Cardiovascular Topics

Comparison of serum lipoprotein(a) levels in young and middle-aged patients presenting for the first time with ST-elevation myocardial infarction: a single-centre study

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Abstract

Background: Lipoprotein(a) [Lp(a)] is associated with coronary artery disease due to its atherogenic and thrombogenic nature. In this study, we aimed to compare the level of Lp(a) in young and middle-aged patients with ST-elevation myocardial infarction (STEMI).

Methods: This retrospective study included 287 patients aged 20–65 years who presented to the emergency department for the first time due to STEMI. The patients were divided into two groups: 20–45 years (young group, n = 111) and 46–65 years (middle-aged group, n = 176). The groups were compared in terms of demographic characteristics, co-morbidities and laboratory findings.

Results: In the young group, smoking (99, 89.2% vs 130, 73.9%; p = 0.001), family history of coronary artery disease (75, 67.6% vs 80, 45.5; p < 0.001), serum Lp(a) level [38.1 ± 27.9 (93 ± 68) vs 23.5 ± 23.2 mg/dl (57 ± 56 nmol/l); p < 0.001], triglyceride level [219.1 ± 231.9 (2.48 ± 2.62) vs 170.2 ± 105.6 mg/dl (1.92 ± 1.19 mmol/l); p = 0.018), ejection fraction (52.4 ± 6.1 vs 47.2 ± 7.7%; p = 0.004) and single-vessel disease (83, 74.8% vs 110, 62.5%; p = 0.031) were higher than in the middle-aged group. In multivariable logistic regression analyses, family history (OR: 2.073, 95% CI: 1.210–3.549; p = 0.008), low high-density lipoprotin cholesterol level (OR: 1.032, 95% CI: 1.003–1.062; p = 0.029) and Lp(a) elevation (OR: 1.981, 95% CI: 1.871–3.991; p < 0.001) were possible independent risk factors for STEMI in young patients.

Conclusion: Lp(a) level was found to be a higher and a possible independent risk factor in young patients who presented with STEMI for the first time, compared to the middle-aged patient group. Lp(a) is a highly atherogenic molecule and it has been associated with stroke, heart failure, aortic stenosis, as well as coronary artery disease. Measurement of Lp(a) levels may be recommended in young patients with high cardiovascular risk.

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Cardiovascular disease is the most important cause of mortality and morbidity all over the world despite advances in diagnosis and treatment.[1] Age, gender, diabetes mellitus (DM), hypertension (HT), smoking, obesity and hyperlipidaemia are the leading causes that increase susceptibility to cardiovascular diseases. These risk factors are also responsible for the development and acceleration of atherosclerosis.[2]

The deposition of lipid particles in the sub-intimal areas is involved in the pathogenesis of atherosclerotic plaques. Particularly low-density lipoprotein particles (LDL) have a highly atherogenic structure.[2] Another important molecule implicated in the pathogenesis of atherogenesis is lipoprotein(a) [Lp(a)], which has become increasingly important in recent years and is similar in structure to LDL.

The Lp(a) molecule, which has been proven to be associated with atherosclerotic cardiovascular diseases in most studies with its apolipoprotein B 100 (apoB100) content, is covalently bound to apoB100 by disulfide bonds unlike LDL particles and it contains apolipoprotein(a).[3,4] Lp(a) has been associated with atherosclerotic cardiovascular disease, aortic stenosis and thrombogenicity in recent years.[5,6] It has been found to be at high levels in those with coronary artery disease at a young age.[7]

In this study, we aimed to investigate the relationship between serum Lp(a) levels in young and middle-aged patients who presented for the first time with ST-elevation myocardial infarction (STEMI).

Methods

The study was planned retrospectively, and patients admitted to the emergency department with STEMI between June 2021 and December 2021 were included. All patients presented with typical chest pain and had percutaneous coronary intervention within 90 minutes. Patients who were delayed more than 90 minutes were excluded from the study.

Lp(a) level was measured in 287 patients who applied to the emergency department with STEMI and who met the inclusion

criteria. The study included 287 patients aged 20–65 years who presented to the emergency department for the first time due to STEMI. After the diagnosis of STEMI was made, the patients were hospitalised and underwent coronary angiography (CAG) for at least 30 minutes. The patients were divided into two groups: 20–45 years (young patient group, n = 111) and 46–65 years (middle-aged group, n = 176). When patients were divided into two classes according to their age, previous studies were taken into account.[8]

Fasting serum glucose, creatinine, cholesterol and Lp(a) levels were measured approximately 24 hours after CAG was performed. Serum concentrations of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured using an automatic biochemistry analyser.

Lp(a) was purified from the participants' plasma, and protein, lipid and carbohydrate components were measured separately. The sum of all elements of this purified Lp(a) was given a value in milligrams/deciliter and was used as the assay calibrator. It was calibrated in milligrams per deciliter of the total Lp(a) mass. The serum Lp(a) component was measured by the immunoturbidimetry method using LASAY Lp(a) auto (SHIMA Laboratories Co, Ltd). In our centre, the normal value of serum Lp(a) was < 39 mg/dl (95 nmol/l), the serum HDL-C value was > 40 mg/dl (1.04 mmol/l), and the serum LDL-C value was <130 mg/dl (3.37 mmol/l).

All patients included in the study had not received antihyperlipidaemic treatment before. Data from the medical records of all patients were retrospectively reviewed. The groups were compared in terms of demographic characteristics, co-morbidities and laboratory findings.

CAG was performed using the Judkins technique, and all patients with lesions ≥ 1.5 mm in diameter and causing 50% stenosis in the coronary artery were included in the study. Patients with acute coronary syndrome had a higher troponin level than the 99th percentile upper reference value before cardiac catheterisation. Persistent chest pain or other symptoms are suggestive of ischaemia, ischaemic changes on the electrocardiogram (ECG), including persistent ST-segment elevations in two contiguous leads or new left bundle branch block.[9] CAG was evaluated by two independent cardiologists.

Those who smoked more than one cigarette per day were defined as current smokers. Standard sphygmomanometers were used to measure blood pressure. Family history for coronary artery disease referred to patients whose first-degree relatives were diagnosed with coronary artery disease (< 55 years in men, < 65 years in women).

Patients with previous CAG due to acute coronary syndrome, coronary artery dissection and those in the MINOCA group (myocardial infarction with non-obstructive coronary arteries), those who had previously received antihyperlipidaemic therapy, patients with chronic kidney failure, nephrotic syndrome, chronic liver disease and hypothyroidism were not included in the study. Patients outside the age range of 20–65 years were also excluded from the study.

Ethics committee approval was obtained from the non-interventional clinical research ethics committee (decision number: 2021/236) before the initiation of the study. Written and verbal consent was obtained from all participants. The Declaration of Helsinki was followed in the application of the ethical rules of the study.

All patients received a 12-lead ECG in the supine position after resting for at least 15 minutes (GE Marquette Mac 1200). Each ECG was taken at a paper speed of 25 mm/s, a gain of 10 mV, and a paper format of 3 × 4. ECGs were independently interpreted by two cardiologists.

According to the recommendations of the American Society of Echocardiography, all patients underwent a transthoracic echocardiographic examination with a commercially available device using 4-MHz probes (Vivid 9 Pro, GE Vingmed, Milwaukee, Wisconsin, USA) in the left lateral decubitus position. Left ventricular ejection fraction (LVEF) was calculated according to Simpson's method.[10]

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD) values or median interval and interquartile (IQR) values, whereas categorical variables are expressed as proportions. Shapiro–Wilk and Kolmogorov–Smirnov tests were performed to determine whether the research data had conformed to a normal distribution. The baseline characteristics of the young and middle-aged patients were compared using the Student's t-test for continuous variables that were normally distributed and Pearson's χ^2 test was used for categorical variables.

Risk factors [smoking, family history, low HDL-C, triglyceride, high Lp(a) levels] that may cause STEMI in young patients were included in the logistic regression analysis. Univariable and multivariable logistic regression analyses were performed for the association between young STEMI patients and possible risk factors. For all statistics, a two-tailed p-value below 0.05 was considered significant.

Results

A total of 287 consecutive patients diagnosed with STEMI were included in the study. The mean (± SD) age of the young patients (n = 111) was 39.8 ± 4.1 years and the middle-aged patients (n = 176) was 52.8 ± 4.9 years (p < 0.001).

In the middle-aged patient group, HT (58, 32.9% vs 17, 15.3%; p = 0.001), DM (72, 40.9% vs 14, 12.6%; p < 0.001), serum glucose level [149.7 ± 68.4 vs 117.6 ± 40.8 mg/dl (8.31 ± 3.80 vs 6.53 ± 2.26 mmol/l); p < 0.001], HDL-C level [40.7 ± 11.3 vs 36.8 ± 9.5 mg/dl (1.05 ± 0.29 vs 0.95 ± 0.25 mmol/l); p = 0.005] and left anterior descending artery (LAD) occlusion rate (124, 70.5% vs 41, 36.9%; p < 0.001) were higher than in the young group.

In the young patient group, smoking rate (99, 89.2% vs 130, 73.9%; p = 0.001), family history (75, 67.6% vs 80, 45.5; p < 0.001), serum Lp(a) level [38.1 ± 27.9 vs 23.5 ± 23.2 mg/dl (93.3 ± 68 vs 57 ± 56 mmol/l); p < 0.001], triglyceride level [219.1 ± 231.9 vs 170.2 ± 105.6 mg/dl (2.48 ± 2.62 vs 1.92 ± 1.19 mm); p = 0.018], LVEF (52.4 ± 6.1 vs 47.2 ± 7.7%; p = 0.004) and single-vessel disease (83, 74.8% vs 110, 62.5%; p = 0.031) were higher than in the middle-aged group (Table 1, Fig. 1).

Univariable regression analyses showed smoking (OR: 2.919, 95% CI: 1.469–5.803; p = 0.002), family history (OR: 2.500, 95% CI: 1.522–4.105; p < 0.001), low HDL-C level (OR: 1.039, 95% CI: 1.013–1.066; p = 0.003), triglyceride level (OR: 0.998,

Table 1. Comparison of demographic and clinical features of young and middle-aged patients who presented with acute coronary syndrome for the first time

Variables	*Young age group (20–45 years) (n = 111)*	*Middle-aged group (46–65 years) (n = 176)*	p-*value*
Age, years, mean (SD)	39.8 (4.1)	52.8 (4.9)	< 0.001
Males, *n* (%)	86 (77.5)	146 (84.9)	0.117
BMI, kg/m², mean (SD)	25.3 (9.7)	26.2 (10.7)	0.456
Hypertension, *n* (%)	17 (15.3)	58 (33.3)	0.001
Diabetes mellitus, *n* (%)	14 (12.6)	72 (40.9)	< 0.001
Current smokers, *n* (%)	99 (89.2)	130 (73.9)	0.001
Family history, *n* (%)	75 (67.6)	80 (45.5)	< 0.001
SBP, mmHg, mean (SD)	129.7 (12.6)	132.4 (18.7)	0.087
DBP, mg/Hg, mean (SD)	82.9 (12.5)	87.3 (15.8)	0.124
Heart rate, beat/min, mean (SD)	75.9 (14.4)	78.7 (16.8)	0.234
Ejection fraction, *n* (%)	52.4 (6.1)	47.2 (7.7)	0.004
SPAP, mmHg, mean (SD)	24.6 (3.3)	25.6 (5.2)	0.083
Glucose, mg/dl, mean (SD)	117.6 (40.8)	149.7 (68.4)	< 0.001
(mmol/l)	6.53 (2.26)	8.31 (3.80)	
Creatinine, mg/dl, mean (SD)	0.8 (0.4)	0.9 (0.2)	0.940
Total cholesterol, mg/dl, mean (SD)	185.3 (49.3)	186.9 (38.9)	0.771
(mmol/l)	4.80 (1.28)	4.84 (1.01)	
LDL-C, mg/dl, mean (SD)	110.6 (37.4)	115.1 (33.6)	0.371
(mmol/l)	2.86 (0.97)	2.98 (0.87)	
HDL-C, mg/dl, mean (SD)	36.8 (9.5)	40.7 (11.3)	0.005
(mmol/l)	0.95 (0.25)	1.05 (0.29)	
Triglycerides, mg/dl, mean (SD)	219.1 (231.9)	170.2 (105.6)	0.01
(mmol/l)	2.48 (2.62)	1.92 (1.19)	
Lp(a), mg/dl, mean (SD)	38.1 (27.9)	23.5 (23.2)	< 0.001
(mmol/l)	93 (68)	57 (56)	
TSH, mg/dl, mean (SD)	1.2 (0.7)	1.4 (1.2)	0.227
Uric acid, mg/dl, mean (SD)	5.5 (1.5)	5.4 (1.3)	0.527
LAD CAO, *n* (%)	41 (36.9)	124 (70.5)	< 0.001
CX CAO, *n* (%)	34 (30.6)	60 (34.1)	0.606
RCA CAO, *n* (%)	53 (47.7)	76 (43.2)	0.467
Single CAO, *n* (%)	83 (74.8)	110 (62.5)	0.03
Two CAO, *n* (%)	18 (16.2)	38 (21.6)	0.263
Three CAO, *n* (%)	10 (9.0)	38 (13.2)	0.093

BMI: body mass ındex, SBP: systolic blood pressure, DBP: diastolic blood pressure, CAO: coronary artery occlusion, CX: circumflex artery, LVEF: left ventricular ejection fraction, HDL-C: high-density lipoprotein cholesterol, LAD: left anterior descending artery, LDL-C: low-density lipoprotein cholesterol, RCA: right coronary artery, SPAP: systolic pulmonary artery pressure, TSH: thyroid-stimulating hormone.

Table 2. Univariable and multivariable logistic regression analysis of risk factors of acute coronary syndrome (STEMI) in young adults

	Univariable logistic regression analysis		*Multivariable logistic regression analysis*	
Variables	*OR (95% CI)*	p-*value*	*OR (95% CI)*	p-*value*
Current smokers	2.919 (1.469–5.803)	0.002	0.559 (0.758–4.035)	0.190
Family history	2.500 (1.522–4.105)	0.001	0.598 (0.966–3.449)	0.064
HDL-C	1.039 (1.013–1.066)	0.003	0.430 (1.010–1.080)	0.012
Triglycerides	0.998 (0.996–1.000)	0.01	0.979 (0.998–1.002)	0.760
Lp(a)	1.979 (1.869–3.989)	< 0.001	0.981 (0.967–0.992)	0.001
Hypertension	1.017 (1.510–5.064)	0.002	1.128 (0.123–0.622)	0.005
Diabetes mellitus	1.568 (2.540–9.059)	0.001	1.506 (0.103–0.473)	0.001
Ejection fraction	0.084 (0.887–0.953)	0.009	0.055 (0.904–1.001)	0.052
LAD lesions	1.404 (0.148–0.406)	0.045	0.804 (0.181–1.023)	0.060
Single CAO	0.576 (1.051–3.009)	0.032	0.206 (0.598–2.527)	0.572

CAO: coronary artery occlusion, HDL-C: high-density lipoprotein cholesterol, LAD: left anterior descending artery.

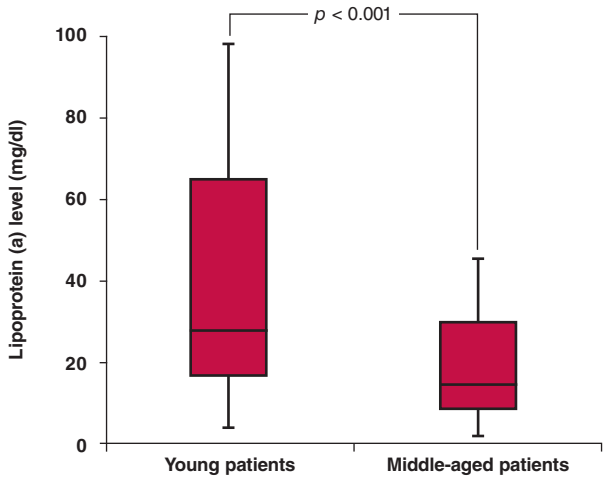

Fig. 1. The association between serum Lp(a) level and young and middle-aged STEMI patients.

95% CI: 0.996–1,000; $p = 0.01$), high Lp(a) level (OR: 1.979, 95% CI: 1.869–3.989; $p < 0.001$), HT (OR: 1.017, 95% CI: 1.510–5.064; $p = 0.002$), DM (OR: 1.568, 95% CI: 2.540–9.059; $p = 0.001$), LVEF (OR: 0.084, 95% CI: 0.887–0.953; $p = 0.009$), LAD occlusion (OR: 0.576, 95% CI: 0.148–0.406; $p = 0.045$) and single-vessel disease (OR: 0.576, 95% CI: 1.051–3.009; $p = 0.032$) were associated with STEMI in the young patient group.

Multivariable regression analysis showed HT (OR: 1.128, 95% CI: 0.123–0.622; $p = 0.005$), DM (OR: 1.506, 95% CI: 0.103–0.473; $p = 0.001$), low HDL-C level (OR: 0.430, 95% CI: 1.010–1.080; $p = 0.012$) and Lp(a) elevation (OR: 0.981, 95% CI: 0.967–0.992; $p = 0.001$) were possible independent risk factors for STEMI in young patients (Table 2).

There was a negative ($r = –0.265$, $p < 0.001$) correlation between Lp(a) level and age, and a positive ($r = 0.214$, $p < 0.001$) correlation between Lp(a) and triglyceride levels and LVEF ($r = 0.166$, $p = 0.005$) (Table 3).

Discussion

In our study, Lp(a) level was found to be higher in young patients who presented with STEMI for the first time, compared to the middle-aged patient group. In addition to Lp(a), a family history of coronary artery disease, low HDL-C levels, high triglyceride levels, HT, DM and smoking were found to be independent risk factors for acute STEMI in young patients. While single-vessel disease was more common in young patients, LAD lesions were more often found in the middle-aged group. Therefore, LVEF was found to be lower in this patient group.

Lp(a) is prothrombotic, pro-inflammatory and pro-atherogenic and causes the development and progression of atherosclerosis.

Table 3. Correlation analyses between Lp(a) level and age, HDL-C and triglyceride levels, and LVEF

Variables	r-*value*	p-*value*
Age	–0.265	< 0.001
HDL-C	–0.061	0.306
Triglyceride	0.214	< 0.001
Ejection fraction	0.166	0.005

Apo(a) is structurally very similar to plasminogen, so it can inhibit or impair plasminogen activation, plasmin formation and fibrinolysis.[11] Lp(a) also binds to macrophages through high-affinity receptors, promoting foam cell formation and cholesterol deposition from atherosclerotic plaques.[12] Numerous studies have shown the relationship between Lp(a) and atherosclerotic cardiovascular diseases. Kamstrup *et al*. revealed in the Copenhagen City Heart Study and Copenhagen Ischemic Heart Disease Study, that genetically elevated Lp(a) level was found to be associated with increased incidence of myocardial infarction.[13]

In the GENdEr and Sex determinantS of cardiovascular disease: from bench to beyond – Premature Acute Coronary Syndrome (GENESIS-PRAXY) study, which included 939 participants with acute coronary syndrome and a mean age of 49 years, the Lp(a) level was found to be > 50 mg/dl (125 nmol/l) and was strongly associated with only high LDL-C level.[14] In our study, there was no difference in LDL-C levels between the young and middle-aged groups, while triglyceride levels were higher and HDL-C levels were lower in the young patients.

In multivariable regression analyses, family history, low HDL-C and high Lp(a) levels were found to be strongly associated with STEMI in young patients. One of the reasons for the different results of our study may be the inclusion of patients who had had a STEMI for the first time and had not used statin therapy before. In this regard, it can be said that our study is unbiased.

Similar to our study, Jubran *et al.* investigated the level of Lp(a) in 134 patients who presented with acute coronary syndrome, and Lp(a) level was found to be higher in the younger group of patients under the age of 45 years (n = 24).[15] Patients with STEMI, non-STEMI and unstable angina were included in this study.[15] The mean age of the study patients was 58 years, the mean LDL-C level was 123 mg/dl (3.19 mmol/l) and the Lp(a) level was 46 nmol/l.

Previous revascularisation, premature coronary artery disease and probable/definitive familial hypercholesterolaemia (FH) has been associated with increased Lp(a) level. In this study, the researchers found that the threshold for increased Lp(a) was 72 nmol/l, which is above 30 mg/dl. In our study, only STEMI patients were included and the number of patients was higher than in their study. Therefore, our results may have been different from their study results.

Liu *et al*. found that all-cause mortality in patients with coronary artery disease was associated with Lp(a) levels ≥ 15 mg/dl (36.7 nmol/l), compared with those with ≤ 15 mg/dl.[16] In our study, serum Lp(a) level was above 20 mg/dl (49 nmol/l) in both groups, but it was higher in younger patients.

The measurement of Lp(a) level differs according to the units used by the laboratories, the genetic structure of the population, the clinical characteristics of the cohort and underlying diseases. Therefore, it is difficult to establish a standard threshold value for Lp(a).[4]

In the multi-ethnic INTERHEART study, 12 943 subjects from seven different populations were included in the study. High Lp(a) levels associated with cardiovascular disease were found to be 27 mg/dl (66 nmol/l) in Africans, while this value was 8 mg/dl (20 nmol/l) in the Chinese population.[17] In our study, the mean Lp(a) level was found to be 38.1 mg/dl (93.3 nmol/l) in young patients who presented with STEMI, and 23.5 mg/dl (57.5 nmol/l) in middle-aged patients.

In the 2018 American Heart Association guideline recommendation, the Lp(a) threshold risk value was > 50 mg/dl (125 nmol/l), and in the 2016 Canada guideline recommendation > 30 mg/dl (75 nmol/l) was the risk threshold.[18,19] In studies conducted in India, an Lp(a) value of ≥ 20 mg/dl (49 nmol/l) was found to be associated with increased incidence of coronary artery disease.[20]

Lp(a) has been studied not only in patients with coronary artery disease but also in asymptomatic patients. Lee *et al*. studied the relationship between Lp(a) and subclinical atherosclerosis using coronary computed tomographic angiography in 7 201 asymptomatic patients.[21] They found a significant relationship between those with high Lp(a) levels and subclinical atherosclerosis. Therefore, it is recommended to measure Lp(a) level in high-risk groups because Lp(a) causes atherosclerosis before symptoms appear.[4]

The Lp(a) level is mainly affected by the genetic make-up of the individual. Apo(a) is encoded by the LPA gene located on chromosome 6q26-27. Genetic studies have shown that serum Lp(a) levels are predominantly inherited in an autosomal co-dominant manner.[22] Due to genetic predisposition, patients with high Lp(a) levels may progress to atherosclerosis early in life and experience acute coronary syndrome. Therefore, Lp(a) levels may be higher in younger patients. Lp(a) levels are generally stable in healthy individuals, but ethnicity, race, gender, age, measurement methods, steroid deficiency, gender, renal failure and acute/chronic inflammation cause changes in Lp(a) levels.[23,24]

Although different in our two study groups, the risk factors seemed to balance each other out. For example, while smoking, familial history, low HDL-C and high triglyceride levels predominated in the young group, factors such as hypertension and DM predominated in the middle-aged group. Therefore, there were serious risk factors in both groups. However, as we stated in the results, familial history, and HDL-C and Lp(a) levels were determined to be independent risk factors for STEMI in young patients.

Screening for Lp(a) levels has not been agreed upon and guidelines differ. The European Society of Cardiology recommends that Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels > 180 mg/dl (> 430 nmol/l) who may have a very high lifetime risk of atherosclerotic cardiovascular disease (ASCVD) similar to those with heterozygous FH.[25]

The American Heart Association/American College of Cardiology cholesterol guidelines recommend that Lp(a) ≥ 50 mg/dl or ≥ 125 nmol/l is an ASCVD 'risk-enhancing factor' that in patients 40 to 75 years old without DM but with a 10-year ASCVD risk of 7.5 to 19.9% would favour initiation of statin therapy.[18]

The National Lipid Association stated that Lp(a) testing is reasonable to clarify ASCVD risk in adults with first-degree relatives with premature ASCVD (< 55 years of age in men; < 65 years of age in women), a personal history of premature ASCVD, primary severe hypercholesterolaemia (LDL-C ≥ 190 mg/dl; 4.92 mmol/l) or suspected FH.[26]

Although there is no protocol that has been proven to reduce cardiovascular mortality rates in patients with elevated Lp(a) levels, lipoprotein apheresis is primarily recommended in current guidelines in patients with familial hyperlipidaemia and coronary artery disease. The efficacy of PCSK-9 inhibitors and statin treatments in reducing Lp(a) level is controversial and current treatments are under investigation.[4]

Limitations

The most important limitation was that it was a single-centre study with a retrospective design. Since there is no genetic testing centre in our institution, genetic research could not be performed for Lp(a) in young patients. Because these patients did not have long-term follow up, the relationship between Lp(a) elevation and mortality and morbidity rates in patients presenting with STEMI could not be evaluated. The lack of standardisation of the Lp(a) measurement is also one of the limitations of this study.

Conclusion

Lp(a) was found to be as important a risk factor as HT and DM in heart attacks in young patients. Lp(a) is a highly atherogenic molecule and it has been associated with stroke, heart failure, aortic stenosis, as well as coronary artery disease. Therefore, measurement of Lp(a) levels is recommended in young patients with high cardiovascular risk. We believe that large-scale studies on the standardisation of the threshold level of Lp(a) in patients with acute coronary syndrome will shed light on this issue.

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