The relationship between paraoxonase, arylesterase, lipoprotein (a) and other lipid parameters in patients with coronary heart disease

Koroner kalp hastalarında paraoksonaz, arilesteraz, lipoprotein (a) ve diğer lipit parametreleri arasındaki ilişki

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Summary

Objective: Millions of people die every year in industrialized countries due to coronary heart disease (CHD) and rank first among the causes of mortality. It is vital to know the causes of CHD and to determine early diagnosis methods. Low antioxidant enzyme paraoxonase (PON1) activity in High Density Lipoprotein (HDL) structure, which prevents Low Density Lipoprotein (LDL) oxidation, is a risk factor for CHD.

Method: For this purpose, serum PON1 activities, ARE activities, Lp (a), apo A, apo B and other lipid parameters were investigated in 80 patients who were diagnosed with CHD who applied to the Cardiology Clinic of Fırat University Medical Faculty Hospital. CHD group; It consists of coronary heart patients who have undergone myocardial infarction to the cardiology outpatient clinic, or who have decided to by-pass operation as a result of coronary angiography, who use antiischemic drugs, have no diabetes, do not drink alcohol and smoke, do not have coronary heart disease in the family history, do not take lipid-lowering drugs.

The control group consists of 40 healthy individuals without cardiovascular disease, diabetes or a disease affecting serum lipid level.

Results: Cholesterol, triglyceride (TG), HDL, LDL, VLDL, serum PON1 and ARE activities, Lp (a), apo A and apo B levels were found statistically significant in the CHD compared to the healthy control group (p <0.05). Serum PON1 activity and ARE activity were lower in the patient groups compared to the healthy control group, and serum Lp (a) levels were higher (p <0.05).

Conclusions: Serum PON1 activity serum Lp (a) levels, which are accepted as important parameters in the diagnosis of CHD, were also found to be significant biochemical markers in our study.

Keywords: Coronary heart disease, paraoxonase, lipoprotein(a).

Özet

Amaç: Koroner Kalp Hastalığı (KKH) nedeni ile endüstrileşmiş ülkelerde her yıl milyonlarca kişi ölmekte, mortalite nedenleri arasında ilk sırada yer almaktadır. KKH'nın nedenlerinin bilinmesi, erken tıbbi yöntemlerin belirlenmesi hayati önem taşımaktadır. High Density Lipoprotein (HDL) yapısında bulunan, Low Density Lipoprotein (LDL)
o ksidasyonu önlenen ve antioksidan bir enzim olan paraoksonaz (PON1) aktivitesinin düşük olması KKH için bir risk faktörüdür. KKH tanısı alan ve etyolojik risk faktörleri taşıyan bireylerde serum PON1, arilesteraz (ARE) ve Lipoprotein(a) (Lp(a)) düzeyleri ile diğer lipit bileşenleri arasındaki ilişkinin araştırılması amaçlandı.

**Yöntem:** Bu amaçla Fırat Üniversitesi Tip Fakültesi Hastanesi Kardiyoloji kliniğine başvuran 80 KKH tanısı alan hastanın serum PON1 aktiviteleri, ARE aktiviteleri, Lp(a), apo A, apo B ve diğer lipid parametreleri araştırıldı. KKH’ları; kardiyoloji poliklinikine gelen miyokard infarktüsü geçirmiş veya koroner anjiografi sonucunda by-pass operasyonuna karar verilmiş, antiiskemik ilaç kullanan, diabeti olmayan, alkol ve sigara içmeyen, aile hikayesinde koroner kalp hastalığı olmayan, lipit düşürücü ilaç almayan koroner kalp hastalarından oluşmaktadır. Kontrol grubu kardiyovasküler hastalığı, diyabeti veya serum lipid düzeyini etkileyen bir hastalığı olan sıfırdan 40 bireyden oluşturuldu.

**Bulgular:** KKH’larında kolesterol, triglisird (TG), HDL, LDL, VLDL, serum PON1 ve ARE aktiviteleri, Lp(a), apo A ve apo B düzeyleri sağlıklı kontrol grubu ile karşılaştırıldığında istatistiksel olarak anlamlı bulunmuş (p<0.05). Serum PON1 aktivitesi ve ARE aktivitesi hasta gruplarında sağlıklı kontrol grubuna oranla düşük, serum Lp(a) düzeyleri ise yüksek bulunmuştur (p<0.05).

**Sonuç:** KKH tanısında önemli parametreler olarak kabul edilen serum PON1 aktivitesi serum Lp(a) düzeyleri çalışmamızda da anlamlı bir şekilde belirtilmiş olarak saptanmıştır.

**Anahtar sözcükler:** Koroner kalp hastalığı, paraoksonaz, lipoprotein(a).

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**INTRODUCTION**

CHD is the most common cardiovascular disease. CHD occurs due to partial or complete interruption of the blood flow of the myocardium as a result of narrowing or occlusion in the coronary arteries feeding the myocardium. Clinical manifestation of CHD, mostly due to atherosclerosis, is generally seen as silent ischemia, stable or unstable angina pectoris, myocardial infarction (MI), heart failure and sudden cardiac death. 

CHD is a chronic, progressive and multifocal intima layer disease and many risk factors such as smoking, hypertension and hypercholesterolemia are held responsible for its development. Numerous risk factors leading to CHD have been identified in epidemiological and clinical studies conducted to date. It is seen that lipids take the first place among these risk factors. Excessive lipids in the blood play a leading role in coronary diseases. It is hoped that correcting these risk factors will prevent the occurrence or progression of the disease. 

The leading cause of death worldwide is cardiovascular diseases, and by 2020, the incidence is expected to increase from 28.9% to 36.3%. Cardiovascular diseases rank first among the top 10 causes of death according to the data of the World Health Organization (WHO). Every year, 4 million people die in Europe due to cardiovascular diseases, and this number accounts for 45% of all deaths. The World Health Organization (WHO), according to 2014 data deaths occurred due to circulatory system diseases in our country is ranked first with 40.4% of ischemic heart disease constitutes 39.6% of it. Among cardiovascular diseases, CHD is the most common and is associated with high mortality and morbidity rates.

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3. Considering the 2012 data of the Heart Disease and Risk Factors study in Turkish Adults, approximately 420,000 coronary events occur annually in our country, of which 120,000 occur as CHD. 

PON1 is an HDL bound enzyme that can hydrolyze lipid peroxides. PON1 is thought to be an antioxidant enzyme that has a protective effect in LDL oxidation and atherosclerosis. In terms of Lp (a) structure, it is very similar to the molecular structure of LDL, it is almost the same in terms of content and is surrounded by the outer apoprotein B-100 as in LDL. Although the role of Lp (a) in the development of atherosclerosis is not fully known, it is known to be effective in atherosclerotic disorders, including CHD.

The relationship between serum PON1, arylesterase (ARE) and Lipoprotein (a) (Lp (a)) levels and other lipid components in individuals diagnosed with CHD and carrying etiological risk factors was aimed to reduce the incidence of CHD and to help it with a good prognosis and treatment.

**MATERIAL AND METHODS**

Serum PON1 activities, ARE activities, Lp (a), apo A, apo B and other lipid parameters were investigated in 80 patients diagnosed with CHD who applied to the Cardiology Clinic of Fırat University Medical Faculty Hospital. CHD group: It consists of coronary heart patients who have had myocardial infarction in the cardiology outpatient clinic or who have decided to undergo by-pass surgery as a result of coronary angiography, who use antiischemic drugs, do not take lipid lowers, do not have diabetes, do not have an infectious disease, do not drink alcohol and smoke, and do not smoke. Do not take coronary heart disease or
lipid-lowering drugs in the family history. The control group consists of 40 healthy individuals who applied to family medicine, did not have cardiovascular disease, did not have diabetes, did not take serum lipid lowers, did not have a disease affecting lipid level and did not have an infectious disease. Our study was completed within 1 year. Total cholesterol, triglyceride, HDL, LDL, VLDL measurements were performed on OLYMPUS AU 600 brand autoanalyst (Olympus Optical Co. Ltd, Tokyo, Japan) using Randox kits (Randox Laboratories, San Francisco, CA, USA). The results of these parameters are given in mg / dl. Lp (a), apo A, apo B levels were studied in protein SPACE device (Schiparelli Biosystem Inc. Netherlands). Results are given in mg / dl for Lp (a) and in g / L for apo A and apo B.

**Statistical analysis:** Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp.). Student t test was used for comparisons between groups. Data were given as arithmetic mean and standard error. The significance level was accepted as p <0.05.

**RESULTS and DISCUSSION**

The average age of the patient group was 52.5±11.02 and the mean age of the healthy control group was 49.8±10.35 and the difference was not statistically significant (p> 0.05). Body Mass Index (BMI) of the patient group was 23.02±1.73 and BMI of the healthy control group was 21.25±2.75 and the difference was not statistically significant (p> 0.05).

Cholesterol, TG, HDL, LDL, VLDL, serum PONI and ARE activities Lp (a), apo A and apo B levels were found to be statistically significant in the CHD compared to the healthy control group (p <0.05).

Serum PONI activities were lower in patient groups compared to healthy control group, and serum Lp (a) levels were high and statistically significant (p <0.05). PONI activities were 173.48±42.88 U / L in CHDs, and it was found to be statistically significantly lower compared to the control group 253.82±51.14 U/L (p <0.05). Cholesterol levels were 211.42±46.77 mg / dl in CHDs, and the control group was found to be statistically high compared to 178.20±32.60 mg/dl (p <0.05). Triglyceride levels were 198.80 ± 44.13 mg / dl in CHDs and it was found to be statistically significant when compared with the control group 113.32±34.31 mg/dl (p<0.05). LDL levels were 125.65±36.59 mg / dl in CHDs, and it was found to be statistically significantly higher compared to the control group 85.98±21.08 mg / dl (p <0.05). HDL levels were 33.96±6.79 mg / dl in CHDs, and it was found to be statistically significantly lower compared to the control group 51.90±9.11 mg/dl (p <0.05). VLDL levels were 40.93±9.61 mg/dl in CHDs, and it was found to be statistically significantly higher compared to the control group 21.80 ± 8.23 mg/dl (p <0.05).

Lp (a) levels were 35.71±6.04 mg/dl in CHDs and it was found to be statistically significantly higher when compared with the control group 85.98±21.08 mg / dl (p <0.05). HDL levels were 33.96±6.79 mg / dl in CHDs, and it was found to be statistically significantly lower compared to the control group 51.90±9.11 mg/dl (p <0.05). VLDL levels were 40.93±9.61 mg/dl in CHDs, and it was found to be statistically significantly higher compared to the control group 21.80 ± 8.23 mg/dl (p <0.05).

Apo A levels were found to be 1.25 ± 0.27 g / L in CHDs and statistically significantly lower when compared with the control group 1.49 ± 0.30 g / L (p<0.05). ARE activity levels were 110.84±31.99 U/ml in CHD, and it was found to be statistically significantly higher when compared to the control group 167.77±38.23 U/ml (p <0.05).

| Table 1: Statistical comparison of PONI and ARE activities, cholesterol, triglyceride, HDL, LDL, VLDL, Lp (a), Apo A and Apo B levels in the control and CHD group compared to the controls (a = p <0.05). |
|---------------------------------------------------------------|
| **Control (n=40)** | **CHD (n=80)** |
| Total Protein (g/L) | 7.80±0.90 | 7.40±0.75 |
| PONI activity (U/L) | 253.82±51.14 | 173.48±42.88a |
| ARE activity (U/ml) | 167.77±38.23 | 110.84±31.99a |
| Cholesterol (mg/dl) | 178.20±32.60 | 211.42±46.77a |
| Triglyceride (mg/dl) | 113.32±34.31 | 195.80±44.13a |
| HDL (mg/dl) | 51.90±9.11 | 33.96±6.79a |
| LDL (mg/dl) | 85.98±21.08 | 125.65±36.59a |
| VLDL (mg/dl) | 21.80±8.23 | 40.93±9.61a |
| Lp(a) (mg/dl) | 8.60±4.30 | 35.71±6.04a |
| ApoA (g/L) | 1.49±0.30 | 1.25±0.27a |
| ApoB (g/L) | 1.00±0.18 | 1.25±0.22a |

PONI: Paraoxonase1, ARE: Arylesterase, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low Density Lipoprotein, Lp(a): Lipoprotein(a), ApoA: ApolipoproteinA, ApoB: ApolipoproteinB
Unlike lipid parameters in CHDs, there is not enough research on PON1, ARE and Lp (a) levels. In our study on CHDs, we found that PON1 and ARE activities were low and Lp (a) levels were high. Since PON1 prevents the development of atherosclerosis, atheroma is an enzyme that has been emphasized recently as a dissolving factor. It has been suggested to do this by preventing the oxidation of lipoproteins and by hydrolyzing phospholipid and cholesterol ester hydroperoxides. Serum PON1 activity, particularly atherosclerotic diseases, has been found to be low in myocardial infarction (MI), when cholesterol levels increase and in diabetes mellitus (DM). In the studies conducted, PON1 enzyme; It has been found to play a role in the etiopathology of CHD, atherosclerosis, rheumatoid arthritis and DM diseases. It has been shown that Lp (a) is found in the atherosclerotic artery wall in excess of plasma levels. It has been shown that Lp (a) is oxidized in the vascular wall and subsequently taken by macrophages just like LDL cholesterol, contributing to the formation of foam cells. In many case-controlled studies, a relationship has been shown between CHD and high Lp (a) levels. Lp (a) ratio has been found to be higher in patients with unstable resting angina than stable angina. It is also suggested that Lp (a) is a protein molecule that plays a role in the complete occlusion of the coronary artery. It has been reported that high serum Lp (a) levels are accompanied by angiographic rapid progress in coronary artery disease and decreased recanalization after myocardial infarction, and serum Lp (a) levels increase 10-100 times in complete occlusion of the coronary arteries. While the most important cause of CHD is thought to be hyperlipidemia worldwide, recent studies have revealed that there are other risk factors. In terms of hyperlipidemia, it has been shown in early epidemiological studies that there is a continuous, graded and strong relationship between serum cholesterol levels and the development of CHD. In studies related to this subject, serum cholesterol levels were found to be higher in countries such as the U.S., Finland, the Netherlands, Italy, and lower in Japan. Many new risk factors are being investigated recently for early diagnosis of CHD. Identifying new risk factors is crucial for early diagnosis and treatment of the frequency of CHD. It is observed that the decrease in serum PON1 and ARE activity levels appears as a risk factor in CHD and etiological factors. It is stated that changes in total oxidant-antioxidant systems seriously affect the risk of CHD. Various studies have shown that lipid peroxides inhibit PON1 activity. PON1 activity in human serum is associated with HDL, and its activity is reduced in disease states affecting circulating HDL levels. In a study by Mackness et al., they found that PON1 activity was significantly lower in CHD compared to the healthy control group. Ayup et al. found that serum PON1 activity was significantly lower in patients with MI compared to the healthy control group. McElveen et al. found serum PON1 activity lower in the patient group compared to the healthy control group in a case-control study conducted in their CHDs. In our study, serum PON1 activities and ARE activities were lower in patient groups compared to healthy control group, and serum Lp (a) levels were higher (p <0.05).

As a result; Detection of changes in PON1 and ARE activity levels, which are an antioxidant enzyme in HDL structure in CHDs, will reveal the relationship between CHD and these enzymes. PON1 slows down LDL oxidation, leading to a decrease in the proinflammatory and proatherosclerotic properties of LDL, thus playing an important role in the pathogenesis of PON1 atherosclerosis and CHD. PON1 inhibits the proatherogenic properties of LDL and at the same time strengthens the antiatherogenic properties of HDL, thereby preventing one of the key steps in the atherosclerosis process. In addition, PON1 reduces oxidative stress of macrophages, prevents foam cell formation and protects the cardiovascular system from atherosclerosis. New research options can be achieved in the prevention of atherosclerosis and accordingly, CHD, by conducting more research on the factors and drugs affecting serum PON1 activity.

This work was supported by Firat University Research Fund (FUNAF-514).

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