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Presence of low lipid levels in patients with Behcet' s disease as a protector against atherosclerosis

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Abstract. – BACKGROUND: A relapsing systemic inflammatory process is a well-known feature of Behcet's disease. Because systemic inflammation and dyslipidemia are involved in the pathogenesis of atherosclerosis, Behcet's disease may play a part in the development of atherosclerosis. Lipid profile in Behcet's disease and the development of atherosclerosis remain to be controversial. In order to learn more about this relationship, our study compared blood lipid levels in healthy controls to those in patients with Behcet's disease during both their active and inactive stages.

PATIENTS AND METHODS: Between December 2010 and March 2012, this prospective, observational study was designed to evaluate three groups The study included 91 Behcet's patients (36 in active and 55 in inactive period) and 61 healthy control subjects matched for age, gender, and body mass index. Data from lipid profiles included total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein. Acute phase reactants were also recorded, including high sensitive C-reactive protein and erythrocyte sedimentation rate levels.

RESULTS: Total cholesterol, low density lipoprotein, and high density lipoprotein cholesterol levels of patients in active stage were significantly lower than those in inactive stage, while total cholesterol and low density lipoprotein levels were lower in the control group ($p < 0.05$).

CONCLUSIONS: Patients with Behcet's disease in the active period may be less susceptible to atherogenic events as compared with the controls and those in the inactive period of the disease.

Key Words:
Behcet disease, Atherosclerosis, Activation, Lipid profile.

Introduction

Behcet's disease (BD) is a multisystem disorder characterized by a relapsing inflammatory process of unknown etiology resulting in serious morbidity or mortality[1]. Vascular complications have been noted, such as deep vein thrombosis, arterial thrombus formation, arterial aneurysm, and myocardial infarction in about 20-35% of cases[2,3]. Systemic inflammation is associated with the pathogenesis of BD and may also have an effective role in the development of atherosclerosis[4]. The changes in lipid profile and atherosclerosis have already been demonstrated in many chronic inflammatory diseases[5-8]. Vascular and cardiac complications are brought about by atherosclerosis. The findings suggestive of atherosclerosis have also been noted in the long term follow-up of BD. Cardiovascular disease seems to have a different course in conditions, like systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), in that it may present lowering mortality rates with disease duration[5,9]. However, conflicting results were gained from the studies of lipid profile and development of atherosclerosis in patients with BD, and the conclusions are still conflicting. We aimed to compare blood lipid levels having a significant part in the etiology of atherosclerosis, both in the patients with BD in the active and those in inactive stage as well as the healthy control groups.

Patients and methods

The study group was comprised of the patients attending to our Rheumatology, Internal Medicine, and Dermatology Outpatient Departments.

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The study included 91 patients with BD (63 males, 28 females) (36 of whom in active stage, 55 in inactive stage according to the International Study Group Criteria[10] and 61 healthy controls (34 males, 27 females) between December 2010 and March 2012. The control group was composed of individuals matched with patients by age, gender, and body mass index (BMI), and none had any known disease or drug use.

The exclusion criteria were as follows: being on the external treatment of colchicine and consuming of any drug, alcohol, or tobacco, the history or findings of systemic inflammatory disease, primary disorders of lipid metabolism, such as familial hyper-lipidemias and hypo-lipidemias, any endocrinologic disease affecting lipid metabolism, like hyper/hypothyroidism, obesity, diabetes mellitus, Cushing's disease, or the presence of abnormal liver and kidney functions tests. A rheumatologist took the clinical history and performed a thorough physical examination on each patient, and afterwards, the patients were also routinely evaluated in by specialists in dermatology, ophthalmology, vascular surgery, neurology, as well as in radiology in order to identify dermal, ocular, vascular lesions, and nervous system involvement. The patients showing no lesions for at least 30 days were regarded being in the inactive stage. Active disease stage refers to the clinical symptoms such as skin, oral, and genital lesions, uveitis, vasculitis, arthritis, arthralgia, neurological involvement, or at least two findings of erythema nodosum accompanied by the increased erythrocyte sedimentation rate (ESR) and/or increased high sensitive C-reactive protein (hs-CRP) levels[11].

Blood samples of all participants (both the patients and the controls) were collected in the morning, after an overnight fast of 12 hours. Serum was collected and analyzed on the same day. Serum stability was tested and approved. Serum total cholesterol (TC), high density lipoprotein (HDL), and triglyceride (TG) levels were measured photometrically with a Roche modular DP auto-analyzer. Low density lipoprotein (LDL) levels were calculated using the Freidewald Formula [LDL = TC – (HDL+TG/5)], valid only if TG levels did not exceed 400 mg/dL[12]. High sensitive C reactive protein levels were measured by a nephelometric method on an image auto-analyzer. Erythrocyte sedimentation rate was measured using Westergreen's method and expressed in mm/h. Height and weight were measured, and BMI was calculated by the ratio of weight/height^2 (kilograms per square meter). Demographic and laboratory data including age, gender, height, weight, BMI measurement and TC, LDL, HDL, TG levels were recorded. This study protocol was in accordance with the declaration of Helsinki and was approved by the Ethic Commitees of Haydarpasa Training and Research Hospital. Written informed consent was obtained from each participant before commencement of the study.

Statistical Analysis

Statistical analyses were performed using the SPSS 14.0 (SPSS Inc., Chicago, IL, USA) statistical package. For multiple groups, we used the Kruskal-Wallis test. Differences between the two groups were evaluated by the Mann-Whitney U test or $\chi 2$ test, whichever was appropriate. To investigate relationships among the variables, we used Spearman's rank correlation test; $p < 0.05$ was accepted as statistically significant.

Results

Table I shows age, gender, and BMI of the active patients, inactive patients, and the controls. There was no statistically significant difference among the study groups for these three parameters ($p = 0.176$; 0.154; 0.476, respectively).

TC levels of active stage patients were found statistically and significantly lower as compared to those of inactive stage patients ($p < 0.001$) and the control group ($p = 0.009$). [No significant difference was determined between inactive stage patents and the control group ($p = 0.259$)]. LDL cholesterol levels of active stage patients were significantly lower than those of the inactive stage patients ($p = 0.001$) and the control group ($p = 0.032$). There was no - significant difference between inactive stage patients and the control group ($p = 0.134$). HDL cholesterol levels of active stage patients were found statistically and significantly lower than those of inactive stage patients and the control group ($p = 0.011$).

Patients with active BD had higher ESR and CRP levels as well as lower TC and LDL levels when compared to patients with inactive BD and the control group. Patients with inactive BD had higher ESR and CRP levels when compared to the control group. TC, LDL, HDL, and TG levels among inactive BD patients and controls were not found significantly different. Table II shows results of parameters of lipid metabolism, hs-CRP, and ESR of active and inactive BD patients and control groups.

Table I. Demographic characteristics of the two groups of patients with Behcet's disease plus the controls.

Parameter	Active patients	Inactive patients	Controls	*p-value*
N	36	55	61	
Gender (M/F)	27/9	36/19	34/27	*0.154*
Age, in years (range)	35.8 ± 9.1 (15-56)	38.3 ± 8.7 (15-59)	35.4 ± 8.7 (18-57)	*0.176*
BMI (kg/m^2)	24.93 ± 2.72	25.62 ± 3.30	25.8 ± 3.95	*0.476*

M (male), F (female), BMI (body mass index).

Discussion

Inflammation has a key role in the pathogenesis of a number of chronic inflammatory systemic diseases (CISD), including psoriasis, rheumatoid arthritis, systemic lupus erythematosus and Crohn's disease, and in the pathogenesis of atherosclerosis as well. Blood lipid levels were reported to be affected in chronic systemic inflammatory diseases; consequently, the condition has been delineated to result in a severe atherosclerotic ground, increasing cardiovascular risk[9,13]. However, a limited number of studies and paradoxical studies relate to this condition and its relationship with BD patients[14-16]. Therefore, cardiovascular risk and the development of atherosclerosis in patients with BD remain in dispute. It also known that high blood lipid levels as well as increased systemic inflammation may per se or by an additive effect lead to the formation of atherosclerosis[17-20]. Atherosclerosis is a progressive disease usually associated with multiple cardiovascular risk factors, including dyslipidemia. The development of atherosclerosis has been well characterized by molecular and inflammatory processes. LDL was shown to be modified by the presence of free radicals, thus, being rapidly phagocytosed by macrophages. The modification process occurring in LDL levels has been considered to be a significant factor in the commencement and development of atherosclerosis[21].

No significant difference was found between blood lipid levels of healthy individuals and those of patients with Behcet's disease in the majority of studies[22,23]. However, most of these studies were not appropriately designed, either due to the limited number of patients or to the study design that did not differentiate between patients in the active and those in inactive stages[17,18]. Furthermore, a variety of studies included patients with additional conditions, such as diabetes mellitus and patients receiving other type of therapies, like corticosteroids, but without comprising well-selected patient groups[22,23]. However, there is only one study demonstrating that blood lipid levels in patients with BD are higher as compared to the blood lipid levels of healthy individuals; it was carried out without taking account of the medications received by the patient and the active stage of the condition[23].

In two studies investigating the risk of atherosclerosis in patients with BD, blood lipid levels

Table II. Comparisons of lipid profile and activation markers in the two groups of patients with Behcet's disease plus the control group.

Parameter	Active patients	Inactive patients	Controls	*Pa-i	**Pa-c	***Pi-c
Total cholesterol (mg/dl)	149 ± 33	179 ± 36	170 ± 39	<0.001	0.009	0.259
LDL cholesterol (mg/dl)	84 ± 32	110 ± 29	100 ± 34	0.001	0.032	0.134
HDL cholesterol (mg/dl)	41 ± 10	47 ± 11	44 ± 12	0.011	0.255	0.111
Triglyceride (mg/dl)	102 ± 48	112 ± 47	123 ± 63	0.249	0.115	0.688
hs-CRP (mg/dl)	4.05 ± 3.96	0.6 ± 0.6	0.43 ± 0.4	<0.001	<0.001	0.003
ESR (mm/hour)	46 ± 28	20 ± 18	11 ± 8	<0.001	<0.001	0.081

LDL (low density lipoprotein), HDL (high density lipoprotein), ESR (erythrocyte sedimentation rate), hs-CRP (high sensitive C reactive protein).
*Pa-i (Comparisons of active patients vs. inactive patients), ** Pa-c (Comparisons of active patients vs. controls), ***Pi-c (Comparisons of inactive patients vs. controls).

were not significantly different from the levels found in the healthy population. Indeed, the appearance of coronary artery disease and acute myocardial infarct were found to be lower than expected[5,14]. Similar to these two studies, in the patients with BD in active stage we found that blood lipid levels were surprisingly low as a protector against atherosclerosis. Actually, excluding patients receiving drugs that may show increased levels of blood lipids (such as systemic corticosteroids) and those suffering from the conditions such as diabetes mellitus (that may predispose them to atherosclerosis), we assumed that the low levels of blood lipids in patients with BD with active stage may be associated with increased systemic inflammation in these patients and the regular administration and use of large doses of colchicine.

In another study where colchicine was considered to demonstrate the effect mentioned above, cholesterol levels were higher in the healthy population as compared to those of the patients with Familial Mediterranean Fever (FMF) receiving colchicine. Thereby cholesterol levels, emphasized the anti-inflammatory and anti-atherogenic effect of colchicine[20]. In another study examining the relationship between blood lipid levels and inflammation, the anti-atherogenic effect of statin drugs not only lowered blood lipid levels, but also lowered blood lipid levels by means of an anti-inflammatory effect[24,25]. In a study of atherosclerosis by Seyahi et al[5] comprising 239 BD patients and 156 healthy controls, atherosclerotic plaques of the carotid and femoral arteries were investigated and intima-media thickness was measured. No difference was found between the patients with BD and the healthy population. However, in another study[16], the carotid intima-media thickness of patients with BD was found to be less as compared to patients with SLE, another chronic inflammatory disease.

Conclusions

Although the etiopathogenesis of the auto-inflammation in Behcet's disease remains controversial, this study gives new insight that the inflammation in BD may develop through a different mechanism from that associated with other rheumatic conditions. In the light of this fact, lipid profile and the development of atherosclerosis may also differ from inflammations observed in other type of systemic conditions.

Conflict of interest

The Authors declare that they have no conflict of interests.

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