Lipid Profile and Inflammation in Degenerative Valvular Disease

Dejeneratif Kapak Hastalığında İnflamasyon ve Lipid Profili

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──────── **Abstract** ────────

Aim: Degenerative valvular heart disease (DVHD) may cause serious cardiac problems and mortality. Determination of the factors related to DVHD may render possible the prevention and/or slowing down the progression of DVHD. In this study, we evaluated the relationship of DVHD with lipid profile, microalbuminuria and high sensitive C-reactive protein (hsCRP) levels.

Methods: 50 patients (age=65.6±12.4 years) with DVHD were compared with the control group including 20 patients (age=57.3±13.9 years) with left ventricle hypertrophy, but no DVHD. Microalbuminuria, blood lipid parameters and hsCRP levels were measured besides routine biochemical tests. Clinical, laboratory and echocardiographic findings were compared between the groups.

Results: Total cholesterol, HDL-cholesterol and LDL-cholesterol levels were significantly higher in DVHD group (215.26±48.59 mg/dL vs. 177.45±22.47 mg/dL, p=0.001; 45.04±11.03 mg/dL vs. 38.90±11.82 mg/dL, p=0.043 and 138.49±40.69 mg/dL vs. 114.26±16.07 mg/dL, p=0.001) compared with control group. hsCRP and microalbuminuria levels were relatively higher in DVHD group.

Conclusion: Hyperlipidaemia is related to DHVD development, and the progress of DHVD may be related to the inflammatory process. Elevated hsCRP levels may be an indicator of pathologies active in DVHD development. Routine echocardiographic analysis in hypertensive patients with high hsCRP and LDL-cholesterol levels might be useful for screening of DVHD. *(The Medical Bulletin of Haseki 2015; 53: 62-6)*

Key Words: Atherosclerosis, heart valve disease, inflammation, lipid

──────── **Özet** ────────

Amaç: Dejeneratif kalp kapak hastalığı (DKKH) ciddi kardiyak problemlere ve mortaliteye neden olabilir. DKKH ile ilişkili faktörlerin tespit edilmesi DKKH'nin önlenmesini ve/veya ilerlemesinin yavaşlatılmasını mümkün kılabilir. Bu çalışmada, DKKH ile lipid profile, mikroalbüminüri ve "high sensitive C-reactive protein (hsCRP)" düzeylerinin ilişkisini inceledik.

Yöntemler: DKKH olan 50 hasta (yaş=65,6±12,4 yıl), sol ventrikül hipertrofisi olup DKKH olmayan 20 hastadan (yaş=57,3±13,9 yıl) oluşan kontrol grubu ile karşılaştırıldı. Hastaların rutin biyokimyasal testler yanında mikroalbüminüri, kan lipid parametreleri ve hsCRP düzeyleri ölçüldü. Grupların klinik, laboratuvar ve ekokardiyografik bulguları karşılaştırıldı.

Bulgular: Kontrol grubu ile karşılaştırıldığında DKKH olan grupta total kolesterol, HDL-kolesterol ve LDL-kolesterol düzeyleri anlamlı derecede yüksekti (215,26±48,59 mg/dL vs. 177,45±22,47 mg/dL, p=0,001; 45,04±11,03 mg/dL vs. 38,90±11,82 mg/dL, p=0,043 ve 138,49±40,69 mg/dL vs. 114,26±16,07 mg/dL, p=0,001). hsCRP ve mikroalbüminüri düzeyleri DKKH grubunda daha yüksek idi.

Sonuç: Hiperlipidemi DKKH gelişimi ile ilişkilidir, ve DKKH'nin ilerlemesi inflamatuvar süreç ile ilişkili olabilir. Yüksek hsCRP düzeyleri DKKH gelişiminde aktif olan patolojilerin bir belirteci olabilir. hsCRP ve LDL-kolesterol düzeyleri yüksek olan hipertansif hastalarda rutin ekokardiyografik inceleme DKKH taraması için yararlı olabilir. *(Haseki Tıp Bülteni 2015; 53: 62-6)*

Anahtar Sözcükler: Ateroskleroz, kalp kapak hastalığı, inflamasyon, lipid

Introduction

Degenerative mitral valve disease involves myxomatous mitral disease, flail mitral valve, mitral valve prolapse (MVP) and Barlow syndrome (1). The pathological changes that cause degenerative aortic valve disease include annular dilatation, leaflet thickening, myxomatous degeneration, and calcification of the annulus and leaflets. These changes lead to a wide spectrum of clinical consequences ranging from mild aortic valve sclerosis to symptomatic aortic stenosis (2). Aortic valve sclerosis is characterized by thickening, increased echogenity and calcification of the valve leaflets. It may lead to symptomatic aortic stenosis that has a poor prognosis unless treated surgically (2). It is seen in 21-26% of individuals older than 65 years; and in 48% of the population aged more than 85 years (2,3). Aortic stenosis (AS) is classified etiologically as senile calcific, bicuspid, rheumatic and congenital. The most frequent reason is chronic inflammation and fibrosis of the valve similar to atherosclerosis of the arteries (4).

Lipoprotein disorder (low high density lipoprotein -HDL- levels, elevated levels of low density lipoprotein -LDL- and lipoprotein-a, and hypertriglyceridemia), smoking, male gender, hypertension, advanced age, diabetes mellitus (DM) may accelerate AS by endothelial dysfunction and fibrosis (5). The duration of hypercholesterolemia has been found to be correlated with the risk of AS in patients with familial hypercholesterolemia (6). Inflammation is an important cause of endothelial dysfunction and aortic sclerosis (7). Aortic sclerosis and endothelial dysfunction share similar risk factors and pathogenesis. Experimental and clinical studies revealed that inflammatory process adds to atherogenesis; and may cause atherosclerotic plaque rupture and erosion (8). C-reactive protein (CRP) is an acute phase protein produced by hepatocytes in response to cytokines like interleukin-6 and tumor necrosis factor-α (9). Inflammatory reaction begins in response to capture of atherogenic lipoproteins by the arterial wall; and causes increased CRP production through cytokine release.

The most extensively studied inflammatory marker acting on atherosclerosis is high sensitive CRP (hsCRP). The production of CRP increases in case of infection, tissue damage and any kind of inflammation (10). Recent studies revealed that hsCRP is a strong predictor of atherosclerosis and vascular deaths; and is superior to lipid levels and other inflammatory markers. This is thought to be due to proatherogenic nature of CRP (11). Besides atherosclerosis; systemic inflammation was shown to be active in patients with AS (12).

Microalbuminuria (MA) is defined as urinary albumin excretion in the range of 20-200 µg/min or 30-300 mg/day (13). Studies have shown that MA is not only a marker of diabetic complications, but also an independent risk factor for cardiovascular diseases (14). MA has been found to be stronger predictor for cardiovascular disease than other classical risk factors including hypercholesterolemia. MA was involved within cardiovascular risk factors in the seventh report of Joint National Committee (JNC-7) (15).

We aimed in this study to examine the relationship of the presence of degenerative valvular heart disease (DVHD) with atherogenesis, inflammation and endothelial dysfunction.

Methods

The study was started after obtaining approval from the local ethics committee. Patients with DVHD were chosen as the patient group among patients who had echocardiographic examination in the echocardiography laboratory of our hospital. This group was compared with the control group consisting of patients with left ventricular hypertrophy, but no DVHD. An informed consent form was signed by all patients.

Patients with DM, renal failure, acute ischemic heart disease, advanced heart failure (ejection fraction (EF) less than 40%) and acute infectious disease, obese patients with a body mass index (BMI) more than 30 kg/m^2, those using antibiotics, steroid, statin or nonsteroid anti-inflammatory drugs, and patients with smoking history were excluded from the study.

Demographic data of the patients including age and gender were recorded as well as medical histories. Systolic and diastolic blood pressures were measured at optimal conditions. BMI was calculated by the formula of weight/(height)2. Blood samples were obtained for laboratory analysis after 8 hours of fasting for measurement of glucose, total, HDL and LDL cholesterol, triglyceride, HbA1c, creatinine and hsCRP levels, and erythrocyte sedimentation rate. Triglyceride and cholesterol levels were measured by enzymatic calorimetric methods using ABBOT Architect/Aeroset machine. hsCRP levels were measured by nephelometric method using Beckman Coulter IMMAGE Immunochemistry Systems machine. To determine microalbuminuria, 24-hour urine was analysed by turbidometric method using ABBOT Architect/Aeroset machine.

Echocardiographic examinations were performed by the same physician using General Electric Vivid 3 Pro machine.

Statistical analysis was conducted by using SPSS (Statistical Package for Social Sciences) version 14.0 for Windows. Numerical parameters were expressed as mean ± standard deviation (SD). Student t-test and Mann-Whitney U test were used for comparison of the two groups. Yates corrected chi-square test and Fischer's exact

test were used for 2x2 contingency tables of nonnumeric variables when necessary. Correlation analysis of numerical and nonnumeric parameters was performed by Pearson and Spearman's rho correlation tests, respectively. A p value of less than 0.05 was considered statistically significant.

Results

Fifty patients with DVHD and 20 patients with left ventricular hypertrophy were included in the study as the patient and the control groups. Male/female ratio was 22/28 and 13/7 in the patient and control groups, respectively. The demographic and clinical data of the patients are presented in Table 1. Groups were similar regarding gender, age, weight, height, BMI and blood pressures. The biochemical data of the groups are presented in Table 2. hsCRP and microalbuminuria levels were detected to be significantly higher in the patient group. The patient group had significantly higher levels of total cholesterol, HDL cholesterol and LDL cholesterol (Figure 1).

Aortic valve degeneration was detected in 6 patients (12%), mitral valve degeneration in one patient (2%); while 43 patients (88%) had both disorders. The mean EF
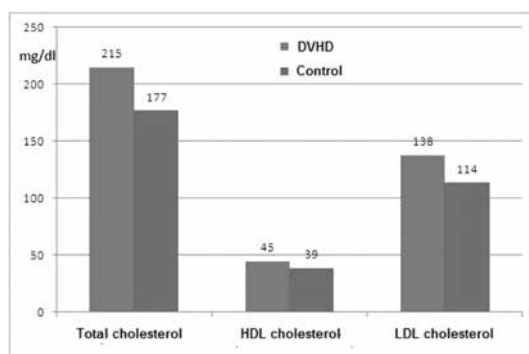
in the patient and the control groups were 58.82±3.14% and 59.00±3.08%, respectively (p=0.828).

There was no significant correlation between hsCRP and microalbuminuria levels in the patient group (r=0.004, p=0.972). The results of the logistic regression analysis are presented in Table 3. The occurrence of DVHD was related with hsCRP levels.

Discussion

The most common reason of acquired AS in developed countries is chronic inflammatory and fibrotic process involving the aortic valve. Elevated total cholesterol, LDL cholesterol, lipoprotein (a), triglyceride, low HDL cholesterol levels, presence of hypertension, DM, male gender, smoking, and advanced age have been found to be related with increased frequency of aortic sclerosis besides being the reasons of endothelial dysfunction and valve damage (3,16,17). The duration of exposure to high cholesterol levels has been reported to be related with AS in patients with familial hypercholesterolemia (6). Pohle et al. found higher progression rates of both coronary and aortic calcification in patients with elevated LDL cholesterol levels (18). In a study by Gerber et al., 23 patients among 246 cases were found to have AS of whom serum total cholesterol, LDL cholesterol and lipoprotein (a) levels were higher than the control subjects (19).

Our findings are consistent with these data. The patient group had significantly higher levels of total cholesterol, HDL cholesterol and LDL cholesterol compared with the control group (Figure 1). There was no difference between the patient and the control groups regarding triglyceride levels. But HDL/total cholesterol ratio was similar in the groups.

Many studies have shown that high CRP level is a good predictor of atherosclerosis (20). hsCRP has been found to be good indicator of endothelial dysfunction (21). Increased inflammatory activity plays important roles in the development of aortic sclerosis. Chandra et al. studied 425 patients, who were admitted to the emergency clinic

Figure 1. Comparison of cholesterol levels in the groups

Table 1. Demographic and clinical data of the groups			
	Patient group (n=50)	**Control group (n=20)**	**p**
Male/Female	22/28	13/7	0.112
Age (years)	62.56±12.40	57.35±13.92	0.130
Height (cm)	162.6±6.5	166.0±8.5	0.790
Weight (kg)	67.1±8.6	68.6±7.7	0.475
BMI (kg/m^2)	26.59±1.87	26.26±1.77	0.510
Systolic BP (mmHg)	148.10±9.08	143.50±8.29	0.054
Diastolic BP (mmHg)	89.50±6.57	88.50±5.15	0.544
BP: Blood pressure			

Table 2. Laboratory results of the patients

	Patient group (n=50)	Control group (n=20)	p
Total cholesterol (mg/dL)	215.26±48.59	177.45±22.47	0.001
Triglyceride (mg/dL)	154.08±83.33	121.45±49.61	0.107
LDL cholesterol (mg/dL)	138.49±40.69	114.26±16.07	0.001
HDL cholesterol (mg/dL)	45.04±11.03	38.90±11.82	0.043
HDL/Total cholesterol	0.217±0.061	0.218±0.057	0.956
HbA1c (%)	5.75±0.46	5.61±0.60	0.274
Glucose (mg/dL)	96.12±10.79	98.10±11.48	0.498
Creatinin (mg/dL)	0.89±0.16	0.89±0.16	0.893
Microalbuminuria (mg/day)	41.35±73.29	12.05±7.98	0.019
Fibrinogen (mg/dL)	370.04±95.70	324.8±96.21	0.079
ESR (mm/hour)	23.98±14.50	17.35±13.98	0.085
hsCRP (mg/L)	1.66±1.81	0.29±0.20	<0.001

ESR: Erythrocyte sedimentation rate

Table 3. Results of logistic regression analysis

	Exp (B) (95% Confidence interval)	p
LDL cholesterol	1.031 (0.996-1.066)	0.081
Microalbuminuria	1.022 (0.969-1.078)	0.431
hsCRP	58.467 (2.220-1539.730)	0.015

with chest pain, and found that those with aortic sclerosis had higher CRP levels; and CRP level was correlated with the severity of sclerosis (22). Galante et al. found higher CRP levels in patients, who were operated due to severe degenerative AS without coronary lesions, compared to that in controls. Skowasch et al. reported a strong correlation between serum CRP levels and CRP levels in the valve tissue (23,24). Contrary to these studies, Gunduz et al. found no difference between total cholesterol and CRP levels in patients with mild, moderate and severe AS; similar to our findings (25). There was no correlation of the severity of AS with hypercholesterolemia and CRP levels; while lipid levels were correlated with coronary lesions. Similarly, Jeevanatham et al. reported no relationship between hsCRP levels and the severity of AS; although patients with aortic sclerosis and AS had higher hsCRP levels compared with the control group (26). We found higher hsCRP levels in the patient group compared with the control group in our study.

Degenerative aortic valvular disease is a dynamic process involving hemodynamic and inflammatory factors and also endothelial damage. Microalbuminuria has been shown by many studies to be an important marker of endothelial damage (27). It was also shown to be related with lipid profile and hsCRP levels (28,29). CRP may be a sign of vascular damage and distorted endothelial function which may cause microalbuminuria. Therefore, high plasma hsCRP levels are related with microalbuminuria and endothelial dysfunction.

Stuveling et al. reported that CRP attenuated the relationship between blood pressure and microalbuminuria, however, not the relationship between microalbuminuria and other cardiovascular risk factors (30).

We detected in the present study that microalbuminuria was significantly higher in patients with degenerative aortic valvular disease compared with the control group. But there was no correlation between CRP and microalbuminuria levels. With logistic regression analysis, hsCRP level was detected to be an indicator of DVHD while LDL cholesterol had an effect with borderline statistical significance while microalbuminuria had no effect.

In conclusion; hyperlipidaemia may be related with development of DVHD similar to the inflammatory process in atherosclerosis. Elevated hsCRP levels may be regarded as a general marker of factors acting on this degenerative and inflammatory process. It may be useful to screen hypertensive patients with elevated hsCRP and LDL cholesterol levels with echocardiographic examination for valvular disease.

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