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Original Article

The relationship between fibrinogen to albumin ratio and carotid artery disease in patients with carotid endarterectomy and patients with non severe carotid artery stenosis

Karotis endarterektomili ve şiddetli olmayan karotis arter darlığı olan hastalarda fibrinojen / albümin oranı ve karotis arter hastalığı arasındaki ilişki.

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ABSTRACT

Aim: To investigate the relationship between fibrinogen to albumin ratio (FAR) and carotid artery stenosis (CAS).

Material and Methods: This study included patients who underwent carotid endarterctomy (CEA) as CEA group and unoperated patients who have CAS less than 50% as non-surgical group. CAS was diagnosed with history and physical examination followed by doppler ultrasonography and carotid angiography. All data retrieved retrospectively from the hospital medical files. Hematologic parameters were measured and recorded. In addition, FAR was calculated.

Results: Fifty patients were included in CEA group (70.0 % male, mean age: 71.0 ± 7.7 years) and 60 patients were invluded in non-surgical group (70.0 % male, mean age: 63.9 ± 8.0 years). In logistic regression analysis advanced age, presence of coronary artery disease and FAR were identified as an independent predictor of the development of CAS. In Receiver operating characteristic (ROC) curve analysis, for predicting development of CAS, there were 68.0% sensitivity and 65.0% specificity for FAR (area under the curve [AUC]: 0.669, 95% CI: 0.566-0.771, log rank p = 0.002).

Conclusion: We found that FAR were identified as an independent predictor of the development of CAS. FAR could be a potential marker on carotid atherosclerosis in patients. But there is a need large studies including all cardiovascular diseases.

Keywords: Carotid artery stenosis; fibrinogen; albümin

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Öz

Amaç: Fibrinojen ile albumin oranı (FAR) ve karotis arter stenozu (KAS) arasındaki ilişkiyi araştırmak.

Gereç ve Yöntemler: Bu çalışma, karotis endarterektomisi (KEA) geçiren hastaları ve % 50'den az karotis arter stenozu olan hastaları içermektedir. KAS tanısı fizik muayene, tıbbi hikaye ve ardından doppler ultrasonografi ve karotis anjiyografi ile konuldu. Tüm veriler hastane tıbbi dosyalarından retrospektif olarak alındı. Laboratuvar kan sonuçları ve kaydedildi ve FAR hesaplandı.

Bulgular: Elli hasta KEA grubuna dahil edildi (% 70 erkek, ortalama yaş: 71.0 ± 7.7) ve 60 hasta cerrahi olmayan grubuna dahil edildi (% 70 erkek, ortalama yaş: 63.9 ± 8.0). Lojistik regresyon analizinde ileri yaş, koroner arter hastalığı ve FAR varlığı KAS gelişiminin bağımsız bir prediktörü olarak tanımlandı. Receiver operating characteristic (ROC) eğrisisi analizinde, KAS gelişimini tahmin etmek için FAR için % 68.0 duyarlılık ve % 65.0 özgüllük vardı (Area Under the Curve [AUC]: 0.669, 95% CI: 0.566-0.771, log rank p = 0.002).

Sonuçlar: FAR'ın KAS gelişiminin bağımsız bir öngörücüsü olarak tanımlandığını bulduk. FAR, hastalarda karotis aterosklerozu üzerinde potansiyel bir belirteç olabilir. Ancak, tüm kardiyovasküler hastalıkları içeren büyük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Karotis arter stenozu; fibrinojen; albümin

Introduction

Carotid artery stenosis (CAS) is a serious disease that is an important cause of strokes particularly in the elderly people [1]. In asymptomatic CAS, the incidence of stroke increases by 0.35-5% and at the same time the incidance and mortality of the heart disease also increase [2].

Serum albumin is an important inhibitor of platelet activation and aggregation [3]. Endothelial dysfunction may be impaired by the increased concentration of free lysophosphatidylcholine which increased viscosity because of the hypoalbuminemia [4]. In previous study, they found that a relationship between low serum albumine levels and increased cardiovascular morbidity and mortality [5].

Plasma fibrinogen is a coagulation factor and an acute-phase inflammatory marker that play role in the pathophysiology of cardiovascular disease (CVD). In various epidemiologic studies shown that is an independent, positive association between high fibrinogen values and CVD [6]. Clinical studies has shown that elevated fibrinogen is correlated with the severity of atherosclerosis which the presence of inflammatory and thrombogenic activity are factors contributing to stenosis progression on both coronary and carotid disease [7-9].

To determine whether relationship between fibrinogen levels and carotid artery atherosclerosis reported in the literature, we aimed to assess the association between plasma fibrinogen to albumin ratio and carotid artery disease.

Material and Methods

Patients

This retrospective observational study included patients who underwent carotid endarterectomy CEA and unoperated patients who have less than 50% CAS. This study was performed between 2017 and 2018 at Bursa Yuksek Ihtisas Training and Research Hospital, Department of Cardiovascular Surgery. The study was approved by the local institutional Ethical Committee of University of Health Sciences.

Carotid artery stenosis was diagnosed with history and physical examination followed by doppler ultrasonography, coronary and carotid angiography. All analyzed data were retrospectively taken from hospital medical records.

Patients with combined coronary artery bypass and CEA surgery, malignite, inflammatory diseases and chronic renal failure were excluded from study. After these exclusion criteria, 50 patients with undergoing CEA included in CEA group and 60 patients with less than 50% CAS included in non-surgical group. All data were recorded as age, gender, comorbidities (hypertension, diabetes mellitus), the presence of coronary artery disease (CAD), statin usage, and body mass index. Patients with undergoing CEA were operated under local anesthesia.

Laboratory measurements

Fasting venous blood samples were taken from an antecubital vein of each patient before operation. The tubes with EDTA were

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used for automatic blood count according to the protocol of our hospital. Hematologic parameters were measured by using an automated hematological analyzer (Coulter LH 780 Analyzer, CA, USA). In addition, fibrinogen to albumib ratio (FAR) was calculated.

Statistical Analysis

Statistical analysis data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA). Continuous and ordinal variables were expressed as mean ± standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test and Shapiro-Wilk tests of normality were used to identify distribution of variables. Student's t test was used to compare two groups for continuous variables with normal distribution. Chi Square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. Predictors of disease progression were identified by using binary logistic regression analysis. For all tests, a p value of < 0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve was applied for the prediction of disease progression and the area under the curve (AUC) was calculated for FAR.

Results

A total of 50 patients in the CEA group (70 % male, mean age: 71.0 ± 7.7 years) and 60 patients in the non-surgical group (70 % male, mean age: 63.9 ± 8.0 years) were recorded in this study. The demographic characteristics of the patients are summarized in Table 1. There were statistically difference between two group in terms of age (p = 0.000), presence of CAD (p = 0.000), presence of hypertension (p = 0.002) and statin therapy (p = 0.007) (Table1).

Table 1. Demographic features of the patients

	CEA group (n=50)	Non-surgical group (n=60)	p value
Age(years)	71.0±7.7	63.9±8.0	0.000 #
Male gender, n (%)	35 (70)	42 (70)	1.000 a
BMI (kg/m2)	27.9±3.8	26.9±4.2	0.177 *
Hypertension, n (%)	32 (64)	21 (35)	0.002 a
Diabetes mellitus, n (%)	20 (40)	32 (53.3)	0.163 a
CAD, n (%)	32 (64)	14 (23.3)	0.000 a
Statin therapy, n (%)	22 (44)	12 (20)	0.007 a

CEA: Carotid endarterectomy, BMI: Body mass index, CAD: Coronary artery disease, a Pearson Chi- Suquare, # Mann-Whitney U test, *Student's-t test

The comparison of laboratory findings are shown in Table 2. Both CEA group and non-surgical group were similar to each other regards to laboratory findings. In addition, there were statistically difference between two group in terms of total protein (p = 0.006), fibrinogen (p = 0.002) and FAR (p = 0.002) (Table2).

Table 2. Laboratory variables.

	CEA group (n=50) (mean ± SD)	Non-surgical group (n=60) (mean ± SD)	p value
Hematocrit (%)	39.7±5.5	38.4±7.1	0.283*
White blood Cell (103/µL)	8.5±2.6	9.0±2.1	0.239*
Platelet (103/µL)	247.3±63.1	258.4±87.2	0.454*
Red cell distribution width (%)	14.5±1.3	14.2±1.5	0.119#
Mean platelet volüme (fL)	8.6±1.3	8.8±1.4	0.453#
BUN (mg/dL)	19.8±6.8	18.8±9.5	0.171#
Creatinine (mg/dL)	1.0±0.3	0.9±0.6	0.284#
Ca (mg/dL)	9.2±0.6	9.1±0.5	0.418*
Mg (mg/dL)	1.8±0.2	1.8±0.2	0.196*
C Reactive protein (mg/dL)	8.4±12.5	11.1±16.4	0.248#
Total protein (g /dL)	6.6±0.8	7.1±0.7	0.006#
Albumin (g /dL)	3.6±0.6	3.8±0.5	0.129#
Fibrinogen (µg / ml)	414.1±87.7	368.0±81.2	0.002#
Fibrinogen to Albumin Ratio	122.7±43.6	99.8±27.4	0.002#
Total Cholesterol (mg/dL)	197.0±58.8	198.8±43.2	0.851*
LDL-C (mg/dL)	119.8±46.9	123.2±37.3	0.679*
HDL-C (mg/dL)	40.3±7.6	43.7±9.2	0.066#
TG (mg/dL)	194.8±131.6	165.3±77.8	0.583#
Free T3 (ng/mL)	2.7±0.5	2.9±0.5	0.083*
Free T4 (ng/mL)	1.1±0.2	1.2±0.2	0.599#
TSH (IU/mL)	1.6±1.3	1.5±1.1	0.919#

CEA: Carotid endarterectomy, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, TG: Triglyceride, # Mann-Whitney U test, *Student's-t test, SD: Standard deviation

Factors related to the development of CAS were included univariate logistic regression analysis. In unadjusted univariate logistic regression analysis, the development of CAS was significantly correlated with advanced age (OR [odds ratio]: 0.885, 95% CI [confidence interval]: 0.835-0.940, p = 0.000), hypertension (OR: 0.303, 95% CI: 0.138-0.663, p = 0.003), presence of CAD (OR: 0.171, 95% CI: 0.075-0.393, p = 0.000) and FAR (OR: 0.982, 95% CI: 0.970-0.994, p = 0.003), but was not correlated with diabetes mellitus and LDL-C levels (Table 3). In addition, advanced age, presence of CAD and FAR were identified as an independent predictor of development of CAS in multivariate analysis (OR: 0.879, 95% CI: 0.817-0.947, p = 0.001 ; OR: 0.092, 95% CI: 0.027-0.316, p = 0.000 ; OR: 0.982, 95% CI: 0.965-0.998, p = 0.027, respectively) (see Table 3).

Table 3. Logistic regression analysis for indepent predictors to identify carotid artery disease

	Univariate analysis			Multivariate analysis		
Variables	p	Exp(B) Odds Ratio	95% C.I. Lower Upper	p	Exp(B) Odds Ratio	95% C.I. Lower Upper
Age	0.000	.885	.834 – .940	0.001	.879	.817 – .947
HT	0.003	.303	.138 – .663	0.233	.538	.194 – 1.491
DM	0.164	1.714	.802 – 3.665	0.059	.345	.114 – 1.043
CAD	0.000	.171	.075 – .393	0.000	.092	.027 - .316
FAR	0.003	.982	.970 – .994	0.027	.982	.965 - .998
LDL-C	0.676	1.002	.993 - 1.011	0.285	1.007	.994 – 1.020

HT; Hypertension, DM; Diabetes mellitus, CAD; Coronary artery disease, FAR; Fibrinogen to albümin ratio, LDL-C: Low density lipoprotein-cholesterol

In ROC curve analysis, for FAR it was determined a cut-off level of 101.18 for predicting progression of CAD (AUC: 0.669, 95% CI: 0.566-0.771, log rank p = 0.002) (Figure 1). In the measurements above their cut-off values, there was 68.0% sensitivity and 65.0% specificity for FAR(Figure 1).

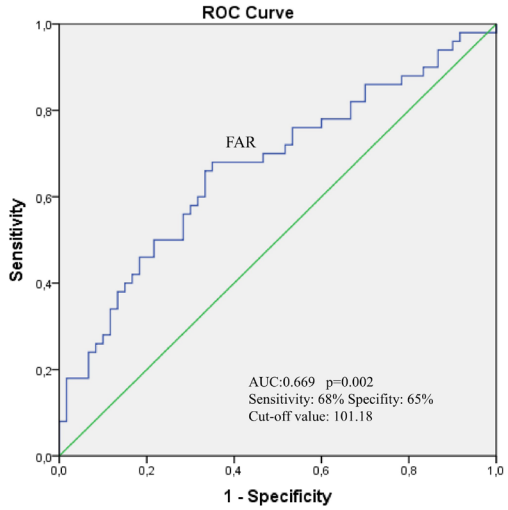

Figure 1.

Discussion

In this study, the association between FAR and CAS progression assessed. We determined the association between higher FAR and CAS progression. In univariate and multivariate logistic regression analysis, we found that higher FAR, advanced age and presence of CAD were as a independent variable predicting CAS progression. Also in ROC analysis, it was determined cut-off level of 101.18 of FAR for predicting CAS with a sensitivity of 68% and a specificity of 65% .

In a systematic review of 17 studies that examined carotid artery intima-media thickness (cIMT), including 10,124 healthy subjects free from cardiovascular disease risk factors, a strong positive relationship has been found between age and cIMT [10]. In the few previous studies, there is strong evidence that middle-aged and elderly people have a higher cIMT than younger adults [11,12]. Our study was not a study investigating the relationship between cIMT thickness and the age, but we found that the mean age was higher in CEA group than in the non-surgical group (p = 0.000). In addition, in our study, in logistic regression analysis, advanced age was defined as an independent predictor of CAS development.

The Atherosclerosis Risk in Communities Study showed that elevated levels of fibrinogen is a risk factor in CAD [13]. Wilhelmsen et al. [14] showed that fibrinogen is a risk factor in the development of stroke and myocardial infarction. Perl et al. [8] found that fibrinogen and glucose are variables indicative of atherosclerosis disease in both coronary and carotid artery vascular beds. Cho et al. [15] in the study that was assessed Association between Fibrinogen and Carotid Atherosclerosis According to Smoking Status in a Korean Male Population, found that fibrinogen levels were positively associated with IMT but no significant association between fibrinogen and IMTIn a smilar study, Ishihara et al. [16] pointed out that the combination of plasma fibrinogen and hsCRP levels could be a potential marker on subclinical carotid atherosclerosis in urban people. In these studies, fibrinogen has been used as a coagulant and inflammatory marker.

Albumin is a negative acute phase protein produced by the liver. Low albumin levels during inflammation may cause associated with the effect of cytokines, such as interleukin-6 and tumor necrosis factor-α [17]. Serum albumin has been shown to have protective properties, such as maintaining physiological homeostasis, antioxidant activity, anti-inflammatory effects, and the prevention of apoptosis [18]. Recently, the association of fibrinogen and albumin started to be investigated in coronary artery disease and in many cancer cases. In many cancer diseases such as hepatocellüler ca [17], breast ca [19], non-squamöz eausofagial ca [20] and lung ca [21], fibrinogen to albumin ratio was calculated and high FAR was associated with bad prognosis. In one of the rare studies on the rate of fibrinogen albumin in coronary artery disease, Karahan et al. [22] showed that FAR is significantly related to SYNTAX Score in predicting the severity of CAD in patients with ST-elevation myocardial infarction.

In the literature, we did not find any study investigating the relationship between carotid artery disease prognosis

and fibrinogen albumin ratio. In addition, it was stated that studies showing that high levels of fibrinogen and low serum albumin are effective in the development of atherosclerosis in the above paragraphs. In our study, we detected that FAR is significantly different between the groups and higher FAR was as a independent variable predicting CAS progression (Table 2)(Table 3). On the other hand, in ROC curve analysis, we found that there were 68.0% sensitivity and 65. % specificity for FAR (AUC: 0.669, 95% CI: 0.566-0.771, log rank p = 0.002)(Figure 1). To sum up, we achieved higher FAR values in patients who underwent CAE than patients without surgery and with less than 50% carotid artery stenosis.

Conclusion

In conclussion, many factors contribute to the development of CAS. Many studies have been done regarding the effect of fibrinogen or FAR on CVD. Although we detected that FAR is independent variable predicting CAS progression ,there is a need large studies including all cardiovascular diseases.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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