Association Between Apolipoprotein-B100 and Apolipoprotein-A1 in Patients with Coronary Slow Flow

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ABSTRACT

Objective: Although several hypotheses have been suggested, the underlying mechanism of coronary slow flow phenomenon (CSFP) has not been well established yet. The aim of this study was to determine the roles of plasma apolipoprotein-B100 (Apo-B) and apolipoprotein-A1 (Apo-A1) in CSFP which have an atherogenic effect and anti-atherogenic effects respectively.

Methods: The study consisted of 31 patients with CSFP (group 1), 28 normal subjects as control group (group 2) and 30 patients with coronary artery disease (CAD) (group 3) detected by coronary angiography. CSFP was diagnosed by the TIMI frame count method. Blood Apo-B, Apo-A1, Apo-B/Apo-A1 ratio, and demographic parameters were compared between the groups.

Results: The Apo-B values were 93±25 mg/dL, 90±26 mg/dL, and 106±27 mg/dL in groups 1, 2 and 3, respectively (p=0.048 between group 1 and 3, p=0.041 between group 2 and 3, p= NS between group 1 and 2). The Apo-A1values were 127±14 mg/dL, 125±21 mg/dL and 106±27 mg/dL in groups 1, 2 and 3 respectively (p=0.028 between group 1 and 3, p=0.021 between group 2 and 3, p= NS between group 1 and 2). The apo-B/apo-A1 ratio were 0.73±0.18, 0.69±0.23 and 0.98±0.20 in groups 1, 2 and 3 respectively (p=0.017 between group 1 and 3, p=0.010 between group 2 and 3, p= NS between group 1 and 2).

Conclusion: Although lower levels of plasma Apo-A1 and higher levels of Apo-B and the ratio of Apo-B to Apo-A1 are related with CAD, there is no relationship between these apolipoproteins and CSFP.

Key Words: Coronary slow flow phenomenon, Apolipoproteins, Atherogenic and anti-atherogenic effects

ÖZET

Koroner Yavaş Akım Hastalarında Apolipoprotein-B100 ve Apolipoprotein-A1 Arasındaki İlişki

Amaç: Koroner yavaş akım fenomenin (KYAF) altta yatan mekanizması henüz tam olarak tanımlanmamış olmasına rağmen çeşitli hipotezler ileri sürülmüştür. Bu çalışmamız da sırasıyla aterojenik ve anti-aterojenik etki gösteren plazma apolipoprotein-B100 (Apo-B) ve apolipoprotein-A1'in (Apo-A1) KYAF'deki rolünü araştırdık.

Yöntemler: Çalışmaya koroner anjiografik olarak KYAF'si olan 31 hasta (grup 1) ile normal kişilerden oluşan 28 kontrol grubu (grup 2) ve koroner arter hastalığı olan 30 hasta (grup 3) alındı. KYAF tanısı TIMI kare sayısı yöntemiyle kondu. Grupların plazma Apo-B, Apo-A1, Apo-B/Apo-A1 oranı ve demografik özellikleri karşılaştırıldı.

Bulgular: Grup 1, 2 ve 3'deki ortalama Apo-B değerlerini sırasıyla 93±25 mg/dL, 90±26 mg/dL, 106±27 mg/dL olarak saptadık (grup 1 ile 3 arasındaki p=0.048, grup 2 ile 3 arasındaki p=0.041, grup 1 ile 2 arasındaki p= AD). Grup 1, 2 ve 3'deki ortalama Apo-A1 değerlerini sırasıyla 127±14 mg/dL, 125±21 mg/dL, 106±27 mg/dL olarak saptadık (grup 1 ile 3 arasındaki p=0.028, grup 2 ile 3 arasındaki p=0.021, grup 1 ile 2 arasındaki p= AD). Grup 1, 2 ve 3'deki Apo-B/Apo-A1 oranını ise sırasıyla 0.73±0.18, 0.69±0.23 ve 0.98±0.20 olarak saptadık (grup1 ile 3 arasındaki p=0.017, grup 2 ile 3 arasındaki p=0.010, grup 1 ile 2 arasındaki p= AD).

Sonuç: Koroner arter hastalığı düşük plazma Apo-A1 düzeyi ile yüksek plazma Apo-B düzeyi ve Apo-B/Apo-A1 oranı ile ilişkilendirilmiş olmasına rağmen apolipoproteinler ile KYAF arasında bu ilişki bulunmamıştır.

Anahtar Kelimeler: Koroner yavaş akım fenomeni, Apolipoproteinler, Aterojenik ve anti-aterojenik etki

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INTRODUCTION

The coronary slow flow phenomenon (CSFP) is characterized by angiographically normal coronary arteries with delayed opacification of the distal vasculature. The pathophysiological mechanisms of CSFP remain uncertain. However, several hypotheses have been suggested for CSFP, including a form of early phase of atherosclerosis (1,2), small vessel dysfunction (3), Hagen–Poiseuille's equation model (4), imbalance between vasoconstrictor and vasodilatory factors (5-7), inflammation (8), platelet function disorder (9,10), and interaction of plasma homocysteine and thyroid hormone concentrations (11).

Recently, several studies have focused on the importance of the lipid-transporting apolipoproteins. Apo-B transports all potentially atherogenic very low-density lipoprotein, intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) particles, and Apo-A1 transports and acts as the major anti-atherogenic protein in the high density lipoprotein (HDL) particles (12). Low levels of plasma Apo-A1, high levels of Apo-B, and the ratio of Apo-B to Apo-A1 are considered to be independent risk factors for coronary heart disease (12, 13). Thus, in this study, we studied the relationship between the level of these apolipoproteins and CSFP.

PATIENTS AND METHODS

Thirty one patients (17 males and 14 females, mean age 50 ± 9 years, group 1) with CSFP detected by coronary angiography by the TIMI "frame count" method were included in this study. Gender and age-matched 28 control subjects with no coronary or valvular disease (15 males and 13 females, mean age 49 ± 10 years, group 2) and 30 CAD patients (16 males and 14 females, mean age 52±12 years, group 3) were included in this study.

Patients with heart failure, valvular heart disease, uncontrolled hypertension, previous myocardial infarction, diabetes mellitus, hypercholesterolemia, arrhythmia and thyroid function disorders were excluded from the study.

Coronary angiography was performed in all patients due to positive exercise test or typical chest pain. CAD was diagnosed when at least one coronary artery was stenosed>% 50 on coronary angiography.

Apolipoproteins were measured by immunochemical assay from serum, based on the measurement of immunoprecipitation in the liquid phase by analyzers (IMMAGE immunochemistry systems, copyright 2000 Beckman coulter, inc. USA). Normal apolipoprotein A-1 reference values were 90-170 mg/dL in males and 107-214 mg/dL in females. Normal apolipoprotein B reference values were 56-162 mg/dL in males and 51-171 mg/dL in females. Apo-B / Apo-A1 ratio exceeding one was suggestive for a high coronary risk and less than one for a low coronary risk.

All participants underwent two-dimensional echocardiographic evaluation by an experienced research echocardiographer using commercially available echocardiography machines equipped with 3.5 MHz transducers (Vivid System Five, GE Vingmed Horten, Norway). Measurements were made according to the American Society of Echocardiography guidelines by a single cardiologist (14). Left ventricular ejection fraction (LVEF) was measured from the apical four-chamber and two-chamber views using the modified Simpson method (14).

Coronary angiography was performed via femoral approach using the standard Judkins technique and iopromide (Ultravist-370, Schering AG, Berlin, Germany) as the contrast agent (cine angiographic equipment: Philips Integris H 3000, Holland; cine frame:30 fps). The angiograms were recorded on a compact disc in DICOM format. We measured the number of cine frames required for the contrast to first reach standard distal coronary landmarks in the left anterior descending coronary artery (LAD), left circumflex artery (Cx), and right coronary artery (RCA). The first frame is defined as the one where the column of nearly or fully concentrated dye is seen extending across at least 70% of the arterial lumen with antegrade dye motion, and the last frame counted is that in which contrast first appears in the distal predefined landmark branch, but full opacification of the branch is not necessary (15). The distal coronary landmarks used for analysis were the distal bifurcation at the apex of the LAD (the mustache, pitchfork, or whale's tail), the distal bifurcation of the major obtuse marginal or the main Cx, whichever was larger, and the site of origin of first branch at the crux or its posterolateral extension for RCA. The cine film was run past the initial opacification of the end branch and then was moved frame by frame in reverse until the end branch disappeared before catching the last frame. Then the frame count for each artery was done by subtracting the first frame from the last frame. The LAD frame count was corrected by dividing with 1.7 to derive a corrected TIMI frame count (CTFC) (15).

Apo-B, ApoA-1, Apo-B/Apo-A1 ratio and demographic parameters were compared among the groups. Written informed consent was obtained from each patient before included to the study, and the protocol was approved by the institutional local ethics committee.

Statistical analysis

Results are presented as mean ± SD or frequency expressed as a percent. Comparison among multiple groups was performed by one-way ANOVA test with Tukey's HSD test for continuous variables. Statistical analysis was performed with SPSS for Windows, version 11.0 (SPSS Inc. Chicago, Illinois). P value of < 0.05 was considered to indicate statistical significance.

RESULTS

The apo-B values were 93±25 mg/dL, 90±26 mg/dL, and 106±27 mg/dL in groups 1, 2 and 3, respectively (p=0.048 between group 1 and 3, p=0.041 between group 2 and 3, p= NS between group 1 and 2; Figure 1).

The apo-A1 values were 127±14 mg/dL, 125±21 mg/dL and 106±27 mg/dL in groups 1, 2, 3 respectively (p=0.028 between group 1 and 3, p=0.021 between group 2 and 3, p= NS between group 1 and 2; Figure 2).

The apo-B/Apo-A1 ratio were 0.73 ±0.18, 0.69±0.23 and 0.98±0.20 in groups 1, 2 and 3 respectively (p=0.017 between group 1 and 3, p=0.010 between group 2 and 3, p= NS between group 1 and 2; Figure 3).

The baseline characteristics of the study groups, TIMI frame count for each artery and biochemical parameters are shown in Table 1.

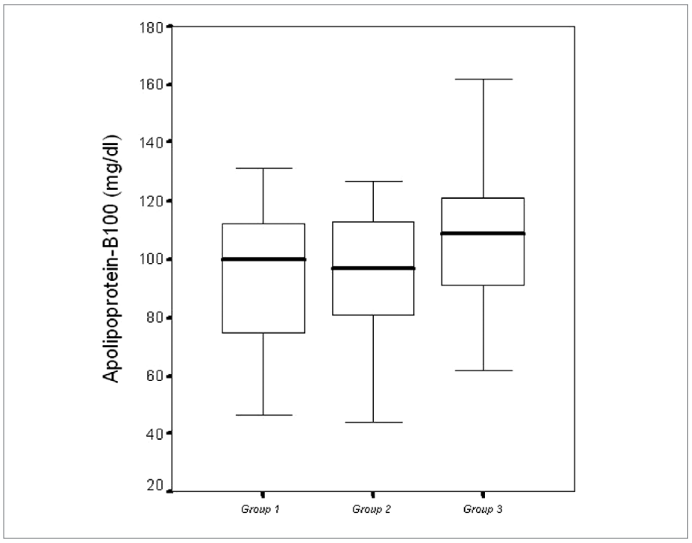

Figure 1: Group 1: Coronary slow flow phenomenon group,
Group 2: Control group,
Group 3: Coronary artery disease group. Bar shows mean values.
p=0.048 between group 1 and 3, p=0.041 between group 2 and 3,
p= NS between group 1 and 2

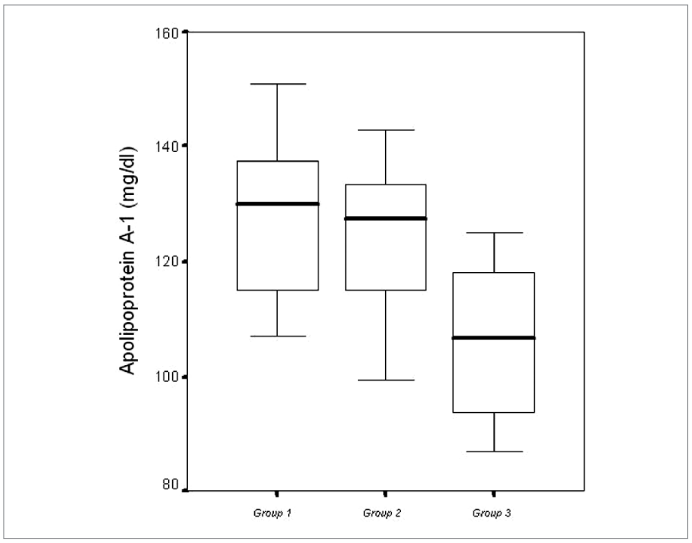

Figure 2: Group 1: Coronary slow flow phenomenon, group
Group 2: Control group,
Group 3: Coronary artery disease, group. Bar shows mean values.
p=0.028 between group 1 and 3, p=0.021 between group 2 and 3
p= NS between group 1 and 2

The corrected TIMI frame count, Cx frame count, and RCA frame count were similar in control subjects and CAD and its means significantly lower in control subjects and CAD than CSFP. There was no difference between the two groups in terms of sex, age, heart rate, systolic blood pressure (BP), diastolic BP, body mass index (BMI), smoking, echocardiographic parameters and biochemical parameters.

DISCUSSION

In this study, we found that Apo-B, Apo-A1, and Apo-B/Apo-A1 ratio are similar in CSFP and control subjects but differed when compared to CAD group. Previous studies done for control subjects (16) and CAD patients

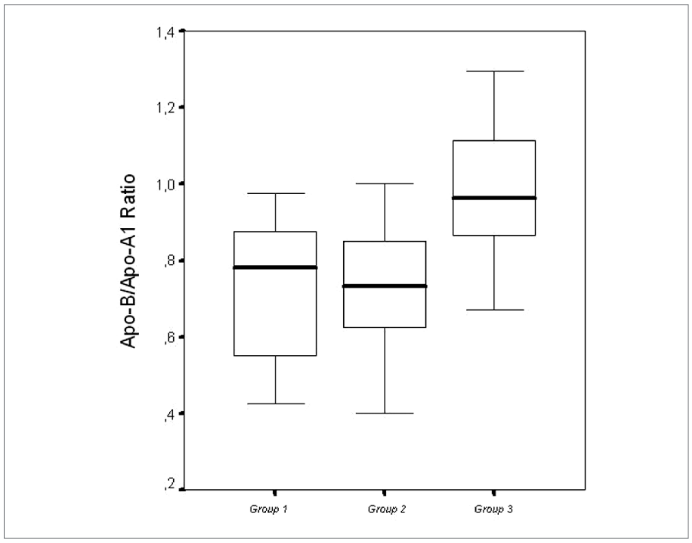

Figure 3: Group 1: Coronary slow flow phenomenon group,
Group 2: Control group,
Group 3: Coronary artery disease group. Bar shows mean values.
p=0.017 between group 1 and 3, p=0.010 between group 2 and 3
p= NS between group 1 and 2

Table 1: The baseline characteristics of the study groups, TIMI frame count for each artery and biochemical parameters are shown.

	Group 1	Group 2	Group 3	P value between groups
Age, year	50 ± 9	49 ± 10	52±12	NS
Male/Female, n	16 / 15	15 / 13	16±14	NS
Heart rate, bpm	72 ± 9	68 ± 8	70±8	NS
Systolic BP, mmHg	121 ± 16	124 ± 16	122±17	NS
Diastolic BP, mmHg	78 ± 7	79 ± 9	80±9	NS
Smoking, n	12	9	13	NS
BMI, kg/m^2	28±4	27±4	29±5	NS
LVEF, %	64 ± 4	66 ± 2	63±4	NS
Glukoz, mg/dl	106±16	102 ±16	107±17	NS
Total cholesterol, mg/dl	194±36	187±42	197±36	NS
Triglycerides, mg/dl	132±88	117±83	151±76	NS
LDL, mg/dl	128± 29	121± 33	133±29	NS
HDL, mg/dl	39±9	41±7	37±7	NS
CTFC, frames/sec	32±11	16±5	18±7	*
RCA TFC, frames/sec	32±10	17±4	18±5	**
Cx TFC, frames/sec	28±8	17±3	19±4	***

* P value < 0.01 between groups 1 and 2, groups 1 and 3.
** P value < 0.01 between groups 1 and 2, groups 1 and 3
*** P value < 0.01 between groups 1 and 2, groups 1 and 3.

Group 1: Coronary slow flow phenomenon group,
Group 2: Control group,
Group 3: Coronary artery disease group. M: Male, F: Female, BP: Blood pressure, BMI:Body mass index, LVEF:Left ventricle ejection fraction, LDL: Low-density lipoprotein, HDL: High density lipoprotein, CTFC: Corrected TIMI frame count for left anterior descending coronary artery, RCA TFC: Right coronary artery TIMI frame count, Cx TFC: Circumflex artery TIMI frame count.

(17) had similar levels of mean apo-B, apo-A1 and the apo-B/apo-A1 ratio as in our study. However, no study exists showing relationship between apoplipoproteins and CSFP. That is why we planned this study.

The pioneering studies on the clinical relevance of apo A1 and apo B were presented about 20 years ago by Avogaro et al. (18,19), who showed, in 218 survivors of myocardial infarction and 160 controls that apolipoproteins were as good as lipids in discriminating and predicting atherosclerotic diseases. Furthermore, the protein moiety of lipoproteins is a better discriminator than lipids between atherosclerotic subjects and controls (18). In addition Sniderman et al. confirmed the clinical relevance of apo-B as a better predictor of coronary atherosclerosis than plasma cholesterol (20). Other clinical trials have also been published, with most pointing to the importance of apo-B and apo-A1 as risk indicators (21, 22). Observations from the INTERHEART (23) and AFCAPS/TexCAPS (24) studies, demonstrated that the single most powerful predictor of all of the routine risk factors for CAD, with a very good linear risk relation, was the apo-B/apo-A1 ratio, which took into account all atherogenic and nonatherogenic lipoprotein species. These results were similar to the results of our CAD group. The results of CSFP group were similar to the control group.

SCFP was first defined by Tambe in 1972 (25) on six patients with chest pain. However, since that time, only a limited number of studies have focused on the etiology of this unique angiographic phenomenon. Histopathologic studies have revealed the existence of the loss of lumen diameter, capillary and endothelial damage in these patients. Although the pathophysiological mechanisms of CSFP remain uncertain, there are several hypotheses that have been suggested. Pekdemir et al. showed diffuse calcification and intimal thickening in all segments of the vessels (26). However, focal stenosis and plaques formation suggesting coronary artery atherosclerosis weren't observed in CSFP cases. In a study carried out by Sezgin et al. a relationship was established between CSFP and low HDL-C and high TG levels while there was no relationship with total cholesterol and LDL-C (27). In our study, apolipoproteins levels of CSFP and control groups were significantly different from CAD group while total cholesterol, LDL-C, HDL-C and TG levels were similar in all three groups. As it was found in our study, a former study done in CAD patients showed no correlation between Apo B/ Apo-A1 ratio and LDL and HDL (13). In previous studies, the cholesterol balance determined as the Apo B/Apo A-1 ratio has repeatedly been shown to be a better marker than lipids, lipoproteins and lipid ratios (12). Generally, CSFP patients have good prognosis (26). This good prognosis may be related with their having different levels of atherogenic and anti-atherogenic apolipoprotein levels compared to CAD patients.

CONCLUSION

Although lower levels of plasma Apo A-1 and higher levels of Apo-B and the ratio of Apo-B to Apo-A1 are related with CAD, there is no relationship between these apolipoproteins and CSFP.

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