients with ST-elevation myocardial infarction and are a potent predictor of cardiovascular and all-cause death **[14].**

The present study was aimed to investigate the possible diagnostic value and transitory course of suPAR and IL-6 compared to traditional biomarkers in patients that have ST-segment elevation myocardial infarction (STEMI), patients with ST-segment depression (stable angina), and the correlation between them.

PATIENTS AND METHODS

Study design

The study comprised of 90 subjects divided into 3 groups. Group (1): 30 patients presenting with chest pain due to MI, Group (2): 30 patients presenting with stable angina, Group (3): 30 healthy volunteers recruited from the Cardiology Department of Banha University hospital, Egypt. Blood samples were obtained from patients on admission before revascularization. The study was conducted from July 2015 to June 2016. This study was

designed to determine the diagnostic utility of measurements of IL-6 and suPAR in patients with STEMI and stable angina patients.

All patient included in this study were subjected to electrocardiogram (ECG) examination and complete blood picture (CBC), lipid profile analysis, cardiac enzyme analysis (Troponin I and CK- MB) and inflammatory markers (suPAR and IL-6). The Patients included in the study are those have CAD for greater than 30 years with, Ischemic patients before medical treatment and surgical intervention .otherwise patients with Neoplastic, infectious, connective tissue and inflammatory diseases, Deep vein thrombosis, Embolism of pulmonary. Patients taking immunosuppressant agents were excluded from the study.

Sample collection

Blood samples were drawn at 5 to 8 hours on admission before the biomarkers of myocardial necrosis (troponin I, creatine kinase-MB) systematically diminish. The whole blood samples were immediately used for CBC, while serum samples were delivered in a vacutainer serum separator tube without anticoagulant and stored at −80°C until subsequent processing and measurement.

Biochemical measurements

Serum levels of IL-6 and suPAR were measured using kits from Assay pro™ ELISA Kits, USA and Cusabio Biotech Co., Ltd., China, respectively according to manufacturer protocol. The concentration of troponin I in serum was determined by the lateral flow immunoassay method. This test was performed by ichroma™ Tn-I kit obtained from (Boditech Med Incorporated, Republic of Korea) according to manufacturer protocols.

Serum CK-MB activity was determined using a colorimetric assay kit method obtained from DiaSys Diagnostic Systems (Germany) and performed according to manufacturer protocols. Total cholesterol (TC), measured by the enzymatic colorimetric method, (cholesterol-LS, BioMed, Germany). Triglycerides (TGs) which were measured by an enzymatic colorimetric method using commercial kits (Spinreact, S.A, Spain), and high-density lipoprotein cholesterol (HDL-C), which was determined by a precipitation method using commercial kits (BioMed, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula, where LDL-C = [TC − HDL-C − (TGs/5)] (Friedewald *et al*., 1972).

Hematological measurements

The Sysmex® automated hematology analyzer KX-21N (Sysmex Corporation, Kobe 651-0073, Japan) was used to determine hemoglobin (Hb) concentration, hematocrit value (HCT), white blood cell count (WBC), red blood cell count (RBCs), and platelet count (PLTs).

Statistical analysis

Data were analyzed using the SPSS statistical package version 16 (USA). The results were reported as the mean ± SD. The Shapiro-Wilk test was used to assess the normality of data. In the normally distributed variables, one way ANOVA with LSD post-hoc multiple comparisons were used for comparison between groups. In the non-normally distributed variables, Mann-Whitney test and Kruskal-Wallis test were used for comparison between groups, as appropriate. Correlation between two continuous variables (either one or both is parametric) was done using Pearson's correlation; while non-parametric correlations were done using Spearman's rank correlation. Receiver operating characteristic (ROC) curves were plotted. An area under the ROC curve was calculated to describe the predictive accuracy of different markers. The cutoff points were determined using Youden-Index .p value ≤0.05" was considered to be statistically significant.

Results

Baseline characteristics of all studied groups are presented in **[Table 1**].In our study the age mean in Group I is 53.3±2.11 with the range from 35 years to 85 years while in Group II the age means is 52.1±2.86 with the range from 33 years to 88 years. The age mean in Group III is 47.4±2.57 with rang from 32 years to 80 years. No significant statistical difference between the three groups.

ISSN: 0975-8585

While in Group I males were 24 (80%) and females were 6 (20%) but in Group II males were 25 (83%) and females were 5 (17%). In group III males were 19 (63%) and females were 11 (37%). There is no also significant statistical difference between the three groups.

Current Smoking was detected in 46% of patients in Group I, 60% in group II and 16% in Group III with significant statistical difference.

In Group I, there was a significant increase ($p < .001$) in serum troponin I 1.61 (0.4-3.8 mg/L) compared with group III 0.14(0.01-0.2) mg /L However, there is no significant difference between Group II and Group III. In Group II, the serum level was 0.17(0.1-0.3) mg /L **[Table 2]**

In Group I, there was a significant increase ($p < 0.001$) in serum CK-MB (60.8±3.24 mg/L) compared with Group III (12.27±0.81 mg/l). However, there was no significant difference between Group II and Group III. In Group II the serum level was (16.4±0.68 mg /L) **[Table 2]**

There was a significant elevation of both IL-6 and suPAR in Group I (0.953±0.12 ng/ml and 1.808±0.13 ng/ml, respectively) compared with Group III (0.284±0.06 ng/ml and 1.566±0.14 ng/ml, respectively). While there was no significant difference in IL-6 between Group II and Group III, suPAR was significantly increased in Group II (1.566±0.14 ng/ml) compared with Group III **[Table 3]**

Serum troponin I showed a significant positive correlation with both serum IL-6 and serum suPAR ($p < 0.001$) in Group I. Serum creatine kinase-MB (CK-MB) showed a significant positive correlation with both serum IL-6 ($p < 0.001$) and serum suPAR ($p < 0.001$) in Group I [**Table 3]**

Combined ROC curves were constructed for estimating the association between angina pectoris and the quantitative measurements of IL-6 and suPAR. Both variables were significantly associated with angina pectoris $P<0.001$. **(Table4, fig.2).** We also determined the association between myocardial infarction and the quantitative measurements of both IL-6 and suPAR. Both variables were significantly associated with myocardial infarctions according to **(Table 4, fig. 1).**

Table (1): Baseline characteristics of all studied groups

Variable	Group I (STEMI)	Group II (Stable angina)	Normal control
Age (years)	53.3±2.11	52.1±2.86	47.4±2.57
Gender male/female	24/6	25/5	19/11
Current Smoking %	no. (%) 14 (46.7)	no. (%) 18 (60.0)	no. (%) 5 (16.7)
Hypertension %	60	55	20
LDL-cholesterol (mmol/l)	188±4.49^{bc}	171±6.53^{a}	159±3.93^{a}
HDL-cholesterol (mmol/l)	43.2±0.82	45.8±1.2	43.6±0.84
TG (mmol/l)	175±6.89	182±8.19^{c}	159±3.25^{b}
Total cholesterol (mmol/l)	264±6.8^{bc}	243±4.06^{ac}	181±3.49^{ab}
Hemoglobin (g/dL)	12.71±0.35	12.16±0.3	12.36±0.3

Data are presented as the mean (±SD), BP blood pressure; HDL: high-density cholesterol, TG: triglyceride, LDL: low-density cholesterol and a: significant vs MI, b: significant vs angina, c: significant vs control. ($P <0.05$)

ISSN: 0975-8585

Table (2): suPAR , IL-6, CK-MB and Troponin I levels in the studied group

Group	IL-6 (ng/ml)	suPAR (ng/ ml)	CK-MB (µg/ l)	Troponin I (µg/l)
Group I (STEMI)	0.953 (.03-2) [bc]	1.808 (0.7-3)[c]	60.8±3.24[bc]	1.61 (0.4-3.8) [bc]
Group II (stable Angina)	0.284 (0.01-1.2)[ac]	1.566 (0.1-2.9)[c]	16.4±0.68[a]	0.17(0.1-0.3)[a]
Group III (control)	0.234 (0.02-1.1)[ab]	0.679 (0.1-2)[ab]	12.27±0.81 [a]	0.14(0.01-0.2)[a]

All measures are expressed as mean±SD (n=30 for each group), except Troponin I, IL6, suPAR as median (min-max)
a: significante vs MI, b: significante vs angina, c: significante vs control.

Table (3): Correlation between suPAR and IL-6 levels and different lipid profile makers and cardiac biomarkers in the STEMI group.

	Total cholesterol (mmol/l)	TG (mmol/l)	Creatine kinase MB (µg/L)	Troponin I (µg/L)	IL-6 (ng/ml)	suPAR(ng/ml)	LDL (mmol/l)
IL-6 (ng/ ml)	0.351	0.332	0.486	0.675	_	0.520	0.246
suPAR (ng/ ml)	0.430	0.342	0.421	0.725	0.520	_	0.252
P value	< 0.01	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.05

Table (4): ROC curve, of suPAR levels for determining susceptibility and severity among STEMI, stable angina patients and IL-6 levels in MI and angina patients.

angina group					
Marker	**AUC**	**p-value**	**cut-off**	**sensitivity**	**specificity**
IL6	0.71	0.005	0.1	0.67	0.73
suPAR	0.79	<0.0001	0.89	0.83	0.80
Troponin I	0.58	0.3	0.2	0.47	0.77
CK-MB	0.74	0.001	18.5	0.40	0.97
STEMI group					
Marker	**AUC**	**p-value**	**cut-off**	**sensitivity**	**specificity**
IL6	0.84	<0.0001	0.12	0.77	0.80
suPAR	0.91	<0.0001	0.89	0.87	0.80
Troponin I	1	<0.0001	0.31	1	1
CK-MB	1	<0.0001	25	1	1

ISSN: 0975-8585

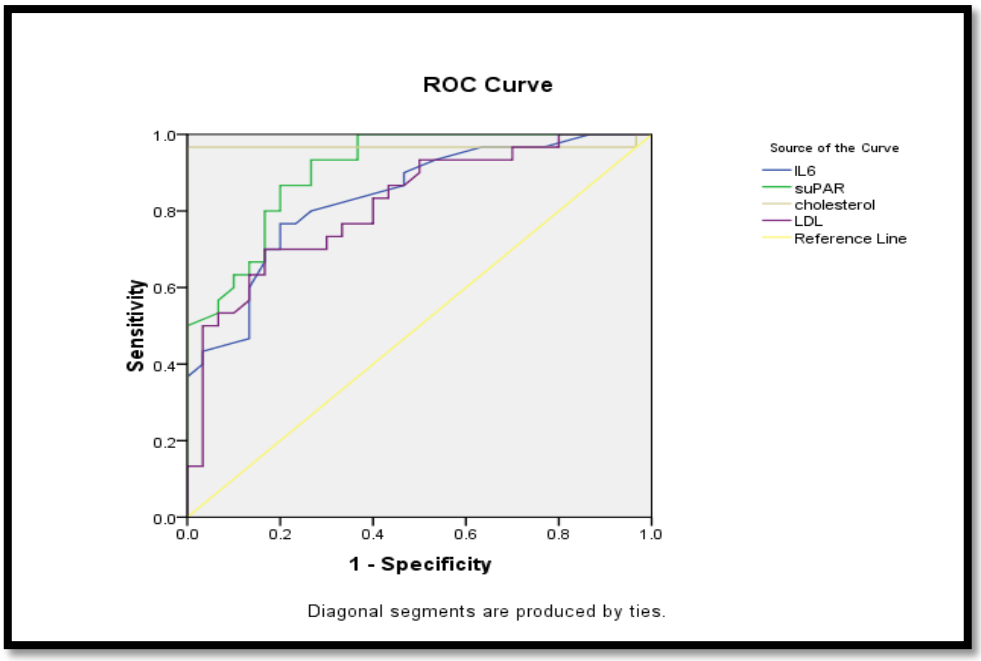

Fig. 1: ROC curve for the diagnosis of STEMI

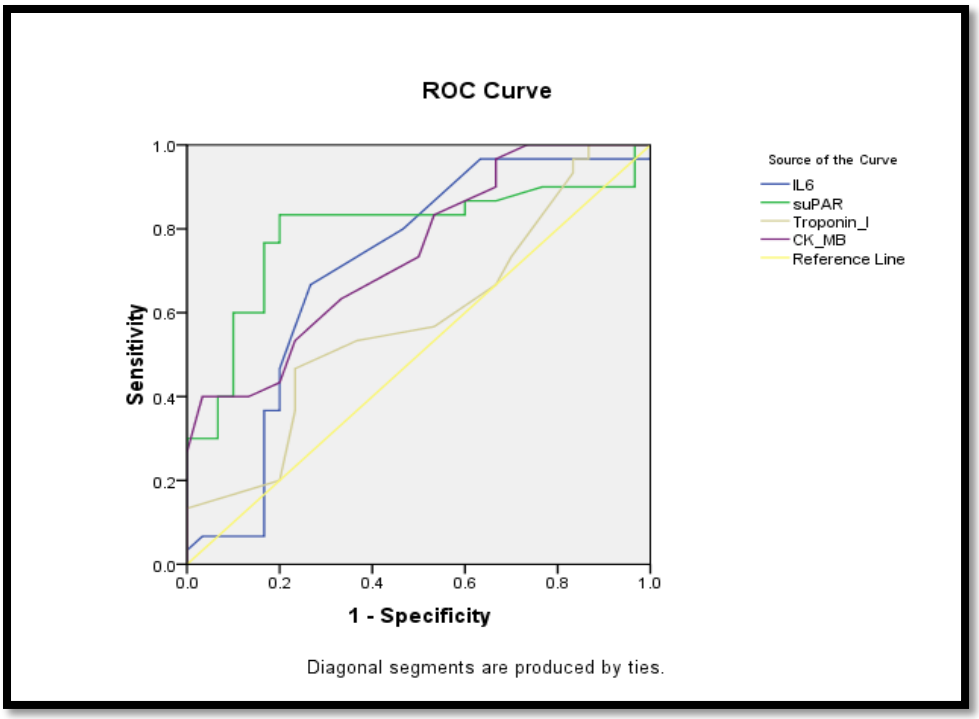

Fig. 2: ROC curve for the diagnosis of angina

DISCUSSION

MI is a complex cascade of inflammatory processes, fibrosis, myocardial injury and hemodynamic processes play a major role for reparation, scar formation and remodeling of the infarcted tissue and are involved in the development of heart failure.Poor prognosis following MI is related to large infarct size, left ventricular dysfunction and adverse remodeling. Measurement of biomarker concentrations after AMI might provide a cost-efficient and widely available tool to assess infarct severity, myocardial dysfunction, and clinical outcome **[15].** Study the complex pathophysiology of acute myocardial infarction (AMI) revealed some biomarkers may aid to measure infarct size, myocardial dysfunction, and clinical outcomes and to recognize highly-risked patients and establish individualized treatment and secondary prevention strategies. Cardiac troponins, especially the new

generation of high-sensitivity cardiac troponins and BNP are widely used for post-MI risk stratification **[16].** We concentrate on newer generation biomarkers in patients suffering AMI and their incremental value for risk stratification.

This study was carried out to examine the significant levels of suPAR and IL-6 in different types of CAD that differentiate according to ECG. CAD patients divided into two groups STEMI patients and ST-segment depression patients (stable angina).

In the present study, data showed that suPAR levels were significantly increased in STEMI patients and patients with stable angina compared with the control group. These result in agreement with **Kollar and his colleague** who found that suPAR levels have a positive correlation with plaque positive atherosclerosis patients, however, the result showed no significant difference between angina groups in comparison with MI group **[17and18]**.

Moreover, the ROC curves data prescribed herein showed high sensitivity (87%) and high specificity (80%) of suPAR as a biomarker in myocardial patients and sensitivity (83%) and specificity (80%) of the biomarker in the angina group. Our results were in line with **Kjellman et al** who showed that suPAR is an independent predictor of mortality in cardiovascular disease patients **[19].**

SuPAR has previously been shown to be a strong marker of death in patients with other critical illnesses **[20and 21].** In our study, the levels of suPAR at baseline correlated with the classical cardiac biomarkers troponin I (+ve r = 0.725) and CK-MB (+ve r = 0.421). SuPAR provides valuable information that is not conveyed by traditional cardiovascular risk factors. The elevation of suPAR levels in STEMI patients and stable angina patients could be attributed to the uPA/uPAR system in the pathogenesis of atherosclerosis**[22and 24]**

The extracellular segment of suPAR could be cleaved and shed from the cell surface into body fluids, thereby serving as a marker for the intensity of atheroma progression **[25].** There is increasing evidence that cells in the atherosclerotic arterial wall, including smooth muscle cell, macrophages, and endothelial cell secrete uPA in high levels in the advanced stages of atherogenesis **[26].** Therefore, our results indicate that suPAR could be considered as a predictor and diagnostic biomarker for STEMI patients and stable angina patients.

Impairment of uPA and/or uPAR functions, or inhibition of their expression lead to increasing evidence that the uPA/uPAR system is attributed with atherogenicity increase, may provide a novel therapeutic approach to mitigate atherosclerosis **[27and 28].**

In our research, in contrast to myocardial necrosis biomarkers (creatinine kinase-MB and troponin I). It was interesting that suPAR levels did not elevate considerably after admission. Therefore, these biomarker characteristics could make suPAR a crucial and suitable candidate in management decisions regarding acute chest pain in patients with suspected ST-elevation acute coronary syndrome **[29].**

SuPAR points out different pathophysiological pathways compared to the more traditional biomarkers clinically used in this setting, further indicating that suPAR could be a worthy addition to current risk algorithms **[30].**

The acute-phase of protein are mostly synthesized in the liver, and their production is stimulated by mainly tumor necrosis factor (TNF)-α. IL-6 serum level is linked to undesired clinical outcomes in patients hospitalized ST-elevated myocardial infarction (STEMI) patients. Moreover; measurement of serum IL-6 may aid in the diagnosis of many chronic conditions that could be reasons for mortality in the elderly patients which have induce and tolerate a systemic inflammatory state **[31]**

In the present study, we also examined the role of IL-6 as a biomarker for the diagnosis of coronary artery disease (CAD). Our results showed that IL-6 levels were significantly increased in groups of CAD (P >.001) compared with control group and positively correlated with the other cardiac biomarkers, troponin I (+ve = 0.675) and CK-MB (+ve = .482) in MI patients. It has been reported that elevated inflammatory agent's levels, such as IL-6, are attributed to acute ischemic conditions and are predictors of recurrent events in patients with coronary artery disease **[32].** Furthermore, the current study revealed that IL-6 has moderate sensitivity 77 % and 80%

specificity in MI patient while having 67% sensitivity and 73 % in angina group this evidence by the number of studies report a positive association between serum IL-6 concentration and the risk of mortality from CAD **[33].**

CONCLUSIONS

This study demonstrated that elevated circulating concentrations of suPAR and IL-6 may have diagnostic value and provided crucial prognostic information in patients with acute chest pain ST-segment depression (stable angina) and STEMI patients. Elevated levels of plasma suPAR and IL-6 are associated with the presence and severity of CAD and are independent predictors of death and MI in patients with suspected or known CAD. These Novel biomarkers reflecting different pathological pathways which significantly up-or downregulated in patients suffering from CAD. Consequently by means of biomarker levels this aid as a guided treatment and tailored secondary prevention program which may improve prognosis in patients suffering CAD.

Ethical approval: The study was approved by the Banha University Ethical Committee and was conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Informed consent: All patients have been assigned an informed consent for their participation in the study.

REFERENCES

[1] Libby P, Ridker PM., Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011; 473: 317-325.

[2] Businaro R, Tagliani A, Buttari B,et al. Cellular and molecular players in the atherosclerotic plaque progression. Ann. N Y. Ac. Ad Sci, 2012;1262:134-141

[3] Libby P. Inflammation in atherosclerosis. Arteriosclerosis Thrombi Vasc Biol 2012; 32(9): 2045-51.

[4] Hoeksema, MA. Stoger, JL., de, Winther MP. Molecular pathways regulating macrophage polarization: implications for atherosclerosis. Curr Atheroscler Rep 2012; 14:254-263.

[5] Cannon CP, Battler A, Brindis RG, et al. Novel biomarkers predicting cardiac function after acute myocardial infarction. Br Med Bull. 2016; 119:63-74.

[6] Wu J, Han Y, Xu J, Lu Y, et al. Chronic Stable Angina Is Associated with Lower Health-Related Quality of Life: Evidence from Chinese Patients. PLoS ONE 2014; 9(5): e97294.

[7] Kyung Chan Park, David C.Gaze, Paul O. Collinson, et al. Cardiac troponin T composition in normal and regenerating human skeletal muscle. Cardiovascular. *Research* 2017; 113:1708–1718.

[8] Clause KC, Tchao J, Powell MC, et al. Developing Cardiac and Skeletal Muscle Share Fast-Skeletal Myosin Heavy Chain and Cardiac Troponin-I Expression 2012; PLoS ONE 7(7): e40725.

[9] Sabesan R, Hofer H, Roorda A. Characterizing the Human Cone Photoreceptor Mosaic via Dynamic Photopigment Densitometry. PLoS ONE 2015 ;10(12): e0144891.

[10] Thuno, M, Macho, B, Eugen-Olsen, J. SUPAR the molecular crystal ball. Dis Markers 2009; 27:157–7

[11] Eugen-Olsen J, Andersen O, Linneberg A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. J.Intern Med 2010; 268:296 –308.

[12] Persson M, Engström G, Björkbacka H , Hedblad B. Soluble urokinase plasminogen activator receptor in plasma is associated with an incidence of CVD. Results from the Malmö Diet and Cancer Study. Atherosclerosis 2012; 220**:**502–505.

[13] Riisbro R, Christensen IJ, Høgdall C, Brünner N, Høgdall E .Soluble urokinase plasminogen activator receptor measurements: influence of sample handling. Int J Biol Markers. 2001; 16:233–239.

[14] Dongfang Su , Zhongxia Li., Xinrui Li. Association between Serum Interleukin-6 Concentration and Mortality in Patients with Coronary Artery. Article ID 726178 (2013).

[15] Nikolaos G. The inflammatory response in myocardial injury, repair and remodeling Nat Rev Cardiol. 2014; 11(5): 255–265.

[16] Feistritzer HJ, Klug G, Reinstadler SJ,et al. Sebastian Wöhrer, Christoph Brenner, Et al. biomarkers predicting cardiac function after acute myocardial infarction. Br Med Bull 2016; 119: 63-74.

[17] Koller L, Stojkovic S, Richter B,et al. Soluble Urokinase-Type Plasminogen Activator Receptor Improves Risk Prediction in Patients with Chronic Heart Failure. JACC. Heart.Fail 2017; 5:268-277.

[18] Gyöngyösi M, Glogar D, Weidinger F, et al. Association between plasmin activation system and intravascular ultrasound signs of plaque instability in patients with unstable angina and non-st-segment elevation myocardial infarction. Am Heart J 2004; 147:158-164.

[19] Kjellman O, Akre O, Gustafsson G ,et al.Soluble urokinase plasminogen activator receptor as a prognostic

marker in men participating in prostate cancer screening. J.Intern Med 2011; 269:299–305.

[20] Huttunen R, Syrjänen J, Vuento R, et al. Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteremia. a prospective cohort study. Intern Med 2011; 270:32– 40.

[21] Koch A, Voigt S, Kruschinski C, et al. Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. Crit Care2011; 15: 1, R63.

[22] Cozen AE, Moriwaki H, Kremen M, et al. Macrophage-targeted overexpression of urokinase causes accelerated atherosclerosis, coronary artery occlusions, and premature death. Circulation 2004; 109:2129–2135.

[23] Kremen M, Krishnan R, Emery I, et al .Plasminogen mediates the atherogenic effects of macrophage-expressed urokinase and accelerates atherosclerosis in apoE- knockout mice. PNAS 2008; 105:17109-17114.

[24] Krishnan R1, Kremen M, Hu JH, et al. Level of Macrophage uPA Expression Is an Important Determinant of Atherosclerotic Lesion Growth in Apoe−/− Mice. Arterioscler.Thromb Vasc Biol 2009; 29:1737-1744.

[25] Fuhrman B. The urokinase system in the pathogenesis of atherosclerosis. Atherosclerosis 2012; 222:8-14.

[26] Farris SD1, Hu JH, Krishnan R,et al. Mechanisms of Urokinase Plasminogen Activator (uPA)-mediated Atherosclerosis Role of the uPA receptor and S100A8/A9 proteins. JBC 2013; 286: 22665-22677.

[27] Chen W, Jin. WQ, Chen LF, Williams T, Zhu WL, Fang Q. Urokinase receptor surface expression regulates monocyte migration and is associated with accelerated atherosclerosis. Int J Cardiol 2012; 161:103–110.

[28] Poland N, Gamliel-Lazarovich A, Coleman R, Fuhrman B. Urokinase-type plasminogen activator (uPA) stimulates triglyceride synthesis in Huh7 hepatoma cells via p38-dependent upregulation of DGAT2. Atherosclerosis 2014; 237: 200-7.

[29] Lyngbæk S, Andersson C, Marott JL,et al. Soluble Urokinase Plasminogen Activator Receptor for Risk Prediction in Patients Admitted with Acute Chest Pain. Clinical chemistry 2013; 59: 1621–1629.

[30] Lyngbæk S, Marott JL, Møller DV, et al. Usefulness of Soluble Urokinase Plasminogen Activator Receptor to Predict Re, peat Myocardial Infarction and Mortality in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention. The American Journal of Cardiology 2012; 110: 1756 –1763.

[31] Nicola R. and Jason J. Role of C - reactive protein at Sites of Inflammation and Infection. Front Immunol 2018; 9: 754

[32] Fan ZX1, Q Hua, Y P Li, R K Liu, Z Yang. Interleukin-6, but not soluble adhesion molecules, predicts subsequent mortality from cardiovascular disease in patients with acute st segment elevation myocardial infarction. Cell Biochemistry and Biophysics 2011; 61:443–448.

[33] E. Z. Fisman, M. Benderly, R. J. Esper, et al. Interleukin-6 and the risk of future cardiovascular events in patients with angina pectoris and/or healed myocardial infarction. American Journal of Cardiology 2006; 98:14–18