The Role of the Lp (a) in Coronary Atherosclerosis

KORONER ATEROSKLEROZDA Lp (a) DÜZEYİNİN ETKİSİ

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Summary

Objectives: The purpose of this study is to determine the role of Lp (a) and to establish the relation of Lp (a) and other lipid fractions in the development of CAD.

Material and Methods: Dyslipidemia is one of the many modifiable risk factors for coronary artery disease. Combined with the traditional lipid profile (Tg , TC, HDL, LDL), Lp (a) , apo AI , apo B and apo AI / B ratio may provide more detailed information about the etiology of coronary artery disease. Traditional lipid profile and Lp (a), apo AI and apo B were measured in 165 consecutive patients who underwent coronary angiography. Patients were classified into two groups. Patients with critical stenosis (n=81) were named as the CAD group, and patients with no signs of coronary lesions (n=84) were named as the non-CAD group.

Results: Results are expressed in terms of mg/dl. Tg, LDL-C, Lp (a) and apo B values were significantly higher in CAD group than in non-CAD group. Tg (173±72 to 134±46 p<0,01) LDL-C (153±28 to 96±17 p<0,01) Lp (a) (41±11 to 25±8 p<0,01) apo B (139±30 to 117±26 p<0,01).

Apo AI and apo AI / B ratio were higher in non-CAD group respectively. Apo AI (130±27 to 112± 28 p<0,01 and apo AI / B ratio (1,11±0,14 to 0,82±0,21 p<0,01).

Conclusions: Our results confirm that Tg, LDL-C, Lp (a), apo AI, apo B, apo AI / B ratios play an important role in the development of coronary atherosclerosis. When these risk factors were evaluated with Backward regression analysis, we found that LDL-C, apo AI, apo B and Tg were more important than Lp (a) at the occurrence of coronary atherosclerosis.

Key Words: Atherosclerosis, Lp (a), Apo AI, Apo B, CAD

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Özet

Amaç: Bu çalışmada Lp(a)'nın, koroner arter hastalığı gelişimindeki rolü ve diğer lipid fraksiyonları ile ilişkisini saptamak amaçlandı.

Materyal-metod: Dislipidemi, koroner arter hastalığı için değiştirilebilir risk faktörlerinden biridir. Geleneksel lipid profili ile birlikte (Tg, TC, HDL, LDL), Lp(a), apo A1, apo B ve apo A1/apo B oranı da koroner arter hastalığının etiyolojisi hakkında daha detaylı bilgiler sunabilir. Bu çalışmada koroner anjiografi yapılan 165 hastada geleneksel lipid profili ile Lp (a), apoA1 ve apo B seviyeleri tetkik edildi. Hastalar iki gruba ayrıldı. Kritik stenozu olan hastalar (n=81) CAD grubuna, kritik koroner lezyonu olmayan hastalar ise (n=84) non CAD grubuna alındı.

Sonuçlar: Sonuçlar mg/dl cinsinden ifade edildi. Tg, LDL, Lp (a) ve apo B değerleri CAD grubunda belirgin olarak yüksekti. Tg (173±72'ye karşı 134±46 p<0,01) LDL-C (153±28'e karşı 96±17 p<0,01) Lp (a) (41±11'e karşı 25±8 p<0,01) apo B (139±30'a karşı 117±26 p<0,01).

Apo A1 ve apo A1/apo B oranı non CAD grubunda yüksekti (130±27'ye karşı 112± 28 p<0,01 ve apo AI / B oranı 1,11±0,14'e karşı 0,82±0,21 p<0,01).

Tartışma: Sonuçlarımıza göre Tg, LDL, apo A1, apo B ve apo A1/ apo B oranı koroner ateroskleroz gelişiminde önemli rol oynamaktadır. Bu risk faktörleri Backward regresyon analizi ile değerlendirildiğinde ise koroner ateroskleroz gelişiminde LDL-C, apo AI, apo B ve Tg'in Lp (a)'ya göre daha belirleyici olduğu saptanmıştır.

Anahtar Kelimeler: Ateroskleroz, Lp (a), Apo AI, Apo B, CAD

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Coronary atherosclerosis is a leading cause of morbidity and mortality and the elucidation of the process underlying is of great potential benefit from a public health prospective. Dyslipidaemia is one of the many modifiable major risk factors for coronary artery disease (CAD). Hypertension, diabetes mellitus, and smoking are the other major risk factors. More specifically, lipoprotein

disorders can lead to the development of coronary atherosclerosis, which can be further accelerated in the presence of multiple risk factors (1). Disorders of lipoprotein metabolism are found in more then 80% of patients with CAD (2).

Sophisticated laboratory methods permit physicians to enter a new era of CAD risk factor detection and treatment. These advances allow for a more scientific approach then did the previously standard epidemiological risk factors and lipid profiles. The current state of the art method of diagnosing and treating lipoprotein disorders has progressed beyond the standard lipid profile which includes total, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol along with fasting triglyceride (Tg) levels (2).

Incorporating aspects of the atherogenic lipid profile; lipoprotein (a) [Lp (a)], apolipoprotein AI (apo AI), apolipoprotein B (apo B) may provide a more detailed information about the etiology of coronary atherosclerosis (1-5).

In this study; Tg, total cholesterol (TC), LDL-C, HDL-C, Lp (a), apo AI, apo B, ratio of apo AI / B values in sera were analysed in 165 consecutive patients who underwent coronary angiography.

Material and Methods

Subject: We studied 165 consecutive patients undergoing coronary angiography. Coronary angiography was performed using the Judkins technique. Films were evaluated by experienced angiographers who were blinded to the patients' conditions. Patients were classified in two groups; CAD group was defined as patients with at least %50 stenosis in one or more of the major coronary arteries; non-CAD group was defined as patients with no signs of coronary lesions in the angiograms despite clinical data suggested CAD. There were 81 patients in CAD and 84 patients in non-CAD group. Patients with major systematic health problems, patients taking lipid lowering drugs or estrogen replacement therapy were excluded from the study. Conventional risk factors for CAD (smoking, hypertension, family history of premature cardiovascular disease, diabetes, hyperlipidemia), height and weight were recorded in all patients. Venous blood samples were collected from patients in the fasting state before angiography. Whole blood samples were centrifuged at 5000 rpm for 5 minute after clotting. Sera were separated after centrifugation

Measurements of Apo AI, Apo B, Lp (a), Tg, TC, LDL-C and HDL-C:

Apo AI, apo B and Lp (a) were determined by immunoturbidometric methods. Tg, TC and HDL-C were analysed with GP/PAP, CHOD/PAP enzymatic colorimetric method and direct CHOD/PAP enzymatic colorimetric method respectively. LDL-C is calculated from the primary measurements using the empirical equation of Friedewald et al (6). The analysing of all these parameters were performed by using Cobas Integra 700 (Hitachi Modular Systems) biochemical analyser (Roche Diagnostics, GmbH, Mamheim, Germany).

Statistical analysis

The results were expressed in terms of arithmetic means (X) ± standard deviation (SD). The statistical significance of the difference between the means was evaluated by “student t-test”. A $P<0.05$ was considered to be significant. After this analysis it was found suitable to consider the variables together and be taken into the model and risk factors that might have been important in differentiating the groups were established by Backward logistic regression analysis.

Results

Baseline characteristics and conventional coronary risk factor of the patients are summarised in Table 1. In CAD group single vessel disease was found in 21 (26%) patients, two vessel disease was found in 18 (22%) patients and triple vessel disease was found in 42 (52%) patients. To 45 (55%) of the patients coronary angioplasty and/or stent application, to 28 (35%) CABG operation and to 8 (10%) of them medical therapy was suggested.

In table 2 serum lipid, lipoprotein and apoprotein levels of patients are given. In the CAD group Tg, LDL-C, Lp (a), apo B, values were significantly higher than the control group. Apo AI and apo AI/B ratio values in the non-CAD group

Table 1. Clinical characteristics of study groups.

Characteristics	CAD group	nonCAD group
Age (years)	56±9	54±11
Male/Female	64/17	59/25
BMI (kg/m²)	26±0.4	25±0.7
Hypertension (%)	33 (40)	29 (30)
Diabetes Mellitus (%)	19 (24)	14 (17)
Smoking (%)	36 (44)	24 (29)
Family history (%)	38 (47)	32 (39)

BMI: Body mass index

were significantly higher than the CAD group. The Backward regression analysis was used to establish which out of the mentioned 5 risk factors is the most important in the identification of the patient group (Table 3). Apo AI/B ratio is a mathematical function of apo AI and apo B. Therefore, this variable was not included in multiple logistic regression analysis since a multicollinearity problem could arise. LDL-C, apo AI, apo B, Tg and Lp (a) values are effective in the outcome of coronary atherosclerosis but the first four are considered to be more effective when compared to others.

Discussion

It is generally agreed that the first step in the development of coronary atherosclerosis is peroxidation of LDL (1, 7). At present some studies have also shown that Lp (a) can be modified too by oxidation (both chemical and cellular mediated) in a fashion similar to LDL (3, 8, 9). However Lp (a) contains the apo B component which is covalently linked to the unique glycoprotein apolipoprotein (a) [apo (a)] that is structure like moiety to plasminogen. Based on the similarity of Lp (a) to both LDL and plasminogen may represent a link between the atherosclerosis and thrombosis (3,8-12). Numerous epidemiological studies have also found a positive association of high serum Lp (a) concentrations with CAD (3-5). The meta-analysis of 27 prospective studies (mean follow-up 10 years) John Danesh et al indicates that people in the general population with Lp (a) levels in the top third of baseline measurement are at 70% increased risk for CAD compared with those in the bottom third (13). Although the physiological role of Lp (a) is totally unknown and its pathogenic mechanisms are only partially elucidated, it is well documented that Lp (a) accumulates at the site of coronary atherosclerotic lesions (10). More recently, the results of several studies have suggested that Lp (a) synergistically contribute to CAD by potentiating the effect of other lipid risk factors. There are studies indicating the positive correlation of Lp (a) with TC, LDL-C and apo B (3,4,8,9). In our study, we found that Lp (a) was also efficient with apo B, apo AI,

Table 2. Serum lipid, lipoprotein and apoprotein levels.

	Tg	TC	HDL	LDL	Lp (a)	Apo AI	Apo B	Apo AI/Apo B
CAD group	173±72*	209±54	37±10	153±28*	41±11*	112±28*	139±30*	0.82±0.21*
Non CAD group	134±46	194±43	41±10	96±17	25±8	130±27	117±26	1.11±0.14

***P<0.01**

****All values are given as mg/dl.**

Table 3. Regression analysis of the identified risk factors.

			95% interval ratio	Confidence for odds
Risk variables	Sig	Odds ratio (Exp (β))	Lower	Upper
TG	0.0069	0.988	0.98	0.99
LDL-C	0.0000	0.966	0.95	0.98
Apo AI	0.0000	1.095	1.06	1.13
Apo B	0.0000	0.927	0.89	0.96
Lp(a)	0.0638	0.988	0.98	0.99

apo AI / B, LDL-C and Tg in the development of CAD. We evaluated the risk factors with Backward regression analysis and found out that LDL-C, apo AI, apo B and Tg are more determinant factors in the development of CAD than Lp (a). The role of Lp (a) in the development of CAD has been documented but Lp (a) seems to be effective independently in the extend, evolution of acute coronary syndromes and acute myocardial infarction (9, 10, 12, 14). This brings forward the thrombogenic feature of Lp (a). In studies concerning the severity of CAD Tg, LDL-C, apo AI, apo B and apo AI / B were found to be the major determinants (11, 14, 15, 16). However Schwartzman et al have shown that elevated plasma Lp (a) is an independent risk factor for mild and severe angiographic CAD in chronic stable angina. In his study, the author has included the patient group taking lipid-lowering drugs. When this group of patients are excluded Tg and LDL-C are found to be effective independently (11).

As a result of our study, we suggest that Lp (a) is not an independent risk factor for CAD but appears to increase the risk together with LDL-C, apo AI, apo B and Tg. With the results we obtained we might forward that it might be effective to explore the presence of CAD only, excluding its extend, severity and clinical presentation.

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