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Soluble triggering receptor expressed on myeloid cells like transcript-1 (sTLT-1) levels in patients with acute coronary syndrome

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Abstract
Background: Acute coronary syndrome (ACS) is a primary ethology for high morbidity and mortality rates worldwide. Soluble Triggering Receptor Expressed on Myeloid cells like transcript-1 (sTLT-1) is a membrane-bound soluble protein released by α-granules. This work was aimed assessing the (sTLT-1) levels among various ACS types with further evaluation of its correlation with other clinical & laboratory parameters.
Methods: Sixty newly diagnosed ST segment elevation myocardial infarctions (STEMI), NSTEMI and unstable angina (UA) patients were involved in our research. In addition, twenty healthy individuals served as control. Participants went through a categorization into the following groups: The first group includes sixty patients suffering from ACS which is subdivided into three equal subgroups: a) STEMI, b) NSTEMI and c) UA. The second group includes twenty healthy individuals (control group).
Results: The main important finding in the present work was significantly increase in sTLT-1 levels in ACS group compared to control group (p<0.001). A positive relationship between sTLT-1 and triglyceride (r=0.349, p=0.006), low density lipoprotein (LDL) (R=0.270, P=0.037) and neutrophil to lymphocyte ratio (NLR) (r=0.259, p=0.046) was documented. A negative relationship between sTLT-1 and HDL (r= -0.262, p=0.043) was documented. No significant association between sTLT-1 and fasting blood glucose (FBG), post prandial blood glucose (PPFBG), age, glycated hemoglobin (HbA1C), cholesterol, hemoglobin (HB), hematocrit, white blood cell (WBCs), creatine kinase-myoglobin binding (CK MB), troponin, platelets count and body mass index (BMI).
Conclusions: ACS is associated with increased level of sTLT-1 suggesting that sTLT-1 could be a potential diagnostic marker in ACS.

Keywords: Triggering receptor, soluble triggering receptor expressed on myeloid cells like transcript-1, acute coronary syndrome, STEMI

Introduction

Acute coronary syndrome (ACS) occurs as a result of reduced blood flow in coronary arteries impacting the proper function of the cardiac muscle, thus leading to death due to the accumulation of fatty deposits (plaques) in and over the coronary arteries wall [1].

Blood clots are often formed due to the plaque deposit splits or rupturing, which impedes the blood flow to cardiac muscles, leading to damage in muscles tissues [2].

ACS involves three types based on the symptoms duration, the electrocardiogram changes and blood testing results: (STEMI, 30%), (NSTEMI) (25%), or (UA, 38%). In general, when the symptom lasts below thirty minutes, UA is often diagnosed. If it lasts for above thirty minutes, acute myocardial infarction (AMI) is diagnosed [3].

The triggering Receptor Expressed on Myeloid cells like transcript-1(TLT) is a type 1, single Ig domain orphan receptor stored in α-granules of the platelet and megakaryocyte. In addition, it is produced as a soluble fragment in the form of sTLT-1 [4].

sTLT-1 impacts hemostasis through promoting actin polymerization, thus increasing the rate of platelets adherence to the endothelium and their aggregation. Thus, sTLT-1 facilitates the atherothrombosis process. When released, it acts as a chemotactic mediator that induces further platelets activation and enhances the organized thrombi attachment over the vascular endothelium as well [5].

Rupture of the atherosclerotic plaque induces lipid core exposure to the vascular lumen, which enhances platelets degranulation, thus evacuating platelets content like sTLT-1 and stimulating platelet aggregation which decrease coronary artery perfusion. ACS is primarily caused by platelet aggregation and thrombus development as a consequence of plaque rupture [6].

Based on the current knowledge,limited literature illustrating the sTLT-1 role in the onset and progression of ACS was documented.Therefore, this work was aimed to assessing sTLT-1 levels in different ACS types with further evaluation of its correlation with other clinical & laboratory parameters.

Patients and Methods

Sixty patients whose age ranges between 40 and 63 years, both sexes, newly diagnosed STEMI, NSTEMI, UA prior to any medications according to ESC about criteria of the definition of AMI were involved in our research. In addition, twenty healthy individuals served as control.

The research was performed following approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt. All participants were asked to fill an informed concent.

Exclusion criteria were patients on antiplatelet therapy, any evidence of acute and chronic inflammatory conditions, malignancy, injury and surgery.

Participants underwent a categorization of two groups: The first Group: (n=60) suffering from ACS which is subdivided into 3 equal subgroups: a) STEMI, b) NSTEMI and c) UA with mean age (52.53±6.76). The second group: (n=20) healthy individuals (control group) with mean age was (36.55±5.17) years.

All patients and control underwent: a medical history taking, physical examination, laboratory testing (Routine laboratory testing: CBC was done on Japanese ERMA PCE-210 N cell counter, glycated hemoglobin (HbA1C) was done on Japanese Tosoh HPLC G8, fasting blood glucose (FBG), postprandial blood glucose (PPFBG), lipid profile, creatine kinase-myoglobin binding (CK-MB) were done on comprehensive automated chemistry analyzer Konelab Prime 60i, Helsinki, Finland and serum Quantitative cTnI was done on Japanese Tosoh AIA 1800 and specific laboratory investigations: assessment of sTLT-1 by enzyme linked immunosorbent assay (ELISA).

Whole blood was obtained during admission before any medical treatment by standard venipuncture in VACUETTE® blood collection tubes (Greiner Bio-One, Kremsmünster, Austria) involving tripotassium (K3) Ethylene Diamine Tetraacetic Acid (EDTA) for CBC, HbA1c & sTLT-1 and tubes containing clot activator/sep for CK-MB & Troponin. Serum samples were allowed to go for clotting at a duration between five and ten minutes at room temperature and then centrifuged for ten minutes. After overnight fasting, whole blood was obtained by standard venipuncture in tubes containing clot activator for routine laboratory investigations as lipid profile, FBG then after 2-hour, postprandial blood glucose was measured.

Determination of sTLT-1

Estimated by Enzyme linked immunosorbent assay (ELISA) kit supplied by Bioassay Technology Laboratory, Catalog number: E7057Hu, China.

Principle of assay

Human sTLT-1 antibody had been pre-coated on the plate. When sTLT-1 from the sample was present, it bound to the antibodies coated on the wells. After that, biotinylated human sTLT-1 antibody was incorporated, and it bound to the sample's sTLT-1. The biotinylated sTLT-1 antibody was then bound by the streptavidin-HRP incorporation. Unbound Streptavidin-HRP was eliminated at the time of washing step following incubation. The quantity of Human sTLT-1 was then associated with colour development in the substrate solution. When incorporating an acidic stop solution, the process ceased, and absorbance was then measured at 450 nm.

Statistical analysis

The research went through a Statistical analysis utlizing IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Quantitative variables were displayed as mean and standard deviation (SD) and a comparison was performed among three groups utilizing ANOVA (F) test with post hoc test (Tukey). Qualitative variables were displayed as frequency and percentage (%) and were analysed using the Chi-square test. Receiver Operating Characteristic curve (ROC) analysis was utilized to determine the parameter overall predictivity and the best cut-off value with detection of sensitivity and specificity at this cut-off value. Pearson correlation coefficient (r) was measured to obtain strength and direction of association among two numerical variables, both are continuous and at least one of them is normally distributed. A two tailed P value < 0.05 was determined to be statistically significant.

Results

Table 1: Comparison between the two studied groups based on demographic data

		Patients (n = 60)	Control (n = 20)	P
Age (years)		52.53±6.76	36.55±5.17	<0.001*
Sex	Male	33(55.0%)	12(60.0%)	0.696
	Female	27(45.0%)	8(40.0%)	
BMI (kg/m^2)		27.31±3.34	27.94±2.93	0.456

Data exhibited as mean ± SD or frequency (%). *Significant p value<0.05, BMI: Body mass index,: ACS: Acute coronary syndrome

Regarding HTN and family history of ACS, there was significant difference among studied groups (P = 0.038, 0.032 respectively). Regarding smoking and diabetic history, there was non-significant difference (P = 0.897 and 0.292 respectively).

Table 2: Comparison between the two studied groups according to routine laboratory investigations:

	Patients (n = 60)	Control (n = 20)	P
Glycemic Profile			
FBG (mg/dl)	131.0±57.86	71.35±15.80	<0.001*
PPBG (mg/dl)	184.1±70.56	126.7±7.80	<0.001*
HbA1C (%)	7.33±1.40	4.95±0.52	<0.001*

Lipid Profile			
Cholesterol (mg/dl)	265.77±40.35	144.10±19.63	<0.001*
Triglyceride (mg/dl)	216.70±55.31	128.35±16.80	<0.001*
HDL (mg/dl)	31.33±7.52	53.80±6.14	<0.001*
LDL (mg/dl)	213.92±27.99	59.75±12.48	<0.001*
	Patients (n = 60)	**Control (n = 20)**	**P**
Hb (gm./dl)	12.38±1.90	12.85±0.97	0.156
Hematocrit (%)	38.11±5.68	39.50±2.85	0.157
WBCs ($\times 10^3$)	13.47±4.58	7.09±1.67	<0.001*
NLR	4.61±1.36	2.38±0.61	<0.001*
Platelets ($\times 10^3$)	216.4±66.57	256.55±51.57	0.016*
CK MB (IU/L)	39.90±12.22	17.15±4.88	<0.001*
Troponin (ng/ml)	2.42±1.51	0.02±0.01	<0.001*

Data exhibited as mean ± SD or frequency (%). *Significant p value<0.05, FBG: fasting blood glucose, PPBG: post prandial blood glucose, HbA1C: glycated hemoglobin, HDL: high density lipoprotein, LDL: low density lipoprotein, CBC: complete blood count, HB: Hemoglobin, WBCs: white blood cell, NLR: neutrophil/lymphocytes ratio, CK MB: creatine kinase-myoglobin binding.

Regarding STLT-1, a significant rise in sTLT-1 level in ACS patient group was documented in comparison with control group (p<0.001). Table 3.

Table 3: Comparison between the four studied groups according to STLT-1

	STEMI (n= 20)	NSTEMI (n= 20)	UA (n= 20)	Control (n= 20)	p
STLT-1 (ng/ml)	6.87±2.29	6.28±2.50	3.25±1.35	1.28±0.40	**<0.001***
p_1	<0.001*	<0.001*	0.001*		
Sig. bet. Grps	p_1<0.001, p_2=0.577, p_3=0.001*, p_4=0.006*				

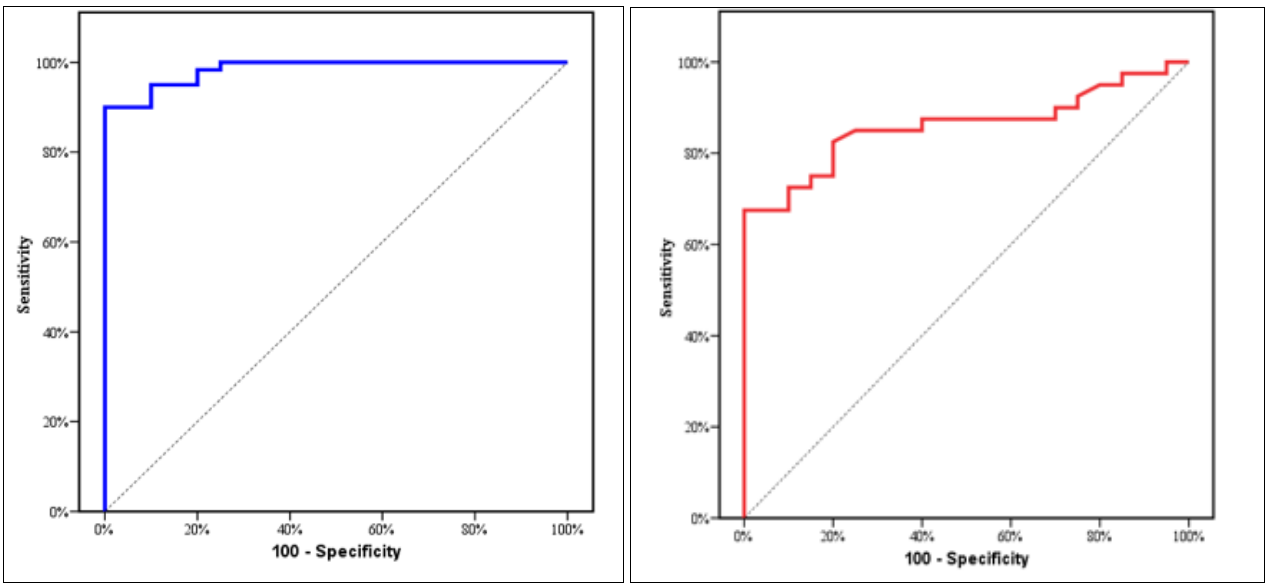
Data are exhibited mean ± SD, *Significant p value<0.05, p1: p value for comparing between Control and each other group,p2: p value for comparing between STEMI and NSTEMI,p3: p value for comparing between STEMI and UA, p4: p value for comparing between NSTEMI and UA, STEMI: ST segment elevation myocardial infarctions, sTLT-1: Soluble Triggering Receptor Expressed on Myeloid cells like transcript-1, UA: Unstable angina.

Table 4: Correlation between sTLT-1 and different parameters in groups

	sTLT–1	
	r	p
Age	0.012	0.928
FBG	0.237	0.073
PPFBG	0.012	0.929
HbA1C	0.166	0.204
Cholesterol	0.005	0.971
Triglyceride	0.349	0.006*
HDL	-0.262	0.043*
LDL	0.270	0.037*
Hb	-0.044	0.740
Hematocrit	-0.048	0.718
WBCs	0.015	0.911
NLR	0.259	0.046*
Platelets	-0.226	0.083
CK. MB	0.009	0.944
Troponin	-0.139	0.291
BMI	0.237	0.068

Rs: Spearman coefficient, sTLT-1: Soluble Triggering Receptor Expressed on Myeloid cells like transcript-1, FBG: fasting blood glucose, PPBG: post prandial blood glucose, HbA1C: glycated hemoglobin, HDL: high density lipoprotein, LDL: low density lipoprotein, HB: Hemoglobin, WBCs: white blood cell, NLR: neutrophil/lymphocytes ratio, CK MB: creatine kinase-myoglobin binding, BMI: Body mass index.

ROC curve: A) The area under the curve (AUC) of 0.984 yielding sensitivity of 95%, specificity of 90%, positive predictive value (PPV) of 96.6 and negative predictive value (NPV) of 81.8. While B) The AUC of 0.860 yielding sensitivity of 82.50%, specificity of 80%, positive predictive value (PPV) of 89.2, negative predictive value (NPV) of 69.6. Figure 1



(A) **(B)**

Fig 1: ROC curve for Soluble Triggering Receptor Expressed on Myeloid cells like transcript-1 to A) discriminate cases (n = 60) from control (n = 20), B) to discriminate MI (ST segment elevation myocardial infarctions and non-ST segment elevation myocardial infarctions NSTEMI (n = 40) from unstable Angina (n= 20)

Discussion

ACS involves clinical symptoms related to acute cardiac ischaemia. It is classified into UA, NSTEMI and STEMI [7].

Traditional risk factors for ACS are often related to low-grade chronic inflammation which has a fundamental relation with the disease occurrence [8]. The proteolytic enzymes secreted by inflammatory cells in the atheroma degrades the fibrous cap and induce its rupture (unstable plaque), thus promoting coagulation and thrombosis formation [9].

In this work, there was significant difference as regard to age in individuals with ACS and the control group (p<0.001). The results were in line with earlier research performed by Özalp *et al*. [10] and Malyutina S *et al*. [11].

Our research reported a significant variation among ACS and control groups regarding fasting, postprandial blood glucose and HbA1C (p<0.001) and same findings were documented by Tarcin *et al*. [12] and Hygriv Rao B *et al*. [13].

Our research also documented a significant increase in cholesterol, triglyceride and LDL in ACS patient group as opposed to control group (p<0.001) and there was significantly decrease in HDL in ACS group as opposed to control group (p<0.001) similarly to that addressed by Zhao, X. *et al*. [14] and Özalp *et al*. [10].

In our research there was significantly difference in WBCs count, neutrophil/lymphocyte ratio and platelets count in ACS group as apposed to control group (p<0.001 and 0.016). Aligned with Budzianowski *et al*. [17], Adam AM *et al*. [16] and Özalp *et al*. [10]. This can be explained by the role of leukocytes in the ACS pathophysiology, given their impact on the atherosclerotic plaques instability. During early stages, leukocytes penetrate endothelial cells then activated once they reach the tunica intima. Microvascularity is then formed there through the induction of these cells. Thus, plaques become more prone to rupture. A close association between cardiovascular mortality and the platelets count or aggregation is present. Platelets have a superior importance in ACS pathophysiology when compounded with fibrin, coronary thrombus is formed.

In this work, regarding the mean value of CK-MB and troponin I there was significant variations among the ACS patient group and control group (p<0.001). Those findings aligned with Ye J *et al*. [18], and Adidharma *et al*. [19].

In this search, group I (ACS patients), sTLT-1 level in STEMI patients ranged between 1.90 – 9.56 ng/ml with mean value of (6.87±2.29) while in NSTEMI patients it ranged between 1.66 – 10.20 ng/ml with mean value of (6.28±2.50) while in UA patients it ranged between 1.60 – 5.70 ng/ml with mean value of (3.25±1.35), in contrast sTLT-1 level in the second group (healthy controls) ranged between 0.61 – 1.94 ng/ml with mean value of 1.28±0.40.

Results obtained from this work revealed that there was significantly increase in sTLT-1 levels in ACS group compared to control group (p<0.001) and this aligned with Shen L. *et al*. [20] and there is significant difference between STEMI, NSTEMI patients with UA patients (p=0.001 and 0.006 respectively). By sticking to endothelial cells and leaving chemotactic mediators on their surface, platelets have an impact on atherogenesis. sTLT-1 could influence hemostasis during inflammation by promoting actin polymerization, which causes platelet aggregation and endothelial adhesion to rise [5].

In this research the results addressed a positive significant association between sTLT-1 level in the patients groups and TG, LDL, N/L ratio (p=0.006, 0.037 and 0.046 respectively), and a negative significant association with HDL (p=0.043) and those results were in the same reported by Shen *et al*. [20] and Zhao, X. *et al*. [14].

In this study, the ROC analysis of sTLT-1 revealed that the best cut off level for of sTLT-1 in discriminating ACS individuals from control groups was 1.81 yielding sensitivity of 95%, specificity of 90%, PPV of 96.6 and NPV of 81.8 while the ROC analysis of sTLT-1 revealed The best cut off level for plasma sTLT-1 in distinguishing ACS patient group from each other was 4.32 ng./ml yielding sensitivity of 82.50%, specificity of 80%, PPV of 89.2 and NPV of 69.6.

Limitations: Of our study were small sample size. Therefore, we advocate doing subsequent studies with a

greater number of patients to enable more extensive statistical analysis. Also our study was applied on patients with similar ethinic background.

Conclusion

ACS is associated with increased level of sTLT-1 suggesting that sTLT-1 could be a potential diagnostic marker that had a great role in the onset and progression of ACS.

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Conflict of Interest: Nil

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