The Role of Lipoprotein (A), Apo AI and Apo B in the Outcome and Severity of Coronary Arterial Disease

KORONER ARTER HASTALIĞININ ŞİDDETİNDE VE SONUCUNDA LİPOPROTEİN (A), APO AI VE APO B'NİN ROLÜ

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Summary

Objective: The importance and reflection of lp(a), apo AI, apo B and apo AI/apo B besides the classical lipid profile investigation in the evaluation and plan of management of the patients with coronary artery disease has been investigated.

Institution: Mersin University School of Medicine.

Materials and Method: The patient and the control groups were determined by coronary angiography. The extend of coronary artery disease was determined by the number of attacked vessels and the severity of the disease was determined by obstruction coefficient and severity coefficient. Lp(a), apo AI and apo B were determined by immunoturbitometric methods.

Results: We found out that lp(a), apo AI, apo B and apo AI/apo B are important determinants in the extend and clinical appearence of coronary artery disease. We also found out that apo AI, apo B and apo AI/apo B are important factors in the severity of coronary artery disease and influence the management protocols.

Conclusion: We beleive lp (a), apo AI and apo B values can be used together with the traditional lipid profile in the evaluation and planning of management of a patient with coronary artery disease.

Key Words: Coronary artery disease, Lp (a), Apo AI, Apo B

T Klin J Cardiovascular Surgery 2002, 3:82-87

Özet

Amaç: Koroner arter hastalığı tanısıyla izlenen hastaların değerlendirilmesi ve tedavilerinin planlanmasında geleneksel lipid profilinin yanında Lp (a), apo AI, apo B ve apo AI/apo B değerlerinin de önemi araştırıldı.

Çalışmanın Yapıldığı Yer: Mersin Üniversitesi Tıp Fakültesi Hastanesi.

Materyal ve metod: Hasta grubu ve kontrol grubu koroner anjiografi ile belirlendi. Koroner arter hastalığının yaygınlığı tutulan damar sayısına göre, şiddeti ise tıkanıklık ve şiddet katsayısına göre belirlendi. Lp (a), apo AI, apo B seviyeleri immünotürbitometrik metodlarla saptandı.

Bulgular: Lp (a), apo AI, apo B ve apo AI/apo B değerlerinin koroner arter hastalığının yaygınlığı ve klinik seyrinin önemli belirleyicileri olduğu tespit edildi. Ayrıca apo AI, apo B ve apo AI/apo B seviyesinin koroner arter hastalığının şiddetinde önemli faktörler olduğu ve tedavi protokolünü etkilediği belirlendi.

Tartışma: Koroner arter hastalarının değerlendirilmesi ve tedavilerinin planlanmasında Lp (a), apo AI, apo B ve apo AI/apo B değerleri geleneksel lipid profili ile birlikte kullanılabilir.

Anahtar Kelimeler: Koroner arter hastalığı, Lp (a), Apo AI, Apo B

T Klin Kalp-Damar Cerrahisi 2002, 3:82-87

Lipoprotein a [lp(a)] is a recently discovered risk factor for coronary atherosclerosis. A number of recent studies have shown that increased plasma concentration of lp (a) is associated with coronary artery disease (CAD) (1-4). Lp (a) is a plasma lipoprotein whose structure contains a low density lipoprotein (LDL) like moiety, in which apolipoprotein B [apo (B)] component is covalently linked

to the unique glycoprotein apolipoprotein (a) [apo (a)]. Apo (a) is a hydrophilic glycoprotein of plasminogen family. It acts as a competitive inhibitor of the tissue type plasminogen activator and inhibits the generation of thrombolytic enzyme plasmin. Based on the similarity of lp (a) to both LDL and plasminogen gives lp (a) potential atherogenic and thrombogenic roles (5,6). In this article we aimed to establish the role of lp (a) whose atherothrombogenic feature has been identified, in the extend and severity of CAD and its effect on the clinical appearance. We investigated this interaction in 92 patients who had stable or unstable angina pectoris and whose coronary lesions were determined by coronary angiography.

Materials and Methods

In Mersin University, School of Medicine, Departments of Thoracic and Cardiovascular Surgery and Cardiology one hundred and seventy six patients were included in this study. 92 of the patients who underwent percutaneous transluminal coronary angioplasty (PTCA) or coronary bypass grafting (CABG) surgery with diagnosis of 50% of stenosis at least in one of the coronary arteries constituted the study group and the other 84 patients whose coronary angiographies turned out to be normal constituted the control group. Stable angina pectoris was expressed by the patients as pain over the chest starting with exercise and recovering with rest or by using nitrates or both and did not change during the last three months. Unstable angina pectoris was determined according to the Braunwald classification. Unstable angina pectoris was described as pain with a crescendo in character in rest or with minimal exercise without the enzymatic and electrocardiographic (ECG) changes of myocardial infarction (MI). The conventional risk factors for CAD (smoking, hypertension, family history, diabetes mellitus) height and body weights of all the patients were recorded. Venous blood samples for lipid profiles were collected from the patients after a 10 hours fasting before taken to angiography. Patients receiving estrogen replacement therapy, antilipidemic therapy and/or having congestive heart failure, severe aortic stenosis, other severe systemic diseases and left main coronary artery disease were excluded from the study.

Coronary Angiography

Selective coronary angiographies were performed with the Judkins technique. The recorded sineangiograms were evaluated by two specialists in cardiology and one cardiovascular surgeon knowing nothing about the clinical status of the patients. The number of diseased vessels were taken into consideration to express the extend of atherosclerosis and the severity of the disease was determined by obstruction coefficient (OC) and severity coefficient (SC). OC was calculated by taking the mean of maximum obstructions in three of the coronary artery branches (LAD, Cx, and RCA). If the diameter of one of these main branches happened to be less than one mm. the diameter of its substitude was taken into consideration. The SC, which is more sensitive in estimating the severity of the lesion, was calculated as follows: All 3 major branches were divided in three equal segments. Three points were assigned to the proximal segments, two points were assigned to the middle segments and one point was assigned to the distal segments. The first diagonal, first septal and obtuse marginal arteries were divided into two segments and two points were assigned for proximal parts and one point was assigned for each distal part for these branches. The second diagonal, second septal, the posterior descending arteries and other equally calibrated arteries were assigned 1 point. The remaining small arteries were assigned one-half point. In case of a hypoplastic main coronary artery branch (diameter less than one mm.) the dominant diagonal, septal or marginal branch was accepted as the main coronary artery branch. The maximum obstruction of each segment (in two decimal points: 0.00) was multiplied by the number assigned to that segment. The final score was obtained by the summation from the scores of the segments of all the vessels. Only lesions greater than 50% were included in the calculations.

Statistics

SPSS 10.0 computer program (Chicago, Illinois Software) was used for calculations of statistical analysis. The results are expressed in terms of mean ± SD. A p value of <0.05 was considered to be significant. The descriptive statistics are arranged as tables. The variables lp (a), apolipoprotein A I (apo AI) and apolipoprotein B (apo B) and standard lipid profile were compared in both patient group and the control group using analysis of variance test. We also used the analysis of variance test in analyzing the effect of variables on the number of vessels affected. The discrepant group was determined by Tukey test. The interaction between the lipid profile, lp (a), apo AI, apo B and SC and OC which determines the severity of the coronary artery disease was analysed by multiple regression analysis. Student – t test was used in comparing the CABG and PTCA groups.

Measurements of lipids, lp (a), apo AI, apo B: Triglycerides (Tg), total cholesterol (TC), and high density lipoprotein – C (HDL-C) were analyzed with GP=/PAP, CHOD/PAP enzymatic colorimetric method and direct CHOD/PAP enzymatic colorimetric method respectively. Low density lipoprotein – C (LDL-C) is calculated from the primary measurements using the Friedwald method. Lp (a), apo AI and apo B were determined by immunoturbitometric methods (7).

The analysis of all these parameters were performed by Cobas Integra 700 (Hitachi Modular Systems) biochemical analyser (Roche Diagnostics, GmbH, Mannheim, Germany).

Results

Baseline characteristics and conventional coronary risk factors of the patients are summarised in Table 1. The lipid profiles of the patients with stable and unstable angina pectoris and the control group are given in Table 2. Lp (a), apo AI, apo B and apo AI/apo B variables were significantly different in 3 groups. TC and LDL-C values were significant in patient groups when compared to the control group and Tg and TC values were significant in patients other than the control and stable angina pectoris group. When a comparison between the stable angina and unstable angina pectoris groups was done it was found out that Tg, HDL, lp (a), apo AI, apo B, apo AI/apo B were the determinants.

The data concerning the extend and severity of the disease are given in Tables 3 and 4. When table 3 is examined it is observed that LDL, lp (a), apo AI, apo B and apo AI/apo B are commonly determinants in the number of attached vessels; either one, two or three vessels are attached. The lp

Table 1. Baseline characteristics and conventional coronary risk factors of the patients.

Characteristics	n=41 group 1	n=51 group 2	n=84 group 3
Age (years)	57+9	60+10	56+8
Male/Female	23/18	35/16	51/33
BMI>25 (%)	11(26)	13(25)	19(22)
Hypertension (%)	17(41)	25(49)	34(40)
Diabetes mellitus (%)	9(22)	12(23)	17(20)
Smoking(%)	21(51)	28(56)	38(45)
Family history (%)	14(34)	19(37)	21(25)
Single -vessel disease (%)	12(29)	14(27)	-----
Double-vessel disease (%)	13(31)	13(25)	-----
Triple-vessel disease (%)	16(39)	24(47)	-----

Group 1 :Patients with stabile angina pecoris
Group 2: Patients with unstable angina pectoris
Group 3: Normal patients
BMI:Body mass index

Table 2. Lipid profiles of the patients with stable angina pectoris, unstable angina pectoris patients and the control group.

Lipid Profiles	Group 1	Group 2	Group 3
TC (mg/dl)	195±38	210±52	173±35
HDL(mg/dl)	42±9	35±8	44±9
LDL(mgIdl)	125±29	138±38	96±29
Tg (mg/dl)	132±60	182±60	134±46
Lp(a) (mg/dl)	45±12	62±23	18±10
ApoAI (mg/dl)	82±29	71±26	130±27
ApoB (mg/dl)	156±23	169±38	117±26
ApoAI/ApoB	0.62±038	0.48±030	1.1±024

Group 1:Patients with stable angina pectoris
Group 2:Patients with unstable angina pectoris
Group 3: Normal patients

Table 3. Relationship between the lipid profiles of the patients and the number of attacked vessels.

	The number of attacked vessels			
Lipid profile	0	1	2	3
TC(mg/dl)	173± 35	194±38	206±52	207±48
HDL(mg/dl)	41±10	38±10	37±9	39±9
LDL(mg/dl)	96±29	127±31	133±38	134±35
Tg(mg/dl)	134±46	169±68	155±66	158±63
Lp(a)(mg/dl)	18±10	37±13	45±18	72±21
ApoAI (mg/dl)	130±27	98±27	84±24	57±14
ApoB (mg/dl)	117±3	136±5	152±5	189±4
ApoAI/ApoB	1.11±0.24	0.81±04	0.61±04	0.32±03

Table 4. Relationship between the lipid profiles of the patients and the severity of CAD

	p value	
Lipid profile	OC	SC
TC	0.12	0.98
HDL	0.08	0.14
LDL	0.14	0.5
Tg	0.64	0.07
Lp(a)	0.03	0.98
ApoAI	0.001	0.001
ApoB	0.001	0.001
ApoAI/B	0.15	0.01

Table 5. Lipid, lp(a), apo AI, apo B and apo AI/apoB values of the patients who underwent CABG or PTCA.

Levene´s test for equality of variances				
Lipid Profile	CABS	PTCA	F	Sig.
TC	200±45	204±47	,025	,875
LDL	133±34	132±35	,071	,791
HDL	38±8	38±9	,414	,522
Tg	148±56	165±68	,870	,354
Lp(a)	61±21	52±24	1,015	,316
ApoAI	60±16	83±28	27,758	,000
ApoB	181±28	157±42	17,926	,000
ApoAI/ApoB	,35	,62	27,037	,000

(a), apo A and apo B variables were effective in OC and apo AI, apo B and apo AI/apo B variables were effective in SC. Table 5 summarizes the evaluation of the data of the patients who underwent either CABG or PTCA. The apo AI, apo B and apo AI/apo B values were found to be significant in patients who were decided to be operated.

Discussion

Because of its structural properties lp (a) contributes to atherothrombotic risk by multiple mechanisms; increased cholesterol deposition, enhanced oxide LDL in the arterial wall and impared fibrinolysis. However at the present time some studies have also shown that lp (a) can be modified by oxidation (both chemical and cellular mediated) in a fashion similar to LDL and than be taken up by macrophages; where it promotes their transformation into foam cells which perpetuate the development of the atherosclerotic plaque (2, 5, 8). Numerous epidemiological studies have also found a positive association of high serum lp (a) concentrations with CAD (1-3). The meta analysis of prospective studies (mean follow-up 10 years) of John Danesh et al. provides the most reliable assessment so far of the association between plasma lp (a) and CAD. It indicates that people in the general population with lp (a) levels in the top third of baseline measurement are at 70% increased risk of CAD compared with those in the bottom third (4). With this shown effect of lp (a) investigations are carried on to figure out the role of lp (a) in the extend and severity of CAD and its clinical manifestations (8-11). Zampoulakis et al. put forward the effect of lp (a), HDL and LDL in the number of attacked vessels (11). In our study we found out that together with lp (a) LDL, apo AI, apo B, apo AI/apo B are also effective in the number of attacked vessels, however Schwartzman et al. reported that lp (a) has no role (10). In another report the apo AI levels and apo AI/apo B ratio was found to be effective (12). Cerne suggested that apolipoproteins especially the apo B/apo AII ratio were better indicators of the presence and the extent of coronary and carotid atherosclerosis (13). In an effort to evaluate the

severity of CAD we estimated the importance of lp (a), apo AI and apo B in OC and apo AI, apo B and apo AI/apoB ratio in SC. It should be emphasised that SC is more sensitive than the OC in the evaluation of the severity of CAD. The investigation of Jadhav et al. also supports the role of apolipoprotiens (14). Although lp (a) has no effect in the severity of CAD, its estimated elevated levels in unstable angina pectoris patients or in patients experiencing a myocardial infarction suggests its thrombogenic effect and role in the rupture of an atherosclerotic plaque (8-11). Dangas et al. showed the presence of lp (a) in arteriosclerotic plaques. In patients with unstable angina pectoris macrophage infiltration and increase in smooth muscle cells were also observed besides the presence of lp (a). This explains the rupture of the plaques (5, 8). On the other hand apo a which is found in the structure of lp (a) competes with plasminogen. Lp (a) has been shown to interfere with several steps in the fibrinolytic pathway; including the binding of plasminogen to endothelial cells and platelets, plasminogen activation on the endothelial surface and the lysis of the platelet-rich thrombi, the binding of plasminogen and t-PA to fibrin and the binding of plasminogen to its activator. This explains its thrombogenic feature (5,6,8-10). The correlation between the macrophages and apo (a) in an atherosclerotic plaque explains the relation between plaque disruption and thrombosis (8) but high lp (a) levels in patients experiencing myocardial infarction without critical lesions expresses its thrombogenic (8-11). When the patients of the angioplasty group and surgery group were evaluated in terms of lipid profiles the apo AI, apo B, apo AI/apo B levels were found to be the determining variables in the surgery group. This can be accepted as the reflection of apo AI and apo B in the attack and severity of CAD.

As a result of the above findings we believe lp(a), apo AI and apo B values can be used together with the traditional lipid profile in the evaluation and planning of management of a patient with CAD.

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Geliş Tarihi: 30.10.2001

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