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Effect of lipid parameters on carotid artery disease progression in patients undergoing carotid endarterectomy and unoperated patients with non-severe carotid artery stenosis

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ABSTRACT

Objectives: We aim to evaluate the relationship between serum lipid indices and carotid artery stenosis (CAS).
Methods: This retrospective observational study included patients who underwent carotid endarterectomy (CEA) and unoperated patients who have CAS less than 50%. CAS was diagnosed with history and physical examination followed by doppler ultrasonography, coronary and carotid angiography. All data retrieved retrospectively from the hospital medical files. Non-high-density lipoprotein-cholesterol (non-HDL-C) level was calculated by removing HDL-C from total cholesterol. In addition, low-density lipoprotein-cholesterol (LDL-C)/HDL-C ratio, non-HDL-C/HDL-C ratio, and triglyceride (TG)/HDL-C ratio were assessed.
Results: CEA group (77.5% male, mean age: 71.35 ± 8.35 years) included 40 patients who underwent CEA, and there were 32 patients who have less than 50% CAS in unoperated group (68.8% male, mean age: 63.94 ± 9.92 years). The development of CAS was not significantly correlated with LDL-C/HDL-C ratio ($p = 0.119$), non-HDL-C/HDL-C ratio ($p = 0.227$) and TG/HDL-C ratio ($p = 0.768$). Advanced age and presence of coronary artery disease were identified as an independent predictor of the development of CAS. For predicting development of CAS, there were 50.0% sensitivity and 65.6% specificity for LDL-C/HDL-C ratio and non-HDL-C/ HDL-C ratio (area under the curve [AUC]: 0.592, log rank $p = 0.183$, AUC: 0.583, log rank $p = 0.227$, respectively).
Conclusions: We found that lipid ratios were not an independent predictors of the development of CAS. But, we think that AUC values which were above 0.5 for lipid ratios are may be important development of CAS.

Keywords: Carotid artery stenosis, lipid levels, disease progression

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Carotid artery stenosis (CAS) is a serious vascular problem for whole population and also an important cause of strokesparticularly in the elderly people [1]. In order to prevent these complications, it is necessary to intervene in symptomatic patients who have severe CAS [2]. In asymptomatic CAS, the incidence of stroke increases by 0.35-5%, and also the incidence and mortality of acute cardiovascular disease significantly increase [3].

Atherosclerosis is related to the inflammation and immunity and it is the main reason for CAS [4]. Traditionally, in the pathogenesis of atherosclerosis, there is accumulation of plasma lipids in the vascular wall, which contributes to the formation of an unstable

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plaque, which can be ruptured [5]. Framingham study showed that extracranial carotid artery atherosclerosis associated with increased plasma concentrations of total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) and also there is an association with decreased plasma concentration of high-density lipoprotein-cholesterol (HDL-C) [6].

Based on this balance, the usage of ratios of the serum lipid levels measurement can maintain the assessment of plaque burden. Consequently, we aim to evaluate relationship of serum lipid levels between patients who underwent carotid endarterectomy (CEA) and unoperatedpatients who have less than 50% CAS.

METHODS

Patients

This retrospective observational study included patients who underwent CEA and unoperated patients who have less than 50% CAS. This study was performed between 2017 and 2018 at Department of Cardiovascular Surgery, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Turkey. 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.

All patients were operated under local anesthesia. The exclusion criteria were level of triglyceride (TG) above 400 mg/dL, combined coronary artery bypassand CEA surgery, familial hyperlipidemia, and chronic renal failure. Eventually, 40 patients undergoing CEA were included in the CEA group, and 32 patients who have less than 50% CAS in unoperated group.

All data were recorded as age, gender, comorbidities (hypertension, diabetes mellitus, and cerebrovascular accident [CVA]), smoking, the presence of coronary artery disease (CAD), statin usage, and body mass index.

Laboratory measurements

Fasting blood samples were taken from an antecubital vein of each patient. Levels of TC, TG, and HDL-C were measured using chemistry analyzer (Beckman Coulter AU5800, CA, USA). The LDL-C was estimated bythe method of Friedewald's formula (TG <400 mg/dl) [7]. Non-HDL-C level was calculated by removing HDL-C from total cholesterol. In addition, LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, and TG/HDL-C ratio were assessed.

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 LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, and TG/HDL-C ratio.

RESULTS

A total number of 40 patients in the CEA group (77.5% male, mean age: 71.35 ± 8.35 years) and 32 patients in the unoperated group (68.8% male, mean age: 63.94 ± 9.92 years) were recorded in this study. The demographic and clinical characteristicsof the patients are summarized in Table 1. There were statistically difference between two group in terms of age ($p = 0.001$), presence of hypertension ($p = 0.035$), previous CVA ($p = 0.001$), presence of CAD ($p = 0.001$) and statin therapy ($p = 0.032$) (Table1).

The comparison of laboratory findingsare shown in Table 2. Both CEA group and unoperated group were similar to each other regards to laboratory findings. In addition, non-HDL-C level, LDL-C/HDL-

Table 1. Demographic and clinical characteristics of the patients

	CEA group (n = 40)	Unoperated group (n = 32)	*p* value
Age (years)	71.4 ± 8.4	63.9 ± 9.9	**0.001**[#]
Male gender, n (%)	31 (77.5)	22 (68.8)	0.403[a]
BMI (kg/m^2)	27.54 ± 4.1	26.96 ± 4.1	0.552[*]
Hypertension, n (%)	25 (62.5)	12 (37.5)	**0.035**[a]
Diabetes mellitus, n (%)	15(37.5)	18 (56.3)	0.113[a]
Previous CVA, n (%)	20 (50)	4 (12.5)	**0.001**[a]
CAD, n(%)	26 (65)	8 (25)	**0.001**[a]
Smoking[¶], n(%)	17 (42.5)	11 (34.4)	0.482[a]
Statin therapy, n(%)	17 (42.5)	6 (18.8)	**0.032**[a]

CEA = Carotid endarterectomy, BMI = Body mass index, CVA = Cerebrovascular accident, CAD = Coronary artery disease, [¶]Current or former smoking,[a]Pearson Chi- Suquare, [#] Mann-Whitney U test, [*]Student's-t test

C ratio, non-HDL-C/HDL-C ratio and TG/HDL-C ratio were not significantly different between the groups ($p = 0.432$, $p = 0.119$, $p = 0.227$ and $p = 0.768$; respectively) (Table2).

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]: 0.913, 95% CI [confidence interval]: 0.860-0.969, $p = 0.003$), hypertension (OR: 0.360, 95% CI: 0.138-0.940, $p = 0.037$) and presence of CAD (OR: 0.179, 95% CI: 0.064-0.503, $p = 0.001$) but was not correlated with diabetes mellitus, smoking, non-HDL-C level, LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio and TG/HDL-C ratio (Table 3). In addition, advanced age

Table 2. Laboratory findings

	CEA group (n = 40) (mean ± SD)	Unoperated group (n = 32) (mean ± SD)	*P value*
Hematocrit (%)	38.9 ± 5.6	39.1 ± 7.7	0.907[*]
Hemoglobin (g/dL)	12.8 ± 1.9	13.4 ± 1.9	0.201[*]
White blood cell (10^3/µL)	8.3 ± 2.6	8.9 ± 2.1	0.252[*]
Platelet (10^3/µL)	248.6 ± 65.2	243.7 ± 71.1	0.760[*]
Red cell distribution width (%)	14.7 ± 1.3	14.3 ± 1.6	0.229[*]
Mean platelet volume (fL)	8.6 ± 1.4	8.7 ± 1.6	0.959[#]
NLR	3.7 ± 1.9	3.1 ± 1.8	0.080[#]
HbA1c (%)	6.5 ± 1.5	6.8 ± 1.5	0.236[#]
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.8	0.398[#]
Ca (mg/dL)	9.2 ± 0.6	9.2 ± 0.6	0.933[*]
Mg (mg/dL)	1.8 ± 0.2	1.8 ± 0.3	0.671[*]
C-reactive protein (mg/dL)	7.5 ± 9.8	7.9 ± 7.1	0.782[#]
Total protein (g/dL)	6.9 ± 0.5	6.9 ± 0.7	0.967[*]
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.5	0.878[#]
Fibrinogen (µg/ml)	402.3 ± 91.2	407.7 ± 84.2	0.910[#]
Total cholesterol (mg/dL)	199.1 ± 59.3	191.7 ± 47.5	0.572[*]
LDL-C (mg/dL)	123.4 ± 45.6	115.8 ± 39.9	0.457[*]
HDL-C (mg/dL)	39.5 ± 7.6	42.1 ± 8.2	0.207[#]
Non-HDL-C (mg/dL)	159.6 ± 59.0	149.6 ± 44.5	0.432[*]
TG (mg/dL)	191.6 ± 137.2	186.9 ± 80.1	0.441[#]
LDL-C/HDL-C	3.2 ± 1.3	2.8 ± 0.9	0.119[*]
Non-HDL-C/HDL-C	4.2 ± 1.9	3.6 ± 1.1	0.227[#]
TG/HDL-C	5.2 ± 4.9	4.7 ± 2.5	0.768[#]

CEA = Carotid endarterectomy, NLR = Neutrophil to lymphocyte ratio, 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

Table 3. Binary Logistic regression analysis to identify predictors of disease progression

	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	**0.003**	.913	.860-.969	**0.003**	.902	.842-.967
HT	**0.037**	.360	.138-.940	0.528	.691	.219-2.179
DM	0.115	2.143	.831-5.526			
CAD	**0.001**	.179	.064-.503	**0.002**	.143	.042-.489
Smoking	0.483	.709	.271-1.854			
Non-HDL-C	0.428	.996	.987-1.005			
LDL-C / HDL-C	0.123	.709	.458-1.098			
Non HDL-C / HDL-C	0.133	.763	.536-1.086			
TG / HDL-C	0.583	.965	.850-1.096			
NLR	0.154	.814	.614-1.080			

HT = Hypertension, DM = Diabetes mellitus, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High-density lipoprotein-cholesterol, TG = Triglyceride, NLR = Neutrophil to lymphocyte ratio

and presence of CAD were identified as an independent predictor of development of CAS in multivariate analysis (OR: 0.902, 95% CI: 0.842-0.967, $p = 0.003$; OR: 0.143, 95% CI: 0.042-0.489, $p = 0.002$) (Table 3).

Additionally, in ROC curve analysis, for LDL-C/HDL-C ratio it was determined a cut-off level of 3.1 for predicting progression of CAD (AUC: 0.592, 95% CI: 0.460-0.723, log rank $p = 0.183$), for non-HDL-C/HDL-C ratio it was determined as a cut-off level of 4.4 for predicting progression of CAS (AUC: 0.583, 95% CI: 0.452-0.715, log rank $p = 0.227$) and for TG/HDL-C ratio, it was determined as a cut-off level of 4.4 for predicting progression of CAS (AUC: 0.480, 95% CI: 0.346-0.614, log rank $p = 0.768$) (Table 4). In the measurements above their cut-off values, there were 50.0% sensitivity and 65.6% specificity for LDL-C/HDL-C ratio, 50.0% sensitivity and 65.6% specificity for non HDL-C/HDL-C ratio, and 47.5% sensitivity and 53.1% specificity for TG/HDL-C ratio (Figure 1).

Table 4. Result of ROC curve analysis

Test Result Variable(s)	**AUC**	**Sensitivity**	**Specificity**	**Cut-off value**	***p* value**	**Asymptotic 95% Confidence Interval**	
						Lower	**Upper**
LDL-C / HDL-C Ratio	**.592**	50%	65.6%	3.1	.183	.460	.723
Non HDL-C / HDL-C Ratio	**.583**	50%	65.6%	4.4	.227	.452	.715
TG / HDL-C Ratio	.480	47.5%	53.1%	4.4	.768	.346	.614

ROC = Receiver operating characteristic, AUC = Area under the curve, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High-density lipoprotein-cholesterol, TG = Triglyceride

DISCUSSION

In our study, we assessed the effect of LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio and TG/HDL-C ratio in the development of CAS. In univariate logistic regression analysis, we found significant correlation among advanced age, hypertension and presence of CAD with the development of CAS. In multivariate logistic regression analysis, advanced age and presence of CAD were detected as independent predictors for the development of CAS. Additionally, in ROC curve analysis, we found that AUC of measured ratios were above 0.5 except from TG/HDL-C ratio (Table 4). However, in our study, all measured indexes were not independent predictors for the development of CAS.

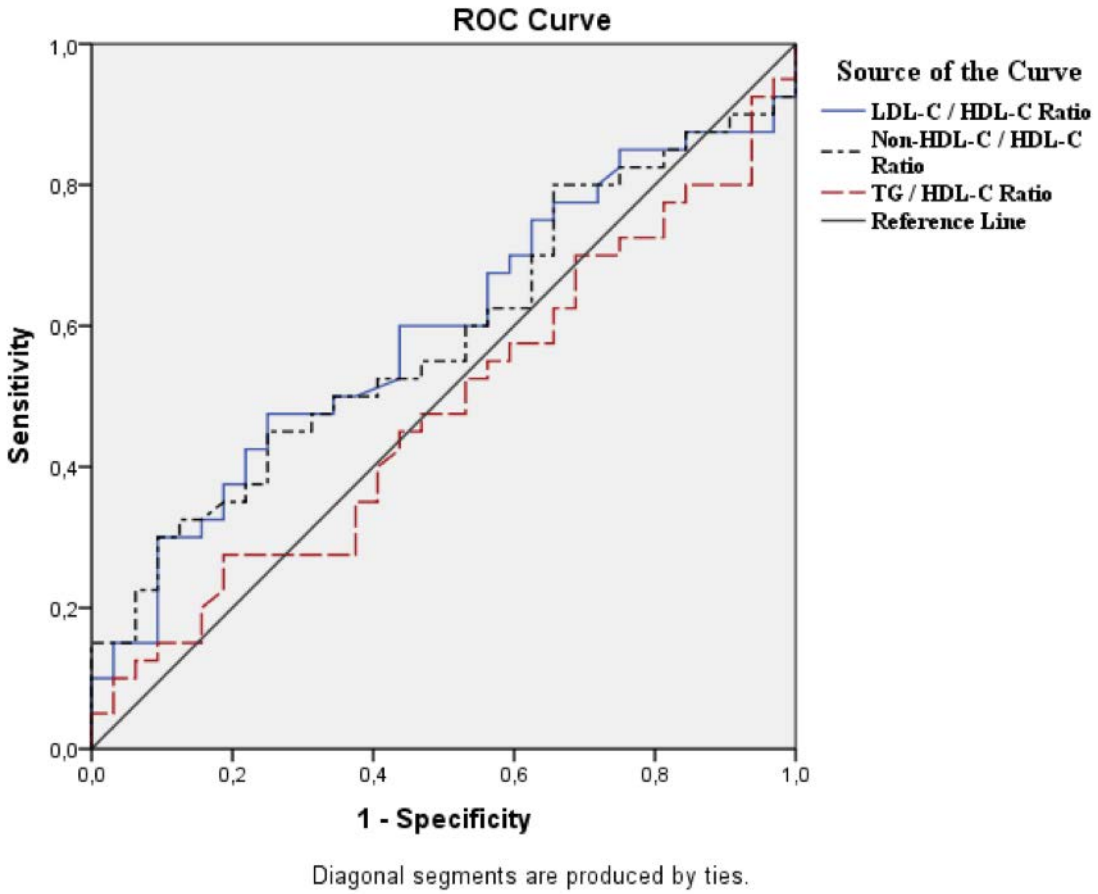

Figure 1. ROC curve and AUC for predicting progression of carotid artery stenosis of LDL-C/HDL-C ratio, non HDL-C/HDL-C ratio, and TG / HDL-C ratio. ROC = Receiver operation characteristic, AUC =Area under the curve, LDL-C = Low-density lipoprotein-cholesterol, HDL-C = High = density lipoprotein-cholesterol, TG = Triglyceride

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 [8]. This study also suggested that cIMT progressed strongly and linearly to advanced age. In the few previous studies, there is strong evidence that middle-aged and elderly people have a higher cIMT than younger adults [9, 10]. 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 unoperated group (p = 0.001). In addition, in our study, in logistic regression analysis, advanced age was defined as an independent predictor of CAS development. Additionally, in logistic regression analysis, we detected that advanced age was an independent predictor of CAS development.

Hyperlipidaemia is a well-documented risk factor in cardiovascular disease assessment. High HDL-C level is related inversely proportional to CAD, ischemic stroke and carotid atherosclerosis [11]. In many previous studies while HDL-C is accepted as an antiatherogenic agent, it has reported that LDL-C is a classical atherogenic lipoprotein [12]. Even though, the LDL-C level has been considered as the primary target of lipid-lowering therapy, non-HDL-C has been recommended as the secondary target of lipid lowering treatment, especially for patients with high TG levels [12]. In some studies, non-HDL-C has found as a more precious predictive value for atherosclerosis and CVD than LDL-C [13]. Furthermore, TC/HDL-C and LDL-C/HDL-C ratios have been considered as better predictors for atherosclerosis than each independent lipid parameter in other studies [14, 15]. Previous

studies have stated that TG/HDL-C ratio is one of the main indicator for cardiovascular diseases, insulin resistance and metabolism syndrome [16, 17]. Formerly published epidemic analysis have shown that non-HDL-C is a bit better than LDL-C as the predictor for CVD risk [13, 18]. Another meta-analysis including more than 300,000 people has demonstrated that the predictive value of non-HDL-C for CVD risk is similar with LDL-C (both measured and calculated) [19].

TC, LDL-C and non-HDL-C have precious predictive values for intima-media thickness and the presence of carotid plaque compared with other lipid parameters. Among these, TC has the greatest predictive value for the presence of carotid plaque. The value of non-HDL-C is not lower than LDL-C for foresight of cIMT and plaque [20]. Non-HDL-C has several advantages as a risk predictor of atherosclerosis. Firstly all potential atherogenic lipid particles included in its structure and it can be calculated in the non-fasting state; lastly, it can be calculated in the presence of hypertriglyceridemia [20].

Siemelink *et al*. [21] revealed in their study including 1,443 CEA patients, that plasma lipid levels were not associated with the carotid atherosclerotic plaque composition. They tried to explain this result to the presence of atherosclerotic disease and co-morbid disease in the patients included in the study and to the fact that the majority of the patients took lipid-lowering drugs. They also noted that with respect to plasma lipids, only a preoperative measurement was made and plasma lipid concentrations could change significantly over time. Accordingly, a recent meta-analysis has shown that statin therapy leads to regression of carotid plaques by improving inflammation, not lipid levels [22].

In our study, we detected that LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio and TG/HDL-C ratio were not significantly different between the groups (Table 2) and in logistic regression analysis (Table 3) we revealed that the progression of CAS was not correlated with LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio, and TG/HDL-C ratio. Our results are similar with the study of Siemelink *et al*. [21]. In our study, atherosclerotic disease (p = 0.001), hypertension as a comorbidity (p = 0.035) and statin therapy (p = 0.032) were statistically different in the CEA group. This may explain that, why in our study lipid ratios are not statistically significant with carotid artery disease.

On the other hand, in ROC curve analysis, we found that there were 50.0% sensitivity and 65.6 % specificity for LDL-C/HDL-C ratio (AUC: 0.592, log rank p = 0.183) and were 50.0% sensitivity and 65.6% specificity for non HDL-C/HDL-C ratio (AUC: 0.583, log rank p = 0.227) (Table 4, Figure 1). We think that in present study AUC values which were above 0.5 are not pointless values for LDL-C/HDL-C ratio and non HDL-C/HDL-C ratio. However, more studies are needed in this regard.

CONCLUSION

In conclussion, many factors contribute to the development of CAS. Many studies have been done regarding the effect of lipid parameters on CAS. Although our results were not statistically significant, we concluded that high lipid ratios may be a factor in the development of CAS. Therefore, there is a need for studies involving patients who are free of atherosclerotic risk factors and who do not use lipid-lowering agents.

Authorship contributions

Consept-Design: KKÖ, USS, ŞY; Data collection: KKÖ, USS, İBŞ; Analysis: KKÖ, FT; Literature search: KKÖ, FT, İBŞ; Writing: KKÖ, USS, ŞY; Critical review: ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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