FREQUENCY OF METABOLIC SYNDROME AND NON ALCOHOLIC FATTY LIVER IN BEHCET'S DISEASE

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ABSTRACT

Objective: *Behcet's Disease (BD) is a syndrome with auto-inflammatory non-granulomatous chronic vasculitis characterized by multi-systemic involvements including as mucocutaneous, urogenital, ocular, vascular, articular, gastrointestinal, pulmonary and neurologic. Several studies report the presence of insulin resistance in BD but incidence of metabolic syndrome (MetS) and nonalcoholic fatty liver disease (NAFLD) in this chronic inflammatory state is not clear yet. In this study, we aimed to assess the frequency of MetS and NAFLD in BD as accelerators of atherosclerosis and cardiovascular complications.*

Material and Method: *Total 115 consecutive BD patients (male/female: 48/67) diagnosed according to International Study Group for Behcet's Disease criteria and 65 healthy controls were analyzed in this observational case-control study. MetS was diagnosed by International Diabetes Federation definition (IDF), NAFLD by ultrasonographic scoring and body and visceral fat ratio by bioelectric impedance.*

Results: *The difference between metabolic parameters of BD and controls were: MetS (53.9% vs 27.5%, p<0.01), NAFLD frequency (47.8% vs 18.4%, p<0.01), HOMA-IR index (2.2±1.4 vs 1.1±0.3, p<0.01), IR (32.2% vs 12.3%, p<0.05), body fat ratio (35.4±9.0% vs 29.8±10.3%, p<0.05) and visceral fat ratio (11.1±4.6% vs 9.8±3.4, p>0.05), respectively. Homocysteine and lipoprotein-a averages in patients vs controls, males vs females and presence of insulin resistance, MetS and NAFLD were not significantly different (p>0.05).*

Conclusion: *BD had significantly higher ratio of MetS, NAFLD and insulin resistance compared to controls. Thus, it can be concluded that cardiovascular and steatosis related risk factors should be taken into account in BD patients.*

Key Words: *Behcet's disease, metabolic syndrome, nonalcoholic fatty liver disease, insulin resistance, visceral fat, body fat* ***Nobel Med 2013; 9(3): 35-42***

BEHÇET HASTALIĞINDA METABOLİK SENDROM VE NONALKOLİK YAĞLI KARACİĞER SIKLIĞI

ÖZET

Amaç: Behçet hastalığı (BH) tekrarlayan oral ve genital ülserler, göz, damar, eklem, gastrointestinal, ürogenital, dermatolojik, pulmoner ve nörolojik lezyonlar ile karakterize oto-inflamatuar, kronik, non-granülomatöz vaskülitle seyreden bir sendromdur. Metabolik sendrom (MetS) ve alkole bağlı olmayan yağlı karaciğer hastalığı (NAFLD) aterosklerozu hızlandırarak ve kardiyovasküler komplikasyonlara yol açarak bu hastalarda prognozu olumsuz etkileyebilir. Bu çalışmada, BH ve sağlıklı kontrollerde MetS, NAFLD ve insulin direnci sıklığı yanısıra vücut yağ kompozisyonu, homosistein ve lipoprotein-a düzeyleri kıyaslandı.

Materyal ve Metod: Bu kesitsel olgu-kontrol çalışmasında, Uluslararası Behçet Çalışma Grubu kriterlerine göre tanılanmış 115 hasta (erkek/kadın: 48/67) ve 65 sağlıklı kontrol incelendi. MetS tanısı için yeni Uluslararası Diyabet Federasyonu (IDF) kriterleri, NAFLD için ultrasonografi, vücut yağ dağılımı için biyoelektrik impedans ölçümü kullanıldı.

Bulgular: BH ve kontrol grubuna ait metabolik parametreler sırasıyla: HOMA-IR (2,2±1,4 ile 1,1±0,3, p<0,05), MetS (%53,9 ile %27,5, p <0,01), NAFLD sıklığı (%47,8 ile %18,4, p<0,01) ve insülin direnci (% 32,2 ile %12,3, p<0,05) olarak belirlendi. Homosistein ve lipoprotein-a düzeyleri açısından hasta, kontrol grubu, cinsiyet, insulin direnci ve NAFLD farklılığı açısından ve kontrol grubu ile fark belirlenmedi (p>0,05).

Sonuç: Kontrol grubu ile kıyaslandığında BH grubunda MetS, NAFLD ve insülin direnci istatistiksel olarak anlamlı derecede yüksek bulundu. Bu konuda daha geniş prospektif kohort çalışmalara ihtiyaç olmakla beraber Behçet hastalığında MetS ve NAFLD ilişkili risk faktörlerinin tedavide göz önüne alınması gerektiği söylenebilir.

Anahtar Kelimeler: Behçet hastalığı, metabolik sendrom, nonalkolik yağlı karaciğer hastalığı, insülin direnci, visseral yağ, vücut yağı **Nobel Med 2013; 9(3): 35-42**

INTRODUCTION

Behcet's Disease (BD) is a syndrome described in 1937 by a Turkish dermatologist Hulusi Behçet (1889-1948) as a triad of oral and genital ulcers with uveitis. It is a multi-systemic, auto-inflammatory vasculitis characterized not only by ophthalmic inflammation and recurrent oral and genital ulcers, but also involvement of joints, skin, gastrointestinal, cardiopulmonary, renal, urologic, neurologic and vascular systems. High prevalence follow along the Silk Road through Far East, Middle East and Mediterranean countries and the incidence varies between 0.38-7.5 of 100,000 population in North America and Europe, 13-20 of 100,000 in Japan and 110-420 in 100,000 in Turkey as the country with highest incidence.[1]

Metabolic syndrome (MetS) involves both insulin resistance (IR) and central obesity as significant factors.[2] There are a number of studies reporting increased MetS in various rheumatologic diseases e.g. rheumatoid arthritis.[3] Genetics, physical inactivity, ageing, a pro-inflammatory state and hormonal changes may also have a causal effect on MetS, but the role of these may vary depending on ethnic groups.[4] Confirmed etiological and prognostic factors of BD are still unclear and vascular lesions, metabolic disturbances and peripheral IR may be frequently seen.[5]

Nonalcoholic fatty liver (NAFLD) is the hepatic manifestation of metabolic syndrome. It is the common cause of ch ronic liver disease worldwide and currently accepted as the atherosclerotic risk factor augmenting cardiovascular disease risk.[6]

The aim of this study was to compare the prevalance of MetS and NAFLD, percentage of body and visceral fat mass, insulin resistance (IR), homocysteine and lipoprotein-a (Lip-a) levels in BD patients and healthy controls.

MATERIAL and METHOD

In this observational case-control study, a total of 115 patients with BD diagnosed as BD according to the criteria of International Study Group for Behcet's Disease 48 men and 67 women; mean age, 47.6±9.1 years (24-76) and 65 healthy control subjects 27 men and 38 women; mean age, 42.7±14.5 years (23-74) were enrolled into the study after the approval of the ethics committee (Göztepe Education and Research Hospital Ethical Committee, 24.11.2010-7/E) and all cases were given informed consent.[7] Patients and controls were all from Turkish descent. They were investigated for HOMA-IR, MetS, NAFLD and visceral fat and total body fat. NAFLD was based on ultrasonographic scoring by Toshiba Aplio Xu 3.75 Mhz probe by the same radiologist without any knowledge of clinical information about the patient. The ultrasonographic scoring was stratified into four levels as Grade 0,1,2,3. Grade 0 representing normal echogenicity, Grade 1 slight increase in →

brightness compared to right kidney echogenicity, Grade 2 distinct increase in echogenicity with a high reflectivity of the fat tissue and finally Grade 3 as marked increase in echogenicity with loss of echoes at the wall of portal vein.[8] Body fat distribution was assessed by Omron BF 510 body composition device with bioelectric impedance. All subjects underwent physical examination including ophtalmologic examination, anthropometric measurements and biochemical screening. Fasting blood glucose (FBG), total cholesterol, triglycerides (TG), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), Hcy, Lip-a were measured from venous blood samples, taken after 12 hours of overnight fasting, were centrifuged (2500 rpm) and the sera were separated. FBG, uric acid, total cholesterol, HDL-C, LDL-C and triglycerides were measured with enzymatic methods. Insulin was measured using an electrochemiluminescence immunoassay (ECLIA). Homocysteine (Hcy) levels were determined using a liquid chromatography tandem mass spectrometry and lipoprotein-a with nephelometric method. The waist circumference was taken as the case standing up, at the end of the expirium, waist area naked, from the middle of costa and crista iliaca distance.[9] Body mass index (BMI) was calculated from measurements of height and weight (kg/m^2).

MetS was diagnosed according to the new IDF definition: Central obesity (as a mandatory component defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women) plus any two of the following four factors: 1) Raised TG level: ≥150 mg/dL or receiving treatment for hypertriglyceridemia, 2) Reduced HDL cholesterol: <40 mg/dL in males and <50 mg/dL in females, or specific treatment for this lipid abnormality, 3) Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension 4) Raised fasting plasma glucose (FPG) ≥100 mg/dL or previously diagnosed type 2 diabetes. The estimate of IR was calculated using the HOMA-IR index using the formula: IR= fasting plasma insulin (in microunits per milliliter) × fasting plasma glucose (in millimoles per liter) / 22.5 (normal if <2.5 and presence of IR if ≥2.5).[10,11]

Data were processed on a personal computer and analyzed using SPSS 20.0 (SSPS Inc.,Chicago,IL,USA). All results were expressed as mean±standard deviation for all subjects and independent samples t test, Mann-Whitney U, Levene test for variance analysis, Chi-square test, Pearson's correlation and one-way analysis of variance (ANOVA) (Kruskal Wallis for the non-parametric groups) were used for statistical analysis. A p-value less than 0.05 was considered to be statistically significant and confidence interval (CI) was 95%.

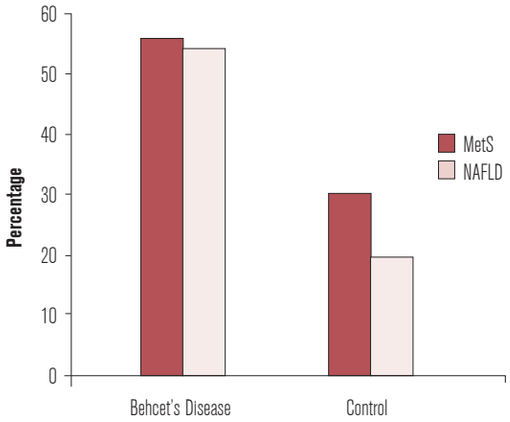


Figure 1: MetS and NAFLD frequency in Behcet's Disease and controls (MetS: Metabolic syndrome, NAFLD: non-alcoholic liver disease)

Table 1: Clinical characteristics of patients with Behcet's disease

	n (%)	
Recurrent Oral Aphtae	115 (100%)	
Genital Ulcers	94 (81.7%)	
Ocular Behcet	48 (41.7%)	
Erythema nodosum	52 (45.2%)	
Papulopustular lesions	47 (40.8%)	
Pathergy positivity	50 (43.5%)	
Neuro-Behcet	13 (11.3%)	
Thrombophlebitis	15 (13.0%)	
Arthritis	41 (35.6%)	
Entero-Behcet	1 (0.9%)	
Pulmonary involvement	1 (0.9%)	
Epididymitis	1 (0.9%)	
Menopause in females	40 (59.7%)	
Family history of BD 1st degree relatives Other relatives	29 (25.2%) 17 (14.9%) 14 (12.2%)	
Age at diagnosis	33.4±7.5 (16-55)	
Male	31.8±5.6	p=0.06
Female	34.5±8.6	
Disease duration (years)	14.3±6.9 (1-34)	

BD: Behcet's disease

RESULTS

One hundred and fifteen BD patients were enrolled for evaluation (67 females and 48 males, age range 11-65), mean duration of disease 14.3±6.9 (1-34) years. Distribution of BD involvement is listed in Table 1. The metabolic parameters of BD and control group were: HOMA-IR (2.3±1.41 vs 1.1±0.3, p<0.05), MetS (53.9% vs 27.5%, p<0.05), NAFLD (52.1% vs 18.4%, p<0.05), body fat ratio (35.4±9.0 vs 29.8±10.3, p<0.05) and visceral fat ratio (11.1±4.6 vs 9.8±3.4,→

Table 2: Clinical and laboratory features of study groups

	Normal Range	BD n (%)	Control Group n (%)	p value
	-	115 (100)	65 (100)	-
Male (n)	-	48 (41.7)	27 (41.5)	p>0.05[a]
Female (n)	-	67 (59.3)	38 (58.5)	p=0.90[a]
Age (yrs)	-	47.6±9.1	46.9±8.8	p>0.05[b]
WC (cm)	All cases Male: 94 cm Female: 80 cm	103.8±12.3 101.0±10.4 105.8±13.3	100.6±11.9 97.5±8,12 102.8±13.6	p<0.05[b] p<0.05[b] p<0.05[b]
BMI (kg/m^2)	<25	28.4±5.0	23.7±4.9	p<0.05[b]
MetS (n)	-	62 (53.9)	18 (27.5)	p=0.001[a]
NAFLD Total Grade 1 Grade 2 Grade 3	 - - -	55 (47.8) 23 (20) 24 (20.8) 8 (6.9)	12 (18.4) 12 (18.4) 0 (0) 0 (0)	p=0.001[a] p=0.80[b]
NASH (n)	None	23 (20.0)c	0 (0)	-
HOMA-IR Index	<2.5	2.2±1.4	1.1±0.3	p<0.05[b]
DM (n)	-	13 (11.3)	0 (0)	p=0.004[a]
IR	-	37 (32.2%)	8 (12.3%)	p<0.01[a]
Hypothyroidism	-	5 (4.3)	0 (0)	p=0.09[b]
Hypertension	-	33 (28.7)	4 (6.2)	p<0.001[a]
Visceral Fat (%)	1-12	11.1±4.6	9.8±3.4	p>0.05[b]
Total Body Fat (%)	15-30	35.4±9.0	29.8±10.3	p<0.05[b]
AST (U/l) NAFLD(+) NAFLD(-)	5-32	27.9±10.4 30.7±11.7 25.2±7.9	25.2±9.3 - -	p>0.05[b] p=0.04[d]
ALT (U/l) NAFLD(+) NAFLD(-)	5-38	32.0±19.8 39.2±23.6 25.3±12.3	29.3±17.5 - -	p>0.05[b] p=0.001[d]
HbA1c (%)	4.3-5.8	5.8±1.1	5.2±0.6	p>0.05[b]
Lipoprotein-a (mg/dl)	<10	11.1±6.6	10.6±4.09	p>0.05[b]
Homocysteine (µmol/L)	<10	8.4±1.2	8.0±1.0	p>0.05[b]
T.Cholesterol (mg/dl)	100-200	199±41	169±38	p<0.05[b]
Triglycerides (mg/dl)	60-150	145±63	135±38	p>0.05[b]
HDL-C	45-65	48.7±11.6	51.9±10.5	p>0.05[b]
HDL-C Male (mg/dl)	45-65	43.0±9.8	41.0±10.1	p>0.05[b]
HDL-C Female (mg/dl)	45-65	52.7±11.2	54.8±10.8	p>0.05[b]
LDL-C (mg/dl)	40-130	125±33	115±31	p>0.05[b]

MetS: Metabolic syndrome, NAFLD: non-alcoholic fatty liver disease , BD: Behcet's disease, HOMA-IR: Homeostasis Model of Assessment - Insulin Resistance , DM: diabetes mellitus , IR: Insulin Resistance, AST: aspartate aminotransferase, ALT: alanine aminotransferase, NASH: nonalcoholic steatohepatitis, M: male, F: female, WC: waist circumference, a: Based on chi-square test, b: Based on Mann-Whitney U test, c: Based on ultrasonographic steatosis and high transaminases, no biopsy, d: Significance between NAFLD(+) and NAFLD(-) patients

p>0.05), respectively. HOMA-IR value was ≥2.5 in 37 (32.2%) for BD patients and 5 (7.6%) of the control group (p<0.05) (Figure 1, Table 2). IR was present in 22 (32.8%) of female and 15 (31.2%) of male BD patients (p>0.05) (Table 3). Patients with IR had significantly higher BMI, serum insulin (p<0.001), fasting plasma glucose, leukocyte count, waist circumference (p<0.01), triglycerides, C-reactive protein (CRP), and uric acid levels (p<0.05) compared to patients without IR. Comparison of patients with IR and without IR is shown in Table 4.

Patients under medication were as follows; colchicine (96.5%), pentoxyphilline (21.7%), azathioprine (12.2%), cyclosporine (6.1%), metformin (4.3%). Active illness was present in 70/115 (60.9%) of the patients during the study. Comorbidity was present in 32.8% of cases; hypertension (28.7%), diabetes mellitus type 2 (11.3%), chronic kidney disease (4.3%), rheumatoid arthritis (0.87%), HCV positivity (0.87%), multiple sclerosis (0.87%) and cranial tumor (0.87%). Age of disease onset was 34.7±6.0 for non-ocular and 31.8±8.7 for ocular BD patients (p=0.04). The parameters for BD cases with and without NAFLD were as follows: HOMA-IR (2.7±1.4 vs 1.8±1.2, p=0.001), HbA1c (6.1±1.5 vs 5.6±0.5, p=0.03), ALT (39.2±23.7 vs 25.3±12.3, p=0.001), Lip-a (11.5±7.012 vs 0±6.2, p=0.40), Hcy (8.5±1.6 vs 8.3±0.8, p=0.47), total body fat (37.4±8.9 vs 33.7±8.9, p=0.03) and visceral fat ratio (12.7±4.6 vs 9.7±4.2, p=0.001). Ultrasonographic scoring for steatosis of liver were graded as 1, 2 and 3 and distribution was 23 (20%), 24 (20.9%) and 8 (7%), respectively. Higher grade was correlated with higher triglycerides, AST, ALT, HOMA-IR (p<0.001), gamma glutamyl transpeptidase (GGT), BMI, total cholesterol, HbA1c and visceral fat ratio (p<0.05), while Lip-a, Hcy, total body fat ratio, LDL, HDL were insignificant (p>0.05) (Figure 2,3,4).

DISCUSSION

The International Study Group Criteria for Behcet's (ISG), created in 1990, have high specificity, but poor sensitivity. The ISG uses five items. In ISG criteria, the presence of oral aphtae is mandatory. Any two of remaining four items (genital aphtae, skin lesions, ocular lesions, positive pathergy) are additionally necessary to classify a patient as BD.[7]

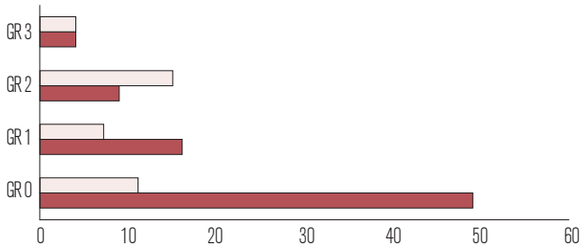
A recent diagnostic scoring, International Criteria for Behcet's Disease (ICBD) was created in 2006 and has better sensitivity, and accuracy than ISG. ICBD uses six items: genital aphtae and ocular manifestations (anterior or posterior uveitis, retinal vasculitis) get 2 points each, oral aphtae, skin lesions (pseudofolliculitis or erythema nodosum), vascular manifestations (superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis or aneurysm) and pathergy positivity receives 1 point each. A patient has to get 3 or more points to be diagnosed as BD.[12]

MetS is a major worldwide health problem and is a risk factor for cardiovascular morbidity and morbidity three times, mortality two times and Type-2 Diabetes mellitus five times.[13] Gradually increasing incidence and prevalence of MetS in children can be attributed to the obesity epidemic in the population and relation →

with some chronic inflammatory diseases.[14,15] MetS prevalence increases with abdominal obesity and seen 27% in the United States, 13% in France, 40% in Pakistan, 29-33% in Turkey, and 40% in India. In the study Metabolic Syndrome Prevalence Survey in Turkey (METSAR) realized by Metabolic Syndrome Association, MetS prevalence was found to be 33.9% (39.6% in women and 28% in men). Another survey TEKHARF study (Turkish Adult Risk Factor Survey) revealed MetS to be 37.1% (31.2%, in males and 42.8% females). Prevalence was 6.7% in the age group of 20-29 years and 43.5% in the age group of 60-69 years. MetS was 53% in coronary heart patients.[3,16,17] Similar to many western populations, abdominal obesity and MetS prevalence are also increasing in Turkey.[18] In our study group 62 (53.9) of BD patients and 18 (27.5%) of the control group had MetS ($p<0.01$). Patients younger than 45 years of age had MetS in 16/43 (37.2%) while 46/72 (63.9%) in 45 years and older ($p=0.005$). The disease duration was 10.2±4.4 and 16.7±7.1 years for patients at age below 45 and ≥45, respectively ($p=0.001$), thus the increase of MetS in older patients is concordant with effect of long term inflammation.

Tumor necrosis factor- alpha (TNF) has been found to inhibit insulin-stimulated glucose uptake in skeletal muscle, supporting the concept that TNF could play a role in the development of IR in humans. Increased levels of serum TNF and IFN have been reported in patients with BD, suggesting the possible role of these cytokines on initiating the resistance to insulin.[19] In our patients active illness or remission groups had no difference by means of IR, MetS nor NAFLD ($p>0.05$). High levels of Lip-a and Hcy have been linked to early cardiovascular diseases.[20] Even though it is well known that BD has a variety of cardiovascular involvements there was no difference in Lip-a and Hcy between BD and controls ($p>0.95$) (Table 2).

NAFLD defines a spectrum of liver disease from benign simple fatty liver disease to non-alcoholic steatohepatitis (NASH), which is associated with fibrosis and progression to cirrhosis and hepatocellular carcinoma. The histological changes In NAFLD are identical to alcoholic liver disease, so diagnosis requires the exclusion of those drinking more than 20 g of alcohol per day. The reported prevalence of NAFLD is about 20-30% and that of NASH is around 2-3%. Risk factors associated with NAFLD are mainly features of the dysmetabolic syndrome: obesity, type 2 diabetes mellitus, IR, hypertension, and dyslipidaemia. Male sex and increased waist circumference are well-established NAFLD risk factors. NAFLD is primarily associated with increased intra-abdominal fat mass and even though the diagnosis of NAFLD is based on liver biopsy, scoring of steatosis by ultrasonographic brightness is widely used.[21,22] The prevalence of NAFLD in western communities is about 20-30%.[23] In our study group, NAFLD was found in 52.1% of →



	GR 0	GR 1	GR 2	GR 3
IR(+)	11	7	15	4
IR(-)	49	16	9	4

Figure 2: Insulin resistance and NAFLD score by ultrasonography (distribution of 115 patients) (IR: Insulin resistance, Gr: grade)

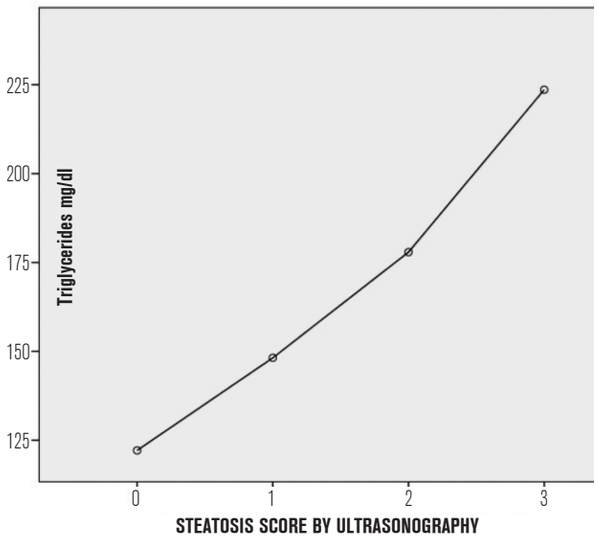


Figure 3: Correlation of triglycerides and hepatosteatosis

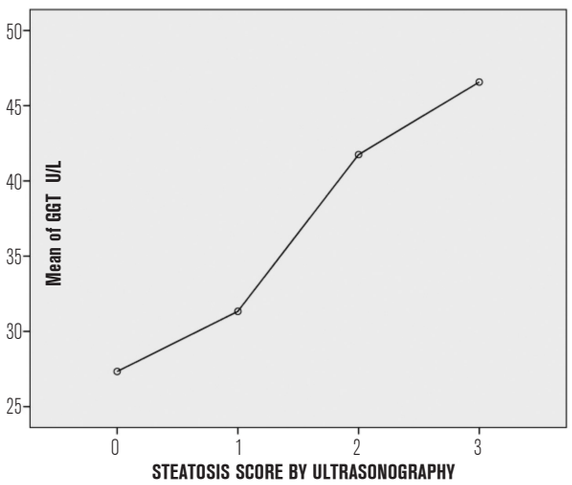


Figure 4: Relation of serum GGT level and nonalcoholic fatty liver score (GGT:Gamma glutamyl transpeptidase)

Table 3: Gender difference in characteristics of BD patients

	Male	Female	p
N	48	67	
Age (years)	45.9±6.8	48.9±10.4	p=0.06
MetS (%)	58.3	50.7	p=0.41
NAFLD (%)	52.1	44.8	p=0.44
NASH (%)	25.0	16.4	p=0.05
BMI (kg/m^2)	27.6±3.9	29.0±5.7	p=0.12
HOMA-IR Index	2.4±1.6	2.1±1.17	p=0.23
T. Cholesterol (mg/dl)	196±44	201±38	p=0.46
Triglycerides (mg/dl)	163±66	132±59	p=0.008
HDL-C (mg/dl)	43.0±9.8	52.8±11.2	p=0.001
LDL-C (mg/dl)	128.0±33.5	122.9±34.0	p=0.43
Homocysteine (µmol/L)	8.4±0.8	8.5±1.5	p=0.98
Lipoprotein-a (mg/dl)	11.9±6.7	11.7±6.6	p=0.85
Body Fat %	30.3±6.7	39.2±8.8	p=0.001
Visceral Fat %	11.6±5.7	10.8±3.7	p=0.37
IR %	31.2	32.8	p>0.05

MetS: Metabolic syndrome, NAFLD: non-alcoholic liver disease, BD: Behcet's disease
NASH: non-alcoholic steatohepatitis, M:male, F:female , IR: insulin resistance
HOMA-IR: Homeostasis Model of Assessment - Insulin Resistance BMI: Body Mass Index, T. Cholesterol: Total cholesterol, HDL-C: High density lipoprotein cholesterol , LDL-C: Low density lipoprotein cholesterol

BD patients and 18.4% of control group (p<0.01). In BD group 39/62 (62.9%) of patients with MetS had NAFLD. Sixteen (13.9%) patients having NAFLD without presence of MetS were another challenging group. This group was not significantly different from the rest by terms of BMI, visceral fat, onset age of BD, total cholesterol, triglycerides (p>0.05), but had higher age, HDL-C, total body fat and anti-TPO levels (p<0.05). There were 22/62 (35.5%) of MetS patients without any sign of steatosis. Thirty patients with BD had normal BMI (<25 kg/m^2) and 7 (23.3%) of them had NAFLD and just 1 (3.3%) patient had ALT elevation over upper level of normal (ULN).

Among Turkish adults, the prevalence of overweight is similar to that of Europe, whereas the prevalence of obesity among women is higher than the European average. Previous studies have found the prevalence of overweight as 36.0% (41.5% in men and 30.6% in women) and the prevalence of obesity as 30.4% (20.6% in men and 39.9% in women) in Turkey. The Turkish population has one of the world's highest prevalence of MetS.[24] In our study the ratio of patients with BMI index over 25 was 73.9% (males 72.9% and females 74.6%).

Early atherosclerosis is a clinical feature common to several inflammatory and immunological diseases, in which atherothrombotic complications represent one of the most important causes of mortality and morbidity.[25] Parameters such as inflammation and IR, which are considered clinical markers of early atherosclerosis, are accepted as predictors of cardiovascular events.[26,27] IR was significantly high in BD patients in our study (p<0.01)(Table 2).

An overexpression of TNF-alpha mRNA is found in the liver and in the adipose tissue of NASH patients. The levels of mRNA-p55 are increased in the liver tissue of NASH patients. These findings suggest that the TNF system may be involved in the pathogenesis of NASH.[28] Cytokines and, in particular, TNF and adiponectin appear to play a central role not only as regulators of insulin sensitivity and development of fatty liver, but also in the inflammatory process and fibrogenesis.[29] The serum level of TNF is elevated in patients with BD, and a dramatic response to anti-TNF antibody treatment suggests the role of TNF in BD.[30] Overproduction of activated monocyte-derived pro-inflammatory cytokines (e.g., IL-1, IL-6, IL-8, and TNF) has been implicated in the BD pathogenesis and their increased levels may represent the disease activity. Recent studies showed increased levels of IL-8, particularly in patients with active oral and neurological manifestations Behçet's disease.[31,32]

Rimar et al. reported a high proportion of NAFLD in a cohort of FMF patients without overt MetS possibility of a novel association between FMF and NAFLD.[33] In our study, 16 (13.9%) of patients had NAFLD without MetS. Four of these patients had elevated ALT levels, which may be regarded as NASH. The similarities and co-existence of FMF and BD need further evaluations by terms of NAFLD.

Some recent studies report that LDL-C/HDL-C ratio, HDL-C size and subgroups (HDL-3 and higher) may predict cardiovascular events in BD patients.[34] LDL-C/HDL-C ratio was 2.7±0.9 and 2.2±0.8 in our BD and control patients (p<0.05). As in our study, Kim et al. reported the number of metabolic syndrome components was correlating with HOMA-IR in BD patients.[35] Even though our BD patients - all subgroups as gender, activity, insulin resistance, NAFLD - had normal Hcy levels, some studies report high levels of Hcy associated with BD patients with thrombosis.[36,37] In our study, NAFLD and non-NAFLD patients had averages of HDL-C (48.7±13.8, vs 48.7±9.3, p=0.99), LDL-C (125.6±40.5 vs 124.6±26.1, p=0.88) TG (169.3±71.8 vs 122.3±44.6, p=0.001), LDL-C/HDL-C ratio (2.7±1.1 vs 2.6±0.6, p=0.42) and TG/HDL-C ratio (3.9±2.1 vs 2.6±1.1, p<0.001), respectively. Patients with MetS and without MetS had averages of HDL-C (46.0±12.6 vs 51.9±9.6, p=0.07), LDL-C (126.5±36.8 vs 123.4±29.9, p=0.63), LDL-C/HDL-C (2.9±1.0 vs 2.4±0.5, p=0.002), TG (174±61.3 vs 110.8±47.4, p=0.001), TG/HDL-C (4.1±1.9 vs 2.2±1.0, p=0.001), respectively. →

This study had some limitations as it was a case-control study and it could not clarify the causal relation of BD with MetS and NAFLD. Another important deficiency of this study was the lack of liver biopsy, which is invasive but gold standard for diagnosing NAFLD and NASH. Also the patients were under medication which may influence and alter the metabolic parameters. Eight patients with BD having ALT values over ULN without evidence of any NAFLD or other chronic liver diseases, suggested that it could be related with colchicine. As in rheumatoid arthritis, interference of corticosteroid usage would change metabolic parameters, especially as an increase in triglycerides, but none of our BD patients were receiving corticosteroids. Another caveat of the study was the single measurement of all data and this might not reflect the changes by time. Although it is insignificant (p=0.13), our male/female ratio (0.7) was different from the expected male dominant ratio (1.08) in Turkish BD cohort and also small sample size could limit the generalizability of our results.[1]

Table 4: Differences between patients with and without IR

	IR (+)	IR (-)	p
N (%)	37 (32.2)	78 (67.8)	
Gender (M/F)	15/22	33/45	p>0.05
Age (years)	50.0±7.3	46.5±9.7	p>0.05
MetS (%)	91.9	35.9	p<0.001
NAFLD (%)	70.3	37.2	p=0.01
NASH (%)	37.8	11.5	p=0.002
Total Cholesterol (mg/dl)	203±38	197±42	p=0.44
Triglycerides (mg/dl)	166±81	134±62	p=0.01
HDL-C (mg/dl)	47±13	49±10	p=0.36
HDL-C Male	38.6±9.2	45.2±9.5	p=0.03
HDL-C Female	53.2±13.6	52.5±10.0	p=0.8
LDL-C (mg/dl)	122±34	126±33.	p=0.56
Homocysteine (µmol/L)	8.4±0.7	8.5±1.5	p=0.84
Lipoprotein-a (mg/dl)	10.4±5.7	12.4±6.9	p=0.12
Body Fat %	39.5±9.0	33.6±6.0	p=0.01
Visceral Fat %	13.8±5.0	9.9±4.0	p=0.001

MetS:Metabolic syndrome, NAFLD: non-alcoholic liver disease, NASH: nonalcoholic steatohepatitis, M:male, F:female IR: insulin resistance, HDL-C: High density lipoprotein cholesterol , LDL-C: Low density lipoprotein cholesterol

CONCLUSION

There was a significant difference between BD and healthy control group in terms of total body fat, frequencies of IR, MetS and NAFLD. Even though visceral fat was higher in BD group the difference was not significant than controls. The interrelation of BD with NAFLD and MetS based on inflammatory cytokines especially TNF-alpha and IL-8 seems to be important. As a chronic inflammatory state, BD may be related with MetS and NAFLD, hence resulting with increased risk of cardiovascular complications.

To conclude, BD is significantly associated with MetS, NAFLD and IR. This might be explained by the diverse consequences of inflammation and endothelial dysfunction in BD. In order to establish a causal relation between Behcet's Disease with MetS, NAFLD and insulin resistance, larger and preferably longitudinal prospective cohort studies focusing on arising metabolic and cardiovascular complications are necessary.

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