

Comparison of risk factors that play a role in extra-cranial carotid artery atherosclerosis

Ekstrakraniyal karotis arter aterosklerozuna neden olan risk faktörlerinin kıyaslanması

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SUMMARY

Objective: Which risk factors are important in preventing or stabilizing possible extra-cranial carotid artery stenosis is unclear. We aimed to investigate risk factors that are associated with extra-cranial carotid artery stenosis in patients with ischemic stroke.

Method: The records of 215 patients with ischemic stroke who were admitted to Taksim Research Hospital were screened. Patients who had been monitored with color Doppler ultrasonography were then categorized on the basis of the degree of stenosis in the carotid artery (group A: 0%–49%, group B: 50%–69%, group C: >70%). Hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, ischemic heart disease, age, and sex were evaluated as risk factors. These risk factors were compared among the three groups by using SPSS version 17.

Results: We found a significant relationship between high mean low-density lipoprotein and the severity of carotid stenosis ($p<0.05$). A similar relationship was found between sex and the severity of carotid stenosis ($p<0.05$).

Conclusions: A high low-density lipoprotein level and male sex are important risk factors for having extra-cranial carotid artery stenosis. Therefore, use of more aggressive lipid-lowering treatments, recommending an appropriate diet, and encouraging physical activity in hyperlipidemic men are important in preventive medical practice.

Keywords: Extra-cranial carotid artery atherosclerosis; low-density lipoprotein; risk factors

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ÖZET

Amaç: İskemik inmenin en önemli risk faktörlerinden biri olan ekstra-kraniyal karotis arter stenozu konusunda birçok çalışma yapılmış olmasına rağmen bu değiştirilebilir risk faktörüne neden olan değişkenlerin hangilerinin primer korumada daha öncelikli olduğu konusu hala çok net değildir. Biz kendi olgu serimizde ekstrakraniyal karotis arter stenozuna neden olduğu söylenen risk faktörlerini kıyaslayarak öncelikli tedavi edilmesi gerekenleri saptamayı amaçladık.

Yöntem: İskemik inme nedeniyle Taksim İlyardım Araştırma Hastanesi'ne başvuran iki yüz on beş hasta renkli Doppler USG ile monitorize edilerek karotis arterlerindeki stenozun derecesine göre üç stenoz grubuna ayrıldı (%0-29, %30-70, %>70). Hipertansiyon, Diabetes Mellitus, hiperlipidemi, sigara, iskemik kalp hastalığı, yaş ve cinsiyet risk faktörleri

olarak değerlendirildi. Bu risk faktörlerinin üç grup arasında önemlilik düzeyinin kıyaslaması SPSS 17 programı kullanılarak yapıldı.

Bulgular: Çalışmamızda ortalama düşük yoğunluklu lipoprotein değeri ve karotid stenozunun ciddiyeti arasında istatistiksel olarak anlamlı bir ilişki saptandı ($p<0.05$). Benzer bir ilişki erkek cinsiyet ve karotid stenozunun ciddiyeti arasında da bulundu ($p<0.05$). Gruplar arasında yaş, hipertansiyon, diabetes mellitus, sigara kullanımı ve iskemik kalp hastalığı açılarından önemli bir fark bulunmadı.

Sonuç: LDL yüksekliğinin ve erkek cinsiyetin ekstra-kranyal karotis arter stenozunun artışında önemli faktörler olarak ortaya çıkması özellikle LDL yüksekliği olan erkek hastaların daha agresif bir yaklaşımla diyet, fiziksel aktivite artırma ve kolesterol düşürücü tedavilerinin düzenlenmesi gerekliliğini ön plana çıkartan sonuçlar oldu. Daha geniş hasta serilerinde yapılacak yeni çalışmalarla, değiştirilebilir bir risk faktörü olan ekstra-kranyal karotis arter stenozunu önlemeye yönelik yeni yaklaşımların da ortaya çıkartılması koruyucu hekimlik açısından önemli olacaktır.

Anahtar sözcükler: Ateroskleroz, ekstra-kranyal karotis arter stenozu, erkek cinsiyet, LDL, risk faktörleri

INTRODUCTION

Innovations that have been made in evaluating acute ischemic stroke in recent years are encouraging regarding a reduction in stroke-related mortality and disabilities in the early period. Evaluating and treating risk factors are important. Most of the risk factors of stroke are related to atherosclerosis¹. Unmodifiable risk factors in stroke are sex, age, race, and family history. Modifiable risk factors that have been identified for stroke are hypertension, diabetes mellitus (DM), hyperinsulinemia, glucose intolerance, cardiac disease, hyperlipidemia, smoking, asymptomatic carotid artery stenosis, and sickle-cell anemia. Other possible modifiable factors include alcohol consumption, obesity, poor dietary habits, physical activity, hyperhomocysteinemia, drug addiction, hormonal therapy (use of oral contraceptives, hormone replacement therapy), hypercoagulability, fibrinogen, inflammation, and migraines².

The incidence of asymptomatic carotid artery stenosis (>50%), which is one of the modifiable risk factors of stroke, is 7%–10% in men older than 65 years and 5%–7% in women older than 65 years. In different studies, the annual risk of ipsilateral stroke was reported to be 1%–2%. This risk increases in progressive stenosis cases, especially when compared with stable stenosis.

In evaluating disease in carotid arteries, direct non-invasive methods, such as magnetic resonance angiography, computed tomography angiography, and color Doppler ultrasonography, can be used. Invasive methods, such as digital subtraction angiography and conventional angiography, are also used to evaluate disease in carotid arteries³.

Among the non-invasive imaging methods, color Doppler ultrasonography is the main diagnostic instrument used for evaluating extra-cranial carotid pathologies because it is easy to apply, has bed-side implementation, requires no equipment, offers

detailed information about hemodynamics, as well as morphological information, can be easily tolerated by the patient, and is an affordable method^{4,5}.

Age, sex, smoking, hypertension, and high blood cholesterol levels are considered as risk factors for carotid artery stenosis. Besides these factors, obesity, oral contraceptive use (together with smoking, especially an age older than 35 years), the presence of peripheral artery disease, and a high hematocrit are also accepted risk factors⁶⁻¹⁸. Moreover, Phan et al.¹⁹ emphasized that, independent from conventional vascular risk factors, the structure of the carotid artery might increase the risk of stenosis and early detection of this condition is important for preventive medicine.

The present study aimed to retrospectively analyze risk factors that play an active role in development of symptomatic carotid artery atherosclerosis in patients who have the diagnosis of ischemic stroke caused by large vessel atherosclerosis.

MATERIAL AND METHODS

Participants and study design

A total of 215 patients, who were hospitalized in Taksim Research Hospital with the diagnosis of acute ischemic cerebrovascular disease caused by large vessel atherosclerosis were retrospectively studied.

Diagnosis of ischemic stroke

The diagnosis of ischemic stroke was interpreted as the loss of focal or global cerebral function, which developed immediately and lasted for longer than 24 hours, and it was not attributed to any reason other than vascular reasons. This vascular character was confirmed by using radiological methods. The patients who had undergone cerebral computed tomography in the early period (at the moment of admission), on the 24th hour of admission and after 72 hours were included in the study.

Exclusion criteria

Patients who had an intracerebral hematoma, subarachnoid hemorrhage, and intracranial space-occupying lesion were excluded. Patients with an akinetic left ventricle, ventricular aneurysm, myocardial infarction earlier than 4 weeks, atrial fibrillation with valvular heart disease, and a prosthetic cardiac valve that was a high-risk source of emboli, as well as patients who were diagnosed with posterior circulation ischemic stroke were not included in the present study. These patients were excluded to be certain about the etiology of ischemic stroke caused by extra-cranial carotid artery stenosis.

Criteria for diagnosis of carotid artery stenosis

There are different approaches for grading of carotid artery stenosis. In the European Carotid Surgery Trial (ECST) for stenosis grading, the classical angiographic method was preferred. In this method, the diameter of the residual lumen is proportioned to the diameter of the artery at the level of stenosis. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study, a modified version of this method was used. In this modified version, grading of stenosis is performed by proportioning the diameter of the residual lumen to the diameter of the artery just after stenosis^{20, 21}.

To minimize the complexities arising from the different approaches, some researchers consider quantitative values for evaluating stenosis, in addition to narrowing of the lumen. Bluth et al.^{20, 22} reported that, at $\geq 80\%$ narrowing, the peak systolic velocity should be higher than 250 cm/s, end-diastolic velocity (EDV) should be higher than 100 cm/s, the systolic velocity ratio should be higher than 3.7, and the diastolic velocity ratio should be higher than 5.5. In the classification of Moneta et al., which is widely used in Turkey, in stenosis higher than 60% according to NASCET and 80% according to ECST, the peak systolic velocity should be higher than 250 cm/s, EDV should be higher than 100 cm/s, and the peak systolic velocity ratio should be higher than 4.0²⁰. Authors of previous studies have emphasized that the best parameter in grading stenosis is peak systolic velocity, which has high sensitivity and specificity²¹. We used the classification of Moneta et al. for diagnosing the severity of extra-cranial carotid artery stenosis in our patient group.

Classifying patients by carotid artery stenosis

The patients were divided into the following three groups on the basis of stenosis grades as determined by colored Doppler ultrasonography (CDUS) using

the Toshiba Aplio (7.5-MHz linear probe) device: group A, mild stenosis group (carotid artery stenosis $<30\%$), group B, moderate stenosis (carotid artery stenosis between 30% and 70%), and group C, severe stenosis (carotid artery stenosis $>70\%$). The groups were compared to determine the effect of risk factors by the grade of stenosis.

Covariants

Hypertension, DM, hyperlipidemia (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol, triglycerides) smoking, ischemic heart disease, age, and sex were examined as risk factors in the groups.

Defining risk factors

Patients who had a diagnosis of hypertension, those who were already taking anti-hypertensive medication, or those who had systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg (hypertension stage 2) according to the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults²³ were considered to have hypertension. Patients with fasting blood glucose levels ≥ 126 mg/dl and randomized blood glucose levels ≥ 200 mg/dl (ADA 2018)⁽²⁴⁾ were considered as diabetic. Patients who smoked within the last 1 year were considered as smokers. Patients were diagnosed as having ischemic heart disease by cardiologists in our Department of Internal Diseases on the basis of a history, physical examination, Electrocardiogram data, and transthoracic echocardiography.

Biochemical parameters

Serum levels of glucose, total cholesterol, triglycerides, and HDL were spectrophotometrically measured by a Roche/Hitachi molecular PP auto-analyzer using an enzymocalorimetric method. LDL and very low-density lipoprotein (VLDL) were calculated using Friedwald's formula. (VLDL = triglycerides/5, LDL = total cholesterol - HDL - triglycerides/5).

Ethics and protocol approval

The present study was carried out in accordance with the current Helsinki Convention of the World Medical Association. Approval of all of the patients was obtained to use their medical records in retrospective file scanning. The Ethics Committee of Community Hospitals Association, Turkish Ministry of Health, approved the present study.

Statistical analysis

The data were analyzed using SPSS for Windows 17.0 statistical package software (SPSS Inc. 2008, Chicago, IL, USA). Qualitative variables were

analyzed by using Chi-square test and Fisher's exact test. Student's *t*-test for independent samples and Mann-Whitney *U* test were used to check against the quantitative variables. One-way ANOVA was used to determine if there were any significant differences in variables, such as mean serum LDL levels, age, sex, hypertension, DM, ischemic heart disease, and smoking among the groups.

RESULTS

The characteristics of the patients involved in the present study are shown in Table 1. The mean age of the patients was 68.5 years (SD=±10.5). There was no significant difference in age among the groups. A total of 128 patients were men and 87 were women. There were 85 men and 72 women in group A, 22

men and 9 women in group B, and 21 men and 6 women in group C. Carotid artery stenosis was significantly more frequent in men than in women ($p<0.05$).

The mean serum LDL level in Group B was significantly higher than that in group A ($p<0.001$). Moreover, the mean serum LDL level in group C was significantly higher than that in groups B and A ($p<0.001$).

There was no significant difference in the rate of hypertension among the groups. There were no significant differences in the rates of DM and ischemic heart disease among the groups. Furthermore, there was no significant difference in the rate of smoking among the groups.

Table 1: Descriptive and comparative results of the three patient groups

	Patient groups			p value
	Group A (stenosis <50%)	Group B (stenosis 50%-69%)	Group C (stenosis >70%)	
Number of subjects (n)	157	31	27	
Age (years)	67.06±12.5	71.23±9.8	67.30±9.6	0.10
Sex, male-female, n (%)	85 (54.2)-72 (45.8)	22 (70.9)-9 (29.1)	21 (77.7)-6 (22.3)	0.02
LDL, mean, (SD)	105±33	139±25	167±24	0.01
HDL, mean, (SD)	34±5	35±4	33±4	0.50
Hypertension, n (%)	114 (72.6)	26 (83.8)	21 (77)	0.30
Ischemic heart disease, n, (%)	53 (33.7)	7 (22.5)	9 (33.3)	0.40
Cigarette smoking, n (%)	72 (45.8)	15 (48.3)	16 (59.2)	0.40
Diabetes mellitus, n (%)	60 (38.2)	13 (41.9)	10 (37)	0.90

Values are mean ± standard deviation or n (%). n; number, LDL; low-density lipoprotein, HDL; high-density lipoprotein.

DISCUSSION

Atherosclerosis is the most common reason for stroke with an ischemic nature. Despite numerous studies on atherosclerosis worldwide, the main factor for causing atherosclerosis is still unknown. Since 1992, studies have focused on the regulative mechanism of smooth muscle cell proliferation for playing an important and integral role in atherogenesis, the role of lipids aggravating and provoking atherogenesis, and recently, the role of inflammatory factors²⁵.

Various studies have shown that the rate of atherosclerosis is higher in men than in women, this incidence increases after menopause in women^{12, 15, 26, 27}. An increase in weight in menopause, a change

in lipids, endothelial function disorder, insulin resistance, homocysteine levels, lipoprotein a levels, and an increase in various coagulation factors might play role in atherosclerosis²⁸. Fabris et al.¹³ reported that, in 457 patients, the incidence of atherosclerosis in men was higher than that in women in any age group. In our study, carotid artery stenosis was less frequent in women than in men, and there was a significant relationship between the level of carotid artery stenosis and male sex.

Hypertension is an important risk factor in the development of stroke. The relationship between carotid atherosclerosis and hypertension has been emphasized by many researchers^{8, 9, 11, 13, 29}. However, Handa et al.²⁶ did not find any

relationship between hypertension and carotid atherosclerosis in patients with stroke. These authors attributed this result to the high incidence of hypertension among the population with stroke. Lemne et al.¹⁵ found no relationship between hypertension and intima-media thickness in the carotid artery. However, Fabris et al.¹³ considered that the hypertension affected intracranial arteries more than extra-cranial vessels. Weber et al.³⁰ reported that systolic blood pressure was a strong determinant of early carotid atherosclerosis. Ertan et al.³¹ compared hypertension and carotid atherosclerosis in patients with stroke and they found that hypertension was not associated with carotid atherosclerosis. Another study showed that, among female and male patients with non-embolic acute ischemic stroke, an increase in the severity of hypertension was directly proportional to the incidence of stroke in all age categories between 45 and 84 years²⁹. An increase in the risk of stroke after the age of 65 years is strongly related to the level of systolic blood pressure²⁹. In the present study, there was no significant association between the degree of stenosis and hypertension.

There is an increased tendency for coronary, femoral, and cerebral artery atherosclerosis among patients with diabetes. Research and prospective studies carried out in patients with stroke have shown an increase in the risk of stroke among patients with diabetes. Epidemiological studies have provided a wealth of data indicating that carotid artery atherosclerosis is found in patients with diabetes more frequently than in those without diabetes. Dempsey et al.²⁹ found no significant relationship between blood glucose levels and the level of carotid artery stenosis, although Fabris et al.¹³ and Bogousslavsky et al.¹² obtained results proving the opposite. Kalogeropoulou et al.³² found that an increase in plasma levels of endothelin-1 and free radicals and a decrease in prostacyclin levels played a role in development of atherosclerosis in DM. In the present study, there was no significant difference in the rate of DM among the groups.

Smoking accelerates the atherosclerotic process through various mechanisms. Smoking increases aggregation of thrombocytes, decreases the use of myocardial oxygen, and causes hypoxia in vascular structures by an increase in carbon monoxide levels. Furthermore, smoking contributes to development and progression of atheroma plaques in the intima through oxidation of lipids³³. Smoking, which is an accepted important risk factor for atherosclerotic cardiac and venous diseases, negatively affects the cholesterol profile of adults. This effect appears in the form of an increase in LDL and VLDL cholesterol levels and a decrease in HDL cholesterol

levels^{33,34}. HDL cholesterol levels of smokers were found to be lower by approximately 10% compared with non-smoking individuals³⁵. A low HDL level is an important risk factor for atherosclerosis. In the present study, there was no significant difference in the rate of smoking among the groups.

The relationship between stroke (especially non-embolic ischemic stroke) and lipid levels in the blood is still unclear. In a meta-analysis of 45 prospective epidemiological studies on 450,000 patients (stroke in 13,000 of them), no significant relationship was found between total serum cholesterol levels and the total incidence of stroke²⁵. Even if the relationship between blood lipids and stroke is unclear, serum lipid levels are known to be directly related to extra-cranial carotid artery atherosclerosis and wall thickness³⁶. The Asymptomatic Carotid Artery Progression Study showed that 20–40 mg daily use of lovastatin, which is a 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitor, decreased extra-cranial carotid artery intima-media thickening in asymptomatic patients with moderately increased serum LDL cholesterol levels and early carotid artery atherosclerosis²⁵. In this previous study, serum cholesterol levels decreased from 156.6 mg/dl to 113.1 mg/dl (by 28%) in a 6-month period and a significant decrease was found in intima-media thickness in extra-cranial carotid arteries in a 36-month period. The Atherosclerosis Risk in Communities study showed that serum total lipid and total cholesterol levels in cases of carotid artery atherosclerosis were significantly higher than those in control cases²⁵. A study on patients with familial hypercholesterolemia reported that a decrease in LDL cholesterol levels significantly decreased intima-media thickening related to carotid artery atherosclerosis³⁷. Varleta et al.³⁸ showed that age, dyslipidemia, systolic blood pressure, and abdominal obesity were predictors of an increase in thickness of the carotid intima-media in a study group of 187 participants. Additionally, Burgess et al.³⁹ reported that LDL levels >100 mg/dl, age, hypertension, and plasma-soluble P-selectin were factors that increased the risk of carotid artery plaques in a study on 597 men. In the present study, no significant difference was found in mean HDL values among the groups. However, the mean serum LDL level was significantly higher in group B than in group A. Moreover, the mean serum LDL level in group C was significantly higher in group C than in groups B and A.

Many studies have shown a close relationship between carotid artery stenosis, ischemic stroke, and ischemic heart disease³¹. Atherosclerosis is a generalized phenomenon, and coronary vessels,

peripheral arteries, intra-cerebral arteries, and carotid arteries are commonly affected. The general incidence of coronary heart disease among patients with stroke has been reported to vary between 25% and 48%^{40,41}. The severity of carotid atherosclerosis is thought to be a determinant of ischemic heart disease. Moreover, the most important etiological factor in patients with stroke after coronary artery bypass surgery is carotid disease⁴². In the present study, there was no significant difference in the rate of ischemic heart disease among the groups.

The incidence of stroke increases as age advances. Therefore, age is accepted to be one of the most important risk factors for stroke. A strong relationship has been found between carotid artery atherosclerosis and age^{13, 15, 16, 26}. In the present study, there was no significant difference in age among the groups. This may be because almost all of the patients involved in the present study visited the hospital for stroke and the total mean age was also high.

The most interesting finding in the present study is that a high LDL level was a risk factor for carotid artery stenosis. LDL levels can be easily altered through medical treatment and lifestyle changes. The significant relationship between the degree of carotid artery disease and male sex is important because of the necessity of more aggressive treatment of all of the risk factors in male patients. However, we did not find any significant differences in age, the presence of hypertension, the presence of DM, the rate of smoking, and the rate of ischemic heart disease among the groups. These variables have been previously shown to be important risk factors for carotid artery stenosis.

One of the limitations of the present study is that we did not examine abdominal obesity, homocysteine levels, and P-selectin levels, which are other risk factors for carotid artery stenosis. Future studies need to be carried out on a larger number of participants to provide additional data to our study results.

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