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Original article

Estimation of Serum Levels of Lipoprotein (A) Might Help to Resolve the Dilemma of Differentiation Between Unstable Angina and Non-ST-Elevation Myocardial Infarction

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Abstract

Objectives: Evaluation of the performance of estimated serum levels of lipoprotein(a) [Lp(a)] and tissue plasminogen activator (t-PA) in the discrimination between patients presenting by cardiac events. **Patients & Methods:** 314 patients presenting with a clinical picture suggestive of an acute cardiac event (ACE) underwent clinical and laboratory workup according to the 2017 ESC Guidelines for the management of acute myocardial infarction (AMI). Blood samples were obtained for ELISA estimation of serum Lp(a) and plasma t-PA levels. **Results:** Clinically, 247 patients had angina, 166 stable angina (SA), 81 unstable angina (UA), 67 patients had AMI, 44 had non-ST-elevation MI (NSTEMI) and 23 patients had STEMI. Serum levels of Lp(a) were significantly higher in total patients' samples especially UA and MI patients compared to control samples, but were lower in those with compared to patients' samples. Further, Lp(a) levels were significantly higher in MI than UA patients' samples. Estimated t-PA levels were significantly higher in patients' than control samples, but were significantly higher in MI than angina patients' samples. Statistical analyses defined high estimated levels of Lp(a), t-PA, total cholesterol, and obesity as the significant differentiating variables between SA and UA patients and defined high levels of LP(a), t-PA, and obesity, and age as the significant predictors for NSTEMI. **Conclusion**: Elevated serum levels of Lp(a) might differentiate between UA patients and SA and NSTEMI with high specificity.

Keywords: Lipoprotein(a),;Tissue plasminogen activator; Unstable angina; Acute myocardial infarction

Introduction

Lipoprotein(a) [Lp(a)] differs structurally from low-density lipoprotein (LDL) in the presence of a second protein, apolipoprotein (a) [apo(a)] that is bound non-covalently to apo B with one single disulfide bridge [(1)]. Plasminogen is a member of the superfamily "serine protease" and is a key component of the fibrinolytic system [(2)]. A domain of inactive protease in apo(a) structure has an amino acid sequence coincident with that of plasminogen in 94%. Replacement of serine by arginine in the serine-protease domains in both apo(a) and plasminogen hinders the activation of the protease by tissue plasminogen activator (t-PA), urokinase, or streptokinase [(3)].

Genetically, the gene encoding for the human apo(a) protein, the *LPA*, showed homology with up to 70% of the human Plg gene, and both genes are located in the same cluster in the long arm of chromosome 6 [(4)].

Acute coronary syndrome (ACS) is one of the main manifestations of coronary artery disease that is associated with high prevalence and the worst prognosis [(5)]. ACS is characterized by an imbalance between myocardial oxygen supply and demand

secondary to either coronary artery narrowing due to a non-occlusive thrombus that has developed on a disrupted atherosclerotic plaque in unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), or to an occlusive coronary lesion in STEMI [(6)]. UA had a risk of major adverse cardiovascular events similar to stable angina (SA), but its 1-year risk of death was higher than SA, and lower compared to NSTEMI [(7)]. Moreover, among patients with acute myocardial infarction, the prevalence of STEMI cases was higher than that of NSTEMI [(8)].

Differentiation between cases of UA and NSTEMI is dependent on the estimation of cardiac injury markers, however, only less than half of patients met the diagnostic UA criteria, and about 20% of patients with a diagnosis of UA could be reclassified to type 1 NSTEMI [(9)]. This dilemma needs the search for other differentiating variables, thus the current study tried to evaluate the performance of estimated serum levels of Lp(a) and plasma t-PA in the discrimination between patients presenting by acute cardiac events (ACE).

Design

Prospective non-randomized comparative case-control clinical trial

Setting

Departments of Cardiology and Medical Biochemistry, Faculty of Medicine, Benha University

Ethical considerations

The preliminary approval of the study protocol was obtained in December 2018 for patients' evaluation, case collection, and obtaining samples for investigations, and the final approval was obtained at the end of case collection by number: RC: 37.11.2022. All enrolled patients or their nearest relatives signed written informed consent before inclusion in the study.

Blindness

The obtained blood samples were sent for estimation of the study variables as numbered samples without a report concerning the clinical diagnosis or the

indication for performing these investigations, and the cardiologist was also blinded about the results of the study investigations, to approach the double-blindness. At the end of case collection, the obtained clinical data were interpreted against the lab results of the targeted investigations.

Patients and Methods

The study was started after the preliminary approval of the study protocol was obtained in December 2018 for patients' evaluation, case collection, and obtaining samples for investigations. All patients attending the emergency department or cardiology outpatient clinic with a clinical picture suggestive of ACE were evaluated for the presence of exclusion criteria. The study also included 20 healthy volunteers who were free of both inclusion and exclusion criteria and accepted to give blood samples as controls for the intended investigations.

Exclusion criteria

Patients with metabolic syndrome and endocrinal disorder, especially obese patients or those arriving in cardiogenic shock, or had liver diseases, coagulopathy, autoimmune disorders, or those on medications affecting liver functions were excluded from the study, as well as patients that refused to sign the fully informed written consent to participate in the study.

Inclusion criteria

Patients who attended an ACE and were free of exclusion criteria were included in the study.

Clinical evaluating tools

Clinical evaluation depended on medical history taking, physical examination, 12-lead ECG, and estimation of cardiac markers' levels at the time of initial presentation. Presence of high serum levels of troponin I, troponin T, or the MB isoenzyme of creatine phosphokinase indicated myocardial injury and excluded angina; SA or UA [(10)]. Acute myocardial infarction (AMI) was diagnosed according to the 2017 ESC Guidelines for the management of AMI in patients presenting with typical angina pectoris-like manifestation with elevated serum creatine kinase and cardiac Troponin I. ST-segment elevation (STE) was used to differentiate between STEMI and NSTEMI and was defined as at least 0.2 mV elevations in ≥2 contiguous precordial leads or at least 0.1 mV elevations in the limbs lead [(11)].

Laboratory investigations

At the time of attendance to the hospital, 6 ml blood samples were obtained and divided into two parts; 2 ml was collected in a plain tube, allowed to clot, and centrifuged at 1500 rpm to separate serum that was collected in Eppendorf tube and kept frozen at -20^{o}C till being ELISA assayed for estimation of serum levels of lipoprotein(a) [Lp(a)] [(12)] using ELISA kits the Simple 90-minutes protocol of Abcam (Abcam Inc., Cambridge, USA; catalog no. ab212165). The other 4 ml was collected in a heparinized tube and divided into two parts one for estimation of plasma total cholesterol (TC), high-, low- and very low-density lipoproteins (HDL, LDL, and VLDL), and triglycerides (TG) levels and the second was kept frozen for ELISA estimation of plasma levels of human t-PA using Abcam kit (catalog no. ab190812), [(13)].

Statistical analysis

The results were analyzed using the SPSS software program (Version 23, 2017; IBM, Armonk, USA) for evaluation of the significance of the differences at a cutoff value of $p<0.05$ indicates significant difference using ANOVA and Chi-square tests. The ability of the demographic data and lab variables to differentiate between clinical diagnoses was assessed using Regression analysis (Stepwise Method), and the Receiver Characteristic Curve (ROC) analysis.

Results

During the duration of the study, 331 ACE patients were evaluated. 17 patients were excluded (6 patients had chronic liver disease, 3 patients had coagulopathy, 3 patients had metabolic syndrome, 3 patients had endocrinopathy, and two patients presented by cardiogenic shock). According to the provisional diagnosis, 166 patients (52.9%) had SA, 81 patients (25.8%) had UA, 44 patients (14%) had NSTEMI and 23 patients (7.3%) had STEMI. Demographic and clinical data of the studied patients showed non-significant differences as shown in table 1.

Table (1): Demographic and clinical data of the enrolled patients categorized according to the provisional diagnosis

Variables		Total	SA (n=166)	UA (n=81)	NSTEMI (n=44)	STEMI (n=23)	*p*-value
Age (years)		61.8±7.4	61.4±6.7	63.7±8.7	60.9±7.2	63.8±8.4	**0.058**
Gender	Males	227 (72.3%)	124 (39.5%)	51 (16.2%)	37 (11.8%)	15 (4.8%)	**0.159**
	Females	87 (27.7%)	42 (13.4%)	30 (9.6%)	7 (2.2%)	8 (2.5)	
BMI (kg/m^2)		31.3±3.4	30.9±2.9	32.4±4.1	31±3.4	31.2±3.7	**0.166**
Smoking	Ex	140 (44.6%)	78 (24.8%)	33 (10.5%)	19 (6.1%)	10 (3.2%)	
	Current	90 (28.6%)	51 (16.2%)	27 (8.6%)	7 (2.2%)	5 (1.6%)	**0.154**
	Non	84 (26.8%)	37 (11.8%)	21 (6.8%)	18 (5.7%)	8 (2.5%)	
Associated medical problems	DM	94 (29.9%)	49 (15.6%)	25 (8%)	13 (4.1%)	7 (2.2%)	**0.528**
	HTN	180 (57.3%)	97 (30.9%)	46 (14.6%)	24 (7.6%)	13 (4.1%)	**0.238**
	CKD	45 (14.3%)	23 (7.3%)	12 (3.8%)	7 (2.2%)	3 (1%)	**0.166**
	COPD	23 (7.3%)	12 (3.8%)	6 (1.9%)	3 (1%)	2 (0.6%)	**0.083**
	Previous MI	**25 (8%)**	**13 (4.1%)**	**6 (1.9%)**	**4 (1.3%)**	**2 (0.6%)**	**0.131**

P-value indicates the significance of the difference between groups; BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; MI: Myocardial infarction; NSTEMI: non-ST-elevation MI

Mean plasma TG, VLDL and TC levels in samples of SA patients were significantly lower in comparison to patients who had UA and STEMI. Moreover, samples of STEMI patients showed significantly higher VLDL levels than that of NSTEMI patients (Table 2).

Serum levels of Lp(a) were significantly higher in total patients' samples especially samples of UA and MI patients, but were non-significantly higher in samples of SA patients compared to control samples. Serum levels of Lp(a) estimated in SA patients'

samples were significantly lower than samples of other patients. Estimated Lp(a) UA patients' samples were significantly lower than MI patients with non-significantly lower levels in NSTEMI than STEMI patients. On the contrary, plasma levels of t-PA estimated in all patients' samples were significantly higher than control levels. Estimated t-PA levels were significantly lower in angina samples than in samples of MI patients with non-significant differences between levels estimated in patients who had angina or MI (Table 3).

Table (2): Plasma lipid levels estimated at the time of enrolment of the studied patients

Variables	Total	SA (n=166)	UA (n=81)	NSTEMI (n=44)	STEMI (n=23)
TC (mg/dl)	194.4±23.8	188.1±23.9	202±21*	198.2±21.1	**205.5±25***
HDL (mg/dl)	42.6±5.4	42.5±5	42.3±6	42.9±5.5	**44.2±6.2**
TG (mg/dl)	61.1±10.3	57.5±9.5*	64.6±8.9*	64.6±10.7*	**68.4±10***
VLDL (mg/dl)	23.7±5.8	22.6±5.8	25.7±5.2*	22.1±5.5	**28±4.7*†**
LDL (mg/dl)	**67±24.9**	**65.6±23.5**	**69.6±24.8**	**68.6±26.6**	**64.9±32**

*: indicates the significance of the difference in marked samples compared to samples of patients who had stable angina; †: indicates the significance of the difference in marked samples compared to samples of patients who had unstable angina

Table (3): Serum levels of lipoprotein(a) and tissue plasminogen estimated at the time of enrolment of the studied patients

	Control (n=20)	SA (n=166)	UA (n=81)	NSTEMI (n=44)	STEMI (n=23)	Total
Lipoprotein (a) (mg/dl)	**11.3±3.2**	**12.9±4**	**14.4±2.8**	**15.63±3.6**	**16.7±4.4**	**13.9±4.4**
Vs. control		0.109	0.0002	0.0098	<0.001	**0.0078**
Vs. stable angina			0.0015	0.011	<0.001	
Vs. unstable angina				0.042	0.019	
Vs. NSTEMI					0.161	
Tissue plasminogen activator (ng/ml)	**10.3±2.2**	**18.5±4.3**	**19.5±4.3**	**22.4±6.5**	**24.4±6.7**	**19.7±5.2**
Vs. control		<0.001	<0.001	<0.001	<0.001	
Vs. stable angina			0.072	<0.001	<0.001	
Vs. unstable angina				0.0035	0.0001	
Vs. NSTEMI					**0.256**	

ROC curve analysis defined high levels of Lp(a), t-PA, TC, and LDL, and high BMI as the significant differentiating variables between SA and UA patients (Fig. 1). Regression analysis of these variables showed higher differentiating ability for high serum LP(a) levels than other variables for SA patients. For differentiation between UA and NSTEMI patients, ROC curve analysis arranged the variables in decreasing order of significance as follows: LP(a), t-PA, BMI, and age, while regression analysis defined high serum levels of Lp(a) and plasma t-PA, and old age as the significant predictors for NSTEMI (Table 4, Fig. 2).

Table (4): Statistical analyses of studied variables as differentiating variables

Analysis	Receiver Operating Characteristic curve				Regression	
Variables	**AUC**	**SE**	**p-value**	**95%CI**	**β**	**p-value**
UA versus SA						
Age	0.541	0.033	0.215	0.476-0.605	0.078	**0.170**
BMI	0.572	0.033	0.028	0.507-0.636	0.081	**0.153**
Total cholesterol	0.629	0.032	<0.001	0.567-0.690	0.135	**0.023**
Low-density lipoprotein	0.542	0.033	0.199	0.477-0.607	0.163	**0.006**
Lipoprotein(a)	0.660	0.031	<0.001	0.599-0.722	0.261	**<0.001**
Tissue plasminogen	0.645	0.031	<0.001	0.584-0.707	0.200	**0.001**
UA versus NSTEMI						
Age	0.691	0.074	0.011	0.545-0.837	0.265	**0.018**
BMI	0.696	0.070	0.009	0.558-0833	0.206	**0.100**
Total cholesterol	0.616	0.074	0.122	0.471-0.760	0.155	**0.218**
Low-density lipoprotein	0.608	0.075	0.148	0.462-0.754	0.124	**0.327**
Lipoprotein(a)	0.744	0.063	0.001	0.621-0.867	0.393	**0.001**
Tissue plasminogen	**0.712**	**0.067**	**0.005**	**0.581-0.843**	**0.295**	**0.017**

AUC: Area under curve; SE: Standard error; CI: Confidence interval; β: Regression Coefficient

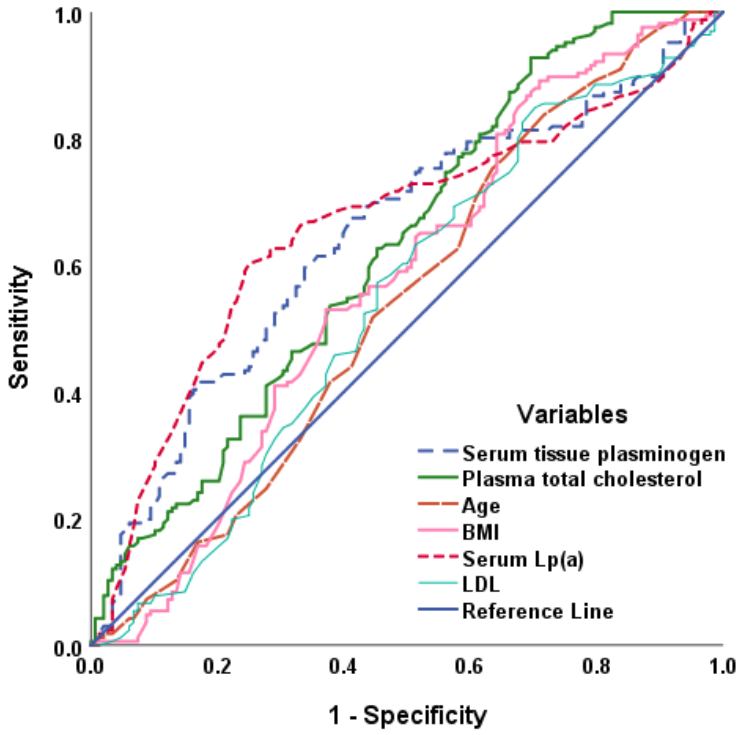

Fig. (1): ROC curve analysis for demographic and lab data for differentiation between SA and UA patients

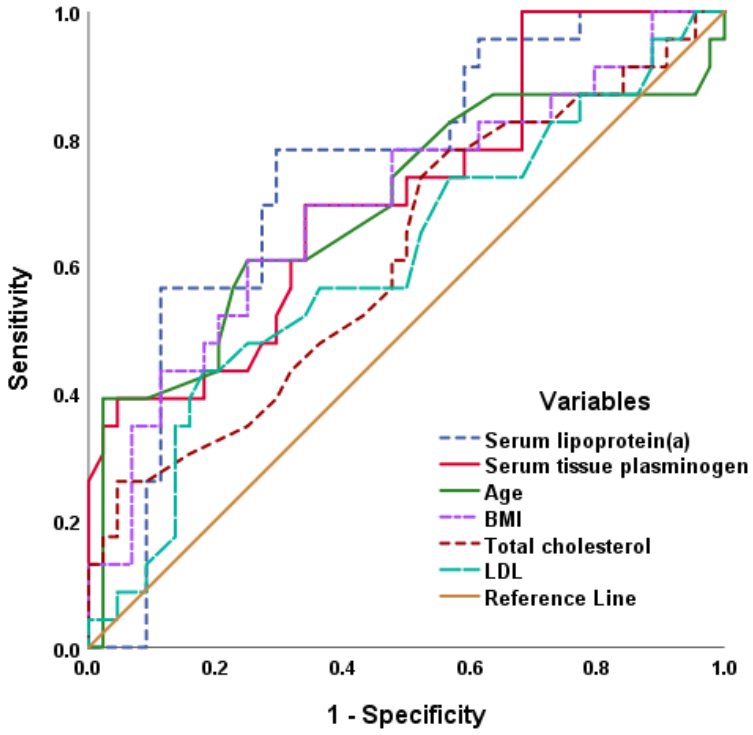

Fig. (2): ROC curve analysis for demographic and lab data for differentiation between UA and NSTEMI patients

Discussion

The differentiation between UA patients and patients with another ACE is still a matter of debate because the dependence on serum levels of cardiac injury is still questionable as previously documented. The current study detected a high ability to the estimation of serum levels of Lp(a) at the time of attendance to the clinic with ACE for differentiation between UA and SA patients on one side and between UA and NSTEMI patients on the other side. Moreover, the addition of estimation of plasma t-PA levels results in superior identification ability for NSTEMI patients. In support of the

application of estimation of serum Lp(a) in patients of ACE, **Xiang et al.** [14] and **Yoon et al.** [15] reported that abnormal Lp(a) levels are an independent risk factor for the development of recurrent ischemic attacks after percutaneous coronary interventions (PCI). **Silverio et al.** [16] evaluated the relationship between Lp(a) levels with long-term outcomes in post-MI patients and found higher Lp(a) levels were significantly associated with the risk of recurrent MI and all-cause death, and very high levels could independently predict the long-term outcome in non-diabetic post-MI patients. Another study defined Lp(a) serum levels as an independent predictor of revascularization in diabetic patients with ACE regardless of LDL-C levels and suggested that Lp(a) measurement may help identify high-risk diabetic patients with ACS [17].

Furtherly, elevated Lp(a) levels were found to be associated with increased risks of all-cause death in statin-treated coronary artery disease patients **(18)**. Moreover, observational and genetic studies documented Lp(a) as a well-recognized independent risk factor for atherosclerotic cardiovascular disease, found a prevalence of high Lp(a) levels in 20% of the population and provided evidence for a causal relationship between high Lp(a) levels and increased risk of atherosclerotic cardiovascular disease-related events [(19)].

Regarding plasma t-PA, estimated levels showed non-significant differences between SA and UA on one side or between NSTEMI and STEMI on the other side, despite the significant differences between angina and MI patients. Statistical analyses showed significant differentiating ability between UA and both SA and NSTEMI, but the significance of its differentiating ability was inferior to that of Lp(a). Similarly, multiple earlier studies detected significantly high tPA levels in MI patients than in UA patients but the significance is mostly at a level of <0.05 [(20-22)]. Moreover, adding tPA to conventional risk factors for chronic cardiac disease resulted in significant but small increases in discrimination and modest reclassification of risk [(23)].

The detected ability of estimation of Lp(a) levels for predicting the severity of the cardiac event could be attributed to the stability of its levels as long as no Lp(a) medications were provided and this stability could be attributed to multiple facts; Lp(a) is synthesized in the liver and so has no relation to dietary lipid intake, metabolism or diet restriction [(24)]. Lp(a) differs from LDL in having two protein moieties, apoB100 and apo(a), so could not metabolize through binding to LDL receptors [(25)]. Furthermore, apo(a) protein is encoded by the *LPA* gene in the long arm of chromosome 6 within region 6q2.6-2.7, so it is a conserved protein [(26)] with steady production rate that is only affected by liver diseases [(27)] and not by statin therapy [(28)]. In support of these assumptions, **Deconinck et al.** [(29)] evaluated the value of repeated estimation of Lp(a) levels through a 17-year follow-up study of patients who had the previous ACE and concluded that estimation of Lp(a) levels are reproducible and recommend only a single Lp(a) measurement in an individual's lifetime under specific circumstances to improve cardiovascular risk prediction.

The reported concomitant elevations of Lp(a) and t-PA levels could be attributed to the homology of the *LPA* gene with the human plasminogen gene [(30)] and the presence of a domain of inactive serine-protease, whose amino acid sequence in Apo(a) coincides with that of plasminogen in 94%, but serine replaced arginine in the activation site equivalent to that of plasminogen, thus hinders the conversion of Lp(a) into active protease by t-PA responsible for activation [(31)]. These structural similarities between Lp(a) and plasminogen lead to the interference with the fibrinolytic cascade despite the increased levels of t-PA and account for the atherogenic mechanism of Lp(a) [(32, 30)].

Conclusion:

The escape from the dilemma of differentiation between patients who had UA and NSTEMI requires new biomarkers than dependence on the conventional

markers. Elevated serum levels of Lp(a) might differentiate between types of angina and between UA and NSTEMI with the high area under the ROC curve indicating its high specificity.

Limitations

The study is a single-center study and the sample size was small, this limited the establishment of the utility of Lp(a) as a marker for discrimination between types of ACE.

Recommendations

Wider-scale studies are required for the identification of cutoff points for differentiation between types of ACE, especially between UA and NSTEMI.

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