Investigation of Risk Factors and High-Sensitive C-Reactive Protein Levels in Patients with Leriche Syndrome Concomitant Coronary Artery Disease and Significant Carotid Stenosis

Karotis Darlığı ve Koroner Arter Hastalığı Bulunan Leriche Sendromlu Olgularda Risk Faktörleri ve Yüksek Duyarlı C-Reaktif Protein Düzeylerinin Araştırılması

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ABSTRACT Objective: Clinical manifestations of atherosclerosis are coronary artery disease (CAD), cerebrovascular disease, and peripheral artery disease. The most advanced clinical form of atherosclerosis is involvement of all the three vascular beds. The aim of the present study is analysis of risk profiles and detection of high-sensitive C-reactive protein (hsCRP) levels of patients with Leriche syndrome concomitant CAD and severe carotid stenosis. **Material and Methods:** Twenty-one patients, who were followed in our clinic with Leriche syndrome and detected CAD and severe carotid stenosis, were recruited as study group. Control group consisted of 25 patients with only CAD who were matched to the study group for age and sex. **Results:** While 85.7% of the patients in the study group had three or more risk factors, this rate was only 36% in the control group (p=0.004). Of the patient in the study group, 95.2% were male, 76.2% were hypertensive, and 38.1% were diabetic. It was remarkable that, in the study group, smoking habit was more (90.5% and 52%, respectively; p= 0.02), and HDL-cholesterol levels were lowest (27.2 ± 3.5 mg/dl and 39.8 ± 6.5 mg/dl, respectively; p< 0.001) than the control group. Compared to the control group, hsCRP levels were higher in the study group (6.39 ± 2.77 mg/L and 2.7 ± 1.43 mg/L, respectively; p< 0.001). **Conclusion:** There are many risk factors in patients with Leriche syndrome concomitant CAD and severe carotid stenosis. High hsCRP levels, smoking habit, and very low HDL-cholesterol levels come into prominence in these patients.

Key Words: Atherosclerosis; carotid artery diseases; coronary artery disease; C-reactive protein, leriche syndrome

ÖZET Amaç: Ateroskleroz, klinik olarak koroner arter hastalığı, serebrovasküler hastalık ve periferik arter hastalığı şeklinde kendini gösterir. Bu 3 damar yatağının da tutulması aterosklerozun en şiddetli klinik şeklidir. Bu çalışmanın amacı, eşlik eden koroner arter hastalığı ve ciddi karotis stenozu olan Leriche sendromlu hastaların risk faktörleri profillerinin ve yüksek duyarlı c-reaktif protein (CRP) düzeylerinin araştırılmasıdır. **Gereç ve Yöntemler:** Çalışma grubu kliniğimizde Leriche sendromu tanısı ile takip edilen ve eşlik eden koroner arter hastalığı ile şiddetli karotis darlığı saptanan 21 hastadan oluşturuldu. Kontrol grubu ise, çalışma grubu ile yaş ve cinsiyet bakımından eşleşen koroner arter hastalığı bulunan 25 olgudan ibaretti. **Bulgular:** Çalışma grubunu oluşturan hastaların %85.7'sinde 3 veya daha fazla risk faktörü mevcut iken, kontrol grubunda bu oran sadece %36 idi (p= 0.004). Çalışma grubundaki hastaların %95.2'si erkek, %76.2'si hipertansif, %38.1'i diyabetik idi. Çalışma grubunda, kontrol grubuna kıyasla sigara içme alışkanlığı daha fazla (sırasıyla %90.5 ve %52, p= 0.02), HDL-kolesterol düzeyleri ise çok daha düşük idi (sırasıyla, 27.2 ± 3.5 mg/dl ve 39.8 ± 6.5 mg/dl, p< 0.001). Çalışma grubundaki yüksek duyarlı CRP düzeyleri ise konrol grubuna kıyasla daha yüksekti (sırasıyla 6.39 ± 2.77 mg/L ve 2.7 ± 1.43 mg/L, p< 0.001). **Sonuç:** Koroner arter hastalığı ve ciddi karotis darlığı olan Leriche sendromlu hastalarda daha fazla risk faktörü birarada bulunmaktadır. Bu hastalarda özellikle yüksek CRP düzeyleri, sigara içme alışkanlığı ve çok düşük HDL-kolesterol düzeyleri dikkat çekmektedir.

Anahtar Kelimeler: Ateroskleroz; karotid arter hastalıkları; koroner arter hastalığı; C-reaktif protein, leriche sendromu

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Although atherosclerosis is classically divided into three types of diseases, which are coronary artery disease, cerebrovascular disease, and peripheral artery disease, it is now considered to be a systemic disease and to develop as a result of common pathologic events, no matter which vascular bed is involved.[1] Atherosclerotic disease in one vascular bed is usually in conjunction with small or large involvement of other vascular beds, as well. In other words, patients with symptomatic lesions in one vascular bed often have clinically silent atherosclerotic lesions in other artery beds, too. Although studies suggested that atherosclerosis started concurrently in more than one vascular bed, they showed that atherosclerosis, particularly in femoral arteries, progressed slower than that in carotid and coronary arteries.[2] Prognosis of patients with atherosclerosis in more than one vascular bed, as expected, is poorer than those with disease in one vascular bed. Patients with severe atherosclerotic stenosis in all three coronary, carotid, peripheral arteries are expected to be the highest risk patient group. In literature, there is no data related to clinical risk profiles and high-sensitive C-reactive protein (hsCRP) levels of patients with diffuse atherosclerosis leading severe stenotic lesions in all these three arterial beds.

The aim of this study is to investigate risk factor profiles and hsCRP levels of patients with Leriche syndrome concomitant coronary artery disease and severe carotid stenosis.

PATIENTS AND METHODS

Twenty-one patients, who were detected to have concomitant coronary arterial disease in coronary angiography and severe stenosis in at least one carotid artery in carotid ultrasonography performed while being followed in our clinic between February 2004 and July 2008 with the diagnosis of Leriche syndrome and detected CAD and severe carotid stenosis, were included in the study. Twenty-five patients, who were diagnosed for coronary artery disease with coronary angiography performed in our clinic, but had no serious stenotic lesions in carotid and peripheral arteries, matching to the study group for age and sex, were included as the control group. Those with inflammatory, neoplastic, or infectious diseases which could lead to elevation in CRP levels were excluded. The study was approved by the local research ethics committee.

Medical histories, records of physical examination, and cardiovascular risk factors of all patients were assessed. Of the major cardiovascular risk factors, presence of family history of premature coronary artery disease (presence of coronary artery disease seen in first degree relatives, and diagnosed before 55 years of age), hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg in at least two distinct readings, or previously receiving antihypertensive medications), diabetes mellitus (fasting blood glucose ≥126 mg/dl, or previously receiving anti-diabetic medications), and smoking habit were recorded.

Total cholesterol, triglyceride, and high-density lipoprotein (HDL) levels of the morning blood samples, obtained from the patients after a 12-hour fasting a day before coronary angiography procedure, were measured with standard enzymatic-colorimetric methods. Low-density lipoprotein (LDL) levels were calculated using Friedewald formula. High-sensitive CRP levels of 17 patients in the study group were measured with nephelometric method and values >3 mg/L were considered as high. High-sensitive CRP levels of four patients in the study group could not be measured.

Coronary angiographies of all patients were performed with standard methods by inserting a sheath in right brachial artery and control groups were performed with Judkins method. Coronary angiograms were assessed by at least two experienced cardiologists. Coronary artery disease was diagnosed at the presence of a lesion causing >50% stenosis in the diameter of at least one coronary artery. The patients were categorized as one-vessel, two-vessel, and three-vessel patients in terms of extensiveness of coronary artery disease according to the number of coronary arteries with stenosis ≥50%.

Both carotid arteries of all patients were assessed with carotid Doppler ultrasonography per-

formed by the same radiologist. Severe carotid stenosis was diagnosed with the presence of findings consistent with stenosis ≥50% in at least one carotid artery.

Statistical analyses were performed by SSPS (version 12) software. Continuous variables were defined as mean (± standard deviation), and categorical variables as percentage. In comparisons between the groups, Mann-Whitney U test was used for continuous variables, and chi-square test was used for categorical variables. Differences between the groups were considered as statistically significant when $p< 0.05$.

RESULTS

Demographic data and conventional risk factors of 21 patients comprising the study group and 25 patients, matched for age and sex, comprising the control group are shown in Table 1 The patients comprising the study group had a much more serious risk profile than those comprising the control group (Figure 1). Of the patients comprising the study group, 85.7% had three or more risk factors, whereas only 36% of the patients comprising the control group had three or more risk factors ($p= 0.004$). While there were two risk factors in 48% of patients in the control group, this rate was only 14.3% in the study group. There were no patients with less than two risk factors in the study group. When looked at the risk factors individually, smoking habit was found statistically significantly higher in patients in the study group (90.5% and 52%, respectively; $p= 0.02$). Of the patients in the study group, 38.1% were diabetic, and 76.2% were hypertensive. Although high rates for both risk factors drew attention, the difference between the groups was statistically insignificant. When lipid profiles were evaluated, it was seen that the patients in the study group had significantly lowest HDL levels (on average 27.2 mg/dl and 39.8 mg/dl, respectively; $p< 0.001$) and that there was no statistically significant difference in total cholesterol, LDL, and triglyceride levels.

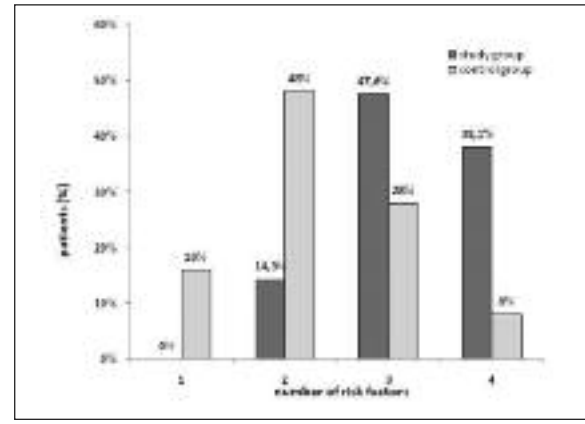

FIGURE 1: Patients (%) with 1, 2, 3, or 4 risk factors.

TABLE 1: Baseline characteristics of the patients.

	Study Group	Control Group	P value
	n= 21	n= 25	
Gender (males)	20 (95.2%)	24 (96%)	0.90
Age (years)	60.5 ± 8.7	59.7 ± 7.2	0.74
Smoking	19 (90.5%)	13 (52%)	0.02
Hypertension	16 (76.2%)	12 (48%)	0.07
DM	8 (38.1%)	6 (24%)	0.34
Family history	5 (23.8%)	4 (16%)	0.71
Total cholesterol (mg/dl)	195 ± 28.8	190 ± 36.8	0.66
LDL-chol (mg/dl)	122.3 ± 25.3	117.3 ± 24.7	0.52
Triglycerides (mg/dl)	225.2 ± 98.5	166.9 ± 73	0.07
HDL-chol (mg/dl)	27.2 ± 3.5	39.8 ± 6.5	<0.001

DM, diabetes mellitus; HDL-chol; high-density lipoprotein cholesterol; LDL-chol; low-density lipoprotein cholesterol.

When extensiveness of coronary artery disease was assessed with respect to coronary angiography results, one-vessel disease was detected in 23%, two-vessel disease in 31%, and three-vessel disease in 46% of the patients in the study group. Of the diabetic patients in the study group, 50% were two-vessel patients and 50% were three-vessel patients.

High-sensitive CRP levels were significantly higher in the study group (mean values for study and control groups are 6.39 mg/L and 2.7 mg/L, respectively; $p<0.001$) (Figure 2). In 82% of patients in the study group, hsCRP levels were above 3 mg/L. In control group, hsCRP levels were above 3 mg/L in only 32% of the patients.

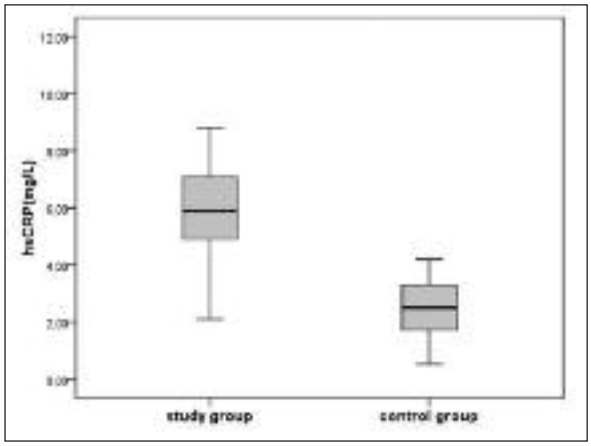

FIGURE 2: Comparison of hsCRP levels (mg/L) between groups.

DISCUSSION

Atherosclerosis is a systemic disease, characterized by progressive accumulation of lipid, inflammatory cells, and fibrous elements in vascular wall, involving large arteries.[1] Clinical manifestations are coronary artery disease, stroke, and peripheral artery disease. The disease starts at an early period of life and progresses clinically silently for a long period of time.[2] As atherosclerosis progresses so as to give clinical finding in an arterial bed, mild or severe involvement could also be expected in other arterial beds. This is particularly valid for peripheral artery disease, because peripheral artery disease often displays an asymptomatic and slow progress. When clinical history and electrocardiography is investigated in patients with peripheral artery disease, the prevalence of concomitant coronary artery disease is found to be 30-40%.[3] Similarly, when assessed with clinical history, presence of previous stroke is about 15%.[4] If more sensitive tests which could also capture the asymptomatic disease are used, it will be seen that these rates significantly increase. When coronary angiography is performed, atherosclerotic involvement of coronary arteries could be detected in 70-90% of those with peripheral artery disease.[5] When carotid ultrasonography is performed in this patient group, findings of atherosclerosis are seen in carotid arteries, as well, in more than 50%.[6] One study on Japanese patients who underwent coronary artery bypass surgery for coronary artery disease found that 13.7% carotid stenosis and 15.3% peripheral artery disease accompanied to coronary artery disease.[7] Given that there were atherosclerotic lesions leading to severe stenosis in all three vascular beds in the patient population included in the present study, it is recognized that the study group was consisted of a specific patient group with the most advanced clinical form of atherosclerosis.

There are seven classical risk factors for atherosclerosis. These are; age, sex, family history for premature atherosclerosis, smoking habit, hypertension, diabetes mellitus, and dyslipidemia. However all these risk factors are valid for three main vascular beds which atherosclerosis may involve, distinct risk factors may come to the forefront for each vascular bed. For example, in peripheral artery disease, smoking; in cerebrovascular disease, hypertension; and in coronary artery disease, dyslipidemia are more potential risk factors.[8] In our study, especially risk factors of smoking habit, hypertension, and low HDL in the study group draw attention at first sight. Almost all the patients (95.2%) were male. Smoking habit in the study group was significantly more prevalent than the control group. Smoking is an independent major risk factor for atherosclerosis. Direct effect of smoking on progress of atherosclerosis was shown in ARIC trial.[9] In the three-year follow-up period, atherosclerosis progress assessed by carotid intima media thickness was 50% higher in smokers. In another trial, serial coronary angiographies showed that smoking both increased the severity of the lesion and accelerated formation of new lesions.[10] In the light of these data, very high smoking rates we encountered in the study group patients with diffuse and severe atherosclerosis was unsurprising. While the rate of hypertensive patients was 76.2% in the study group, it was 48% in the control group (p= 0.07). No statistical difference between the groups despite quite high percentage of hypertensive patients in the study group may be due to small number of patients.

Probably the most remarkable finding in our study was the presence of very low HDL levels in

patients in the study group. Mean HDL value was 27.2 mg/dl in the study group, while it was 39.8 mg/dl in the coronary artery patients comprising the control group ($p<0.001$). It was remarkable that HDL values were ≤30 mg/dl in 14 (66.6%) of these 21 patients with diffuse and severe atherosclerosis. It is known that HDL molecule has an antiatherogenic activity by the mechanism of reverse cholesterol transport.[11] Low HDL level are seen more frequently in those with premature coronary artery disease.[12] In literature, there are no trials demonstrating a relation between low HDL levels and concurrent extensive involvement of atherosclerosis in distinct vascular beds. We think that this interesting finding in the present study should be investigated in larger series of patient.

When the patients in the study group were assessed with respect to the number of risk factors they had, it would be seen that the majority of these patients (85.7%) had three or more risk factors. In fact, coexistence of many risk factors in this patient group with all the forms of atherosclerotic cardiovascular disease is an expected finding. This finding supports that patients with atherosclerosis should be treated aggressively in terms of risk factors before they clinically reach such an advanced stage.

During the last two decades, a lot of clinical and experimental data have been collected on the importance of inflammation in the pathogenesis of atherosclerosis. The most intensively investigated among the biomarkers of inflammation has been CRP. Over 30 epidemiologic studies indicated an association with elevated CRP concentrations and prevalence of atherosclerosis, and recurrent cardiovascular event risk.[13] Evidence has also been reported on that CRP plays a direct role on the pathogenesis of atherosclerosis, namely that it is not only a risk indicator for adverse cardiovascular events but also a risk factor for atherosclerosis. It was shown in vivo that CRP molecule accelerated the progress of atherosclerosis in mice.[14] In literature, it was reported that CRP level was associated with severity of peripheral artery disease and was an independent predictor of progress rate of premature carotid atherosclerosis.[14-16] Rotterdam trial demonstrated that CRP was associated with extensiveness and progress of atherosclerosis in coronary, carotid, and vascular beds.[17] In that study, number of carotid plaques and progress rate of these plaques in people with CRP levels above 3 mg/L were found significantly higher than those with CRP levels below 1 mg/L. Similarly, an independent and gradual relation was detected between CRP levels and ankle-brachial index, and deterioration of this index within years. In our study, consistent with data in literature, hsCRP levels in the study group with diffuse and severe atherosclerosis were found significantly higher, compared to the control group with only coronary artery disease. High sensitive CRP levels were above 3 mg/L in 82% of the patients in the study group. This case may be associated with the presence of diffuse severe atherosclerosis but also explained as CRP is a risk factor with proatherogenic features.

The most important limitation of our study is the small number of patients. Given that patients with Leriche syndrome concomitant severe stenosis in coronary and carotid arteries comprised the study group in this one-center study, small number of patients could be understood. Multi-center studies are needed to be carried out on such patient group comprising the most advanced form of atherosclerosis.

CONCLUSION

There are many risk factors together in patients with Leriche syndrome concomitan coronary artery disease and severe carotid stenosis. Smoking habit, hypertension, and very low HDL levels among the classical risk factors particularly come to the forefront in these patients. The results of our study support that risk factors of atherosclerosis, which is a systemic disease, should be treated aggressively before the disease reaches the advanced clinical forms.

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