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# THE INTERRELATIONSHIP OF METABOLIC SYNDROME AND BEHCET'S DISEASE IN A COHORT OF EGYPTIAN PATIENTS (A CROSS-SECTIONAL STUDY)

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## *ABSTRACT*

The prevalence of metabolic syndrome (Met S) increased in chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis. Behçet's disease (BD) is a chronic, multisystem disease with immuno-inflammatory etioloy. The study was aimed to assess the prevalence of Met S among Egyptian Behcet patients. We also tried to detect the relationship of Met S and its various aspects with activity and severity of BD and oral ulcer activity. The study population consisted of 60 BD patients and 60 healthy, age and sex matched controls. BD patients were diagnosed according to the criteria of the International Study Group of Behçet's disease. Clinical data were collected at the time of enrollment as body mass index (BMI), waist circumference (WC), and arterial blood pressure. Total cholesterol (TC), low-density lipoprotein (LDL-c), high density lipoprotein (HDL-c), triglycerides (TGs), and C-reactive protein (CRP) were measured. Fasting plasma glucose (FPG), fasting insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR) were estimated. Met S diagnosis was established according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. The prevalence of Met S in sixty BD patients was 30%, while in the healthy, age and sex matched control group was 16.6 % ($p>0.05$). Among males, Met S prevalence was 28.5% in BD patients and 9.3% in controls, while in females, Met S prevalence was 33.3% in Behçet patients and 35.9% in controls. The BD severity and activity as well as oral ulcer activity were negatively correlated with the duration of the disease and patients' age ($p<0.5$). The disease severity and activity were positively correlated with fasting insulin, HOMA-IR, TC, TGs, LDL-c, IL-6, and hsCRP, while oral ulcer activity was positively correlated with insulin and TGs ($p<0.05$). It was concluded within the limits of this study that BD patients should be followed up regularly for diabetes mellitus, hyperlipidemia, and hypertension to prevent Met S development.

**KEY WORDS:** Behcet disease; metabolic syndrome; lipid profile; insulin resistance.

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## INTRODUCTION

Behçet's disease (BD) is a systemic vasculitis manifested by recurrent orogenital aphthosis, ophthalmic, cutaneous, articular, gastrointestinal, urogenital, neurological, pulmonary, and cardiovascular manifestations.[1] Many genetic and enviromental factors play an essential role in the development of BD, especially the human leukocyte antigen B51 allele which is present in the major histocompatibility complex locus.[2] Several cytokines are suggested to share in the pathogenesis of BD particularly tumor necrosis factor-α (TNF-α) which might contribute in disease occurrence. Moreover, anti-TNF-α agents have been used successfully in BD treatment.[3] Interleukin-6 (IL-6) was detected in higher concentration in cerebral fluid of BD patients with CNS involvement.[4]

Overexpression of these proinflammatory cytokines was found to be associated with insulin resistance and metabolic syndrome (Met S). Met S is characterized by hypertension, dyslipidemia, impaired carbohydrate metabolism, and central obesity. Insulin resistance was associated with atherosclerosis and high coronary heart disease risk. Insulin resistance has also been detected in inflammatory diseases as systemic lupus erythematosus and rheumatoid arthritis. [5,6] Moreover, psoriasis was found to be associated with high cardiovascular risk, this may be attributed to the chronic inflammatory condition of the disease that is considered as a predisposing factor of metabolic syndrome. [7] Few researchers have studied the prevalence of Met S in BD patients; however, their results were contradictory. [8, 9]

The aim of this study was to investigate the prevalence of Met S and its components among Egyptian Behcet patients. We also tried to detect the relationship of Met S and its different components with activity and severity of BD and oral ulcer activity.

## MATERIALS AND METHODS

### Study design

This cross-sectional study was approved by the institutional review board of the Faculty of Medicine, Mansoura University. The test group included 60 BD patients who were diagnosed according to the International Study Group for Behçet's Disease[10]. BD patients were selected from the Oral Medicine clinic at the Faculty of Dentistry, and from the Rheumatology and Rehabilitation clinic at Mansoura University Hospital, Mansoura University, Egypt between February and December, 2016. The control group included 60 healthy subjects with age, and sex matched to test group. All enrolled subjects signed informed consent for participation in the study. Exclusion criteria included the presence of any other systemic disease.

All BD patients were assessed by ophthalmology, gastroenterology, neurology rheumatology, and thoracic disease consultants (as part of the study for definitive diagnosis and to detect disease severity and activity and different organ affected). Blood pressure, weight, height, waist circumference (WC), and body mass index (BMI) were measured for all participants. We assessed the BD activity according to Behçet's Syndrome Activity Score (BSAS) [11], the Behçet disease severity according to Krause et al [12], and oral aphthous ulcer activity according to Mumcu et al index. [13]

### Biochemical assessment

Fasting blood samples were withdrawn from all participants. Total cholesterol (TC), low-density lipoprotein (LDL-c), high density lipoprotein (HDL-c), triglycerides (TGs), and C-reactive protein (CRP) were measured. Fasting plasma glucose (FPG), fasting insulin, and the homeostasis model assessment of insulin resistance (HOMA-IR) were estimated. Serum levels of IL-6 were assayed by using interleukin- 6 (IL-6) ELISA kit (Elabscience, Bethesda, MD, USA).

**Assessment of the metabolic syndrome (Met S)**

Patients having three of the following criteria were diagnosed as metabolic syndrome (Met S), according to the Adult Treatment Panel (ATP) -III Criteria (14): 1- Abdominal circumference > 40 inch in men and > 35 inch in women; 2- Serum triglycerides level > 150 mg/dl or using drugs for lowering the level of triglycerides; 3- HDL-c level < 40 in men and < 50 mg/dl in women, or using drugs for increasing HDL level; 4- Fasting plasma glucose level > 100 mg/dl or using hyperglycemic drugs; and 5- Blood pressure > 130/80 or using of hypertension drugs.

**Statistical analysis**

All statistical analyses were carried out with SPSS (statistical package for social sciences) 14.0 standard version. Chi-square and Student's t-tests were used for the statistical analysis between groups, while Mann–Whitney U-test and Fischer's exact test were used for the statistical analyses between the subgroups. Pearson's correlation test was used to evaluate the relationships between different data. P values < 0.05 were considered statistically significant.

## RESULTS

A total of 120 individuals were enrolled for participation in the present study and were divided into two groups; the BD group (n=60) and the age and gender matched individuals who represent the control group (n=60). All BD patients were treated with glucocorticoids prescribed by Rheumatology specialists. Table 1 showed the comparison of clinical and laboratory findings of male and female BD patients. There were significant differences between males and female Behçet patients as regards to the age of the patients and duration of BD. Behçet disease severity, oral ulcer activity, skin, joint, and genital lesions were significantly higher in males than females. BD activity was also higher in males than in females, but was not significant. No female patients showed DVT, neurological or vasculitis lesions. However, ocular lesions were higher in females. All components of Met S were not significantly different among BD patients when assessed by gender except waist circumference. IL-6 and hs-CRP were not significantly different between male and females.

The prevalence of Met S in the sixty Behçet's disease patients was 30%, while in age and sex matched healthy control group was 16.6 % (P=0.12). Table 2 shows the characteristics of BD patients and control subjects according to gender. Among males, Met S occurred in 12 BD patients (28.5%) and 4 controls (9.3%) with a significant difference, whereas in females, Met S occurred in 6 Behçet patients (33.3%) and 6 controls (35.9%) with no significant difference. Age and BMI of BD patients and control were insignificantly different among both genders. As regards to the components of Met S, there were significant differences of TGs, and diastolic blood pressure (DBP) between Behçet patients and control in males only, however, FPG was significantly higher in Behcet patients than control in both genders. Waist circumference, TC, HDL-c, and LDL-c were insignificantly different between patients and control in both genders. HOMA-IR, insulin, and CRP were significantly higher in Behçet patients than control in both genders. However, IL-6 was significantly higher in BD patients than controls in males only.

Table 3 showed the comparison of clinical and biochemical data between BD cases with and without Met S. In BD patients, higher Behçet disease severity and activity, DVT and vasculitis lesions, and IL-6 values were associated with the development of Met S ($p<0.05$). However, ocular lesions were higher in Behçet patients without Met S. The age and gender of patients, duration of disease, oral ulcer activity, skin, genital, joint, and neurological lesions, insulin, HOMA-IR, and hs-CRP were not associated with the Met S ($p>0.05$).

All Met S components were significantly higher in Behçet patients with Met S than those without Met S.

Table 4 indicates the correlation of different parameters with BD activity and severity and oral ulcer activity in BD Patients. There were statistically significant negative correlations between BD severity, activity, oral ulcer activity, the duration of the disease, and age of the patients ($p<0.5$). Moreover, BD severity and activity were correlated positively with insulin, HOMA-IR, TC, TGs, LDL-c, IL-6, and hs-CRP, while oral ulcer activity was positively correlated with insulin and TGs ($p<0.05$).

TABLE (1) Comparison of clinical and biochemical findings of male and female Behcet's disease (BD) patients:

| **Parameter** | **Total (n=60)** | **Male (n=42)** | **Female (n=18)** | **p -value** |
|---|---|---|---|---|
| **Age (years)** | 34.1±7.1 | 31.1 ± 5.2 | 41 ±5.9 | < 0.001* (t) |
| **Duration of BD (years)** | 4.5 (1.5-11) | 4 (1.5-10) | 9.0 (2-11) | = 0.001* (Z) |
| **BD severity** | 17.6±3.9 | 18.8±3.4 | 16.3±4.1 | = 0.02* (t) |
| **BD activity** | 34.2±8.7 | 34.4±8.4 | 31.7±11.1 | = 0.06 (t) |
| **Oral ulcer activity** | 6.5±1.8 | 7.3±1.5 | 4.5±0.8 | =0.001*(t) |
| **Skin,** n (%) | 57 (95) | 42 (100) | 15 (83.3) | = 0.02 (F) |
| **Joint,** n (%) | 42 (70) | 24 (57.1) | 18 (100) | < 0.001* (F) |
| **Eye,** n (%) | 36 (60) | 18 (42.9) | 18 (100) | = 0.05* (F) |
| **DVT,** n (%) | 6 (10) | 6 (14.3) | 0 (0) | = 0.17 (F) |
| **Neurological,** n (%) | 3 (5) | 3 (7.1) | 0 (0) | = 0.55 (F) |
| **Vasculitis,** n (%) | 3 (5) | 3 (7.1) | 0 (0) | = 0.55 (F) |
| **Genital,** n (%) | 48 (80) | 42 (100) | 6 (33.3% ) | < 0.001* (F) |
| **BMI (kg/m$^2$)** | 28.8±5.9 | 27.9±5.8 | 32.1±4.8 | 0.053 (t) |
| **WC (cm)** | 36.9±6.6 | 34.8±6.1 | 41.7±4.9 | < 0.001* (t) |
| **SBP (mmHg)** | 121.8±5.8 | 121.8±6.2 | 121.7±4.9 | = 0.28 (t) |
| **DBP (mmHg)** | 85±3.2 | 85.4±3.0 | 84.166±3.6 | = 0.09 (t) |
| **FPG (mg/dL)** | 96.1±10.7 | 95.6 ± 10.7 | 97.3 ± 11.1 | = 0.28 (t) |
| **Fasting insulin (pmol/L)** | 12.7 (5.6-28) | 12.8 (6.8-22) | 11.1 (5.6-28) | = 0.47 (Z) |
| **HOMA-IR** | 3.1 (1.3-5.7) | 3.1 (1.3-5.4) | 2.6 (1.5-5.7) | = 0.87 (Z) |
| **TC (mg/dL)** | 182.9±18.7 | 183.2±19.1 | 182.2±18.5 | = 0.42 (t) |
| **TGs (mg/dL)** | 125.8±21.9 | 128.2±23.1 | 120±18.1 | = 0.09 (t) |
| **HDL-c (mg/dL)** | 54.7±8.9 | 55.5±7.1 | 52.7±12.2 | = 0.13 (t) |
| **LDL-c (mg/dL)** | 103.2±21.9 | 102.1±19.4 | 105.6±27.4 | = 0.28 (t) |
| **IL-6 (pg/mL)** | 13.3 (2.9-40) | 14.6 (8.3-40) | 11.3 (2.9-35) | = 0.15 (Z) |
| **hs-CRP (mg/dL)** | 7.0 (2-48) | 7.0 (2-24) | 5.5 (4-48) | = 0.25 (Z) |

***Statistically significant when p < 0.05.***

***t=Student-t test; values are expressed as mean±standard deviation.***

***Z= Mann- Whitney U test; values are expressed as median and range.***

***F= Fischer's exact test; values are expressed as frequency (%).***

***DVT= Deep venous thrombosis; BMI= Body mass index; WC=Waist circumference; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; FPG=Fasting plasma glucose; HOMA-IR=Insulin resistance assessed by homeostasis model of assessment; TC=Total cholesterol; TGs=Triglycerides; HDL-c=High density lipoprotein-cholesterol; LDL-c= Low density lipoprotein-cholesterol; IL-6= interleukin-6; hs-CRP=High-sensitvity C-reactive protein.***

TABLE (2) Characteristics of patients and control subjects according to gender:

| Parameter | Male (n=85) | | p-value | Female (n=35) | | p-value |
|---|---|---|---|---|---|---|
| | Patients n=42 | Controls n=43 | | Patients n=18 | Controls n=17 | |
| **Met S (%)** | 12 (28.5) | 4 (9.3) | =0.03* (F) | 6 (33.3) | 6 (35.2) | =1 (F) |
| **Age (years)** | 31.1 ± 5.2 | 32.2± 6.3 | =0.18 (t) | 41.0±5.9 | 38.6± 7.2 | =0.14 (t) |
| **BMI (kg/m$^2$)** | 27.9±5.8 | 28.2±5.7 | =0.38 (t) | 32.08±4.8 | 31.4±5.7 | =0.35 (t) |
| **WC (cm)** | 34.8±6.1 | 34.9±6.8 | =0.46 (t) | 41.7±4.8 | 40.1±6.2 | =0.20 (t) |
| **SBP (mmHg)** | 121.7±6.2 | 116.4±6.6 | =0.17 (t) | 121.7±4.8 | 123.2±7.3 | =0.22 (t) |
| **DBP (mmHg)** | 83.2±6.2 | 79.4±6 | =0.002* (t) | 85±5.1 | 82.4±5.9 | =0.08 (t) |
| **FPG (mg/dL)** | 95.6±10.7 | 84.9±21.7 | =0.002* (t) | 97.3±11.1 | 89.5±10.7 | =0.02* (t) |
| **Fasting insulin (pmol/L)** | 12.75 (6.8-22) | 7.3 (0.5-10) | <0.001* (Z) | 11.05 (5.6-28) | 6.8 (2.4-10) | <0.001*(Z) |
| **HOMA-IR** | 3.1(1.3-5.4) | 1.4 (0.1-2) | <0.001*(Z) | 2.6 (1.5-5.7) | 1.6 (0.7-2) | <0.001*(Z) |
| **TC (mg/dL)** | 183.3±19.1 | 179.5±18.7 | =0.18(t) | 182.2±18.5 | 174.4±25.8 | =0.15 (t) |
| **TGs (mg/dL)** | 128.2±23.1 | 110.8±20.8 | <0.001*(t) | 120±18.1 | 127.4±24.2 | =0.15 (t) |
| **HDL-c (mg/dL)** | 55.5±7.1 | 53.6±7.5 | =0.11 (t) | 52.7±12.2 | 53.7±7.3 | =0.38 (t) |
| **LDL-c (mg/dL)** | 102.1±19.4 | 105.3±19.1 | =0.22 (t) | 105.7±27.4 | 105.3±19.1 | =0.09 (t) |
| **IL-6 (pg/mL)** | 14.6 (8.3-40) | 11.32 (5.4-16.2) | <0.001* (Z) | 11.15 (2.9-35) | 10.3 (5.4-13.3) | =0.63 (Z) |
| **hs-CRP (mg/dL)** | 7 (2-24) | 2 (1-5) | <0.001* (Z) | 5.5 (4-48) | 2 (1-4) | <0.001* (Z) |

***Statistically significant when p < 0.05.***

***t=Student-t test; values are expressed as mean±standard deviation.***

***Z= Mann- Whitney U test; values are expressed as median and range.***

***F= Fischer's exact test; values are expressed as frequency (%).***

***Met S= Metabolic syndrome; BMI= Body mass index; WC=Waist circumference; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; FPG=Fasting plasma glucose; HOMA-IR=Insulin resistance assessed by homeostasis model of assessment; TC=Total cholesterol; TGs=Triglycerides; HDL-c=High density lipoprotein-cholesterol; LDL-c= Low density lipoprotein-cholesterol; IL-6= interleukin-6; hs-CRP=High-sensitvity C-reactive protein.***

TABLE (3) Comparison of clinical and laboratory findings between BD cases with & without metabolic syndrome:

| Parameter | BD without Met S (n=42) | BD with Met S (n=18) | p-value |
|---|---|---|---|
| **Age (years)** | 33.4± 7.8 | 35.5 ± 4.7 | = 0.15 (t) |
| **BD duration (years)** | 5 (1.5-11) | 3.5 (2-10) | =0.43 (Z) |
| **Gender**<br>**M**<br>**F** | <br>30 (71.4%)<br>12 (28.8%) | <br>12 (66.6%)<br>6 (33.3%) | =0.76 (F) |
| **BD severity** | 17.4± 3.8 | 19.3 ± 3.3 | = 0.03* (t) |
| **BD activity** | 33.5 ± 8.4 | 37.6 ± 7.9 | =0.04* (t) |
| **Oral ulcer activity** | 6.6±1.7 | 6.8±2.2 | =0.36 (t) |
| **Skin%** | 39 (92.9) | 18 (100) | = 0.55 (F) |
| **Joint%** | 30 (71.4) | 12 (66.7) | = 0.71 (x) |
| **Eye%** | 21 (50) | 15 (83.3) | =0.02* (x) |
| **DVT%** | 0 (0) | 6 (33.3) | <0.001*(F) |
| **Neurological%** | 3 (7.1) | 0 (0) | = 0.55 (F) |
| **Vasculitis%** | 0 (0) | 3 (16.6) | =0.02* (F) |
| **Genital%** | 36 (85 ) | 12 (66.7) | =0.16 (F) |
| **BMI (kg/m$^2$)** | 25.8±2.8 | 36.7±3.4 | <0.001*(t) |
| **WC (cm)** | 33.6±4.9 | 44.3±2.6 | <0.001*(t) |
| **SBP (mmHg)** | 120.7±3.76 | 124.2±8.6 | =0.02*(t) |
| **DBP (mmHg)** | 83.6±2.3 | 86.7±3.8 | <0.001*(t) |
| **FPG (mg/dL)** | 93.9 ± 10.4 | 101.3 ± 9.7 | =0.006*(t) |
| **Fasting insulin (pmol/L)** | 13.9±5.4 | 13 ±5.6 | =0.29 (t) |
| **HOMA-IR** | 3.1 (1.3-5.7) | 2.65 (1.8-5.4) | =0.47 (Z) |
| **TC (mg/dL)** | 178.7±17.2 | 192.8±18.9 | =0.003* (t) |
| **TGs (mg/dL)** | 116.6±17.9 | 147.2±13.9 | <0.001*(t) |
| **HDL-c (mg/dL)** | 57.4±7.7 | 48.2±8.3 | <0.001*(t) |
| **LDL-c (mg/dL)** | 98±19.6 | 115.2±22.9 | =0.002*(t) |
| **IL-6 (pg/mL)** | 15 (2.9-40) | 17.8 (11-28.8) | =0.04* (Z) |
| **hs-CRP (mg/dL)** | 6 (2-48) | 9 (4-40) | =0.04* (Z) |

***Statistically significant when p < 0.05.***

***t=Student-t test; values are expressed as mean±standard deviation.***

***Z= Mann- Whitney U test; values are expressed as median and range.***

***F= Fischer's exact test; values are expressed as frequency (%).***

***x= $\chi$2 test; values are expressed as frequency (%).***

TABLE (4) Correlation of different parameters with disease activity, severity&oral ulcer activity in Behcet patients:

| Parameter | | Disease activity | Disease severity | Oral ulcer activity |
|---|---|---|---|---|
| **Age** | r | -0.36 | -0.29 | -0.43 |
| | p | 0.004** | 0.023* | 0.001** |
| **BD Duration** | r | -0.154 | -0.124 | -0.31 |
| | p | 0.241 | 0.343 | 0.02* |
| **BMI** | r | 0.032 | 0.080 | -0.045 |
| | p | 0.806 | 0.544 | 0.732 |
| **WC** | r | -0.019 | 0.015 | -0.177 |
| | p | 0.886 | 0.910 | 0.177 |
| **SBP** | r | 0.037 | 0.081 | -0.159 |
| | p | 0.781 | 0.539 | 0.225 |
| **DBP** | r | -0.038 | 0.035 | -0.032 |
| | p | 0.774 | 0.792 | 0.807 |
| **FPG** | r | 0.053 | 0.027 | 0.242 |
| | p | 0.689 | 0.837 | 0.063 |
| **Fasting Insulin** | r | 0.728 | 0.664 | 0.307 |
| | p | 0.000** | 0.000** | 0.017* |
| **HOMA-IR** | r | 0.681 | 0.620 | 0.241 |
| | p | 0.000** | 0.000** | 0.063 |
| **TC** | r | 0.305 | 0.360 | -0.024 |
| | p | 0.018* | 0.005** | 0.853 |
| **TGs** | r | 0.586 | 0.594 | 0.321 |
| | p | 0.000** | 0.000** | 0.013* |
| **HDL-c** | r | -0.431 | -0.511 | -0.057 |
| | p | 0.001** | 0.000** | 0.667 |
| **LDL-c** | r | 0.294 | 0.373 | -0.082 |
| | p | 0.023* | 0.003** | 0.534 |
| **IL-6** | r | 0.511 | 0.519 | -0.026 |
| | p | 0.000** | 0.000** | 0.844 |
| **hsCRP** | r | 0.555 | 0.632 | 0.190 |
| | p | 0.000** | 0.000** | 0.145 |

***** Correlation is significant at the 0.01 level (2-tailed).***

**** Correlation is significant at the 0.05 level (2-tailed).***

## DISCUSSION

Behçet's disease (BD) is a chronic multisystemic vasculitis of unknown etiology. It is presumed that BD is caused by Th1 type lymphocytes leading to cytokines secretion and neutrophil chemotaxis. Increased expressions of pro-inflammatory cytokines as IL-2, IL-6, IL-8, and TNF-α in BD, propose a crucial function of these cytokines in the pathogenesis of the disease. [3-6]

The effect of pro-inflammatory cytokines in the occurrence of insulin resistance, Met S, and atherosclerosis is well- investigated. [15] On the other hand, the role of obesity in the occurrence of Met S and inflammation has been discussed and it is caused by adipocytokines. Moreover, patients with rheumatic inflammatory diseases because of limited physical activity and their use of drugs as glucocorticoids that lead to obesity might be liable to develop metabolic syndrome (Met S). [16]

In this study, the prevalence of Met S in sixty BD patients was 30%, while in control group was 16.6 %. This result was in agreement with Yalcin et al. 2013 who found that the prevalence of Met S in BD patients and the control group was 35.4% and 20%; respectively. [8] However, Nakhjavani et al detected lower prevalence of Met S in Behçet patients (25.5%), they did not include a control group in their study design. [9] Another study conducted on SLE also detected lower prevalence of Met S (18%).[6]

In our study, the prevalence of Met S in BD and control among females (33.3% and 35.2%) were higher than the prevalence among males (28.5% and 9.3%). This finding is in contradiction with the results of Nakhjavani study that detected the increased prevalence of Met S in male Behçet patients (24.4%) than in female patients (28.6%). [9] Other studies detected higher Met S prevalence in females than males in Behcet patients [8], and in general populations.[17] The higher prevalence of Met S among females can be explained by several factors specific to women as pregnancy-related weight gain, use of hormonal

contraceptives, polycystic ovary syndrome, gestational diabetes, preeclampsia and eventually menopause that can impact the characteristics of the metabolic syndrome in women. [17]

Our data exhibited that in BD patients; fasting plasma glucose, plasma insulin level, and HOMA-IR were found to be significantly higher than those in the control group. The increased insulin resistance in BD patients can be explained by the presence of higher serum pro-inflammatory IL-6 level and hs-CRP. Insulin resistance and altered glucose metabolism were closely associated with inflammatory markers as leukocyte count, CRP, and fibrinogen level [18]. IL-6 was suggested to increase insulin resistance in diabetic patients with Met S [19]. These findings supposed that low-grade chronic inflammation produced by systemic proinflammatory cytokines triggers insulin resistance and furthermore leads to the occurrence of Met S.

In this study, BMI of both study groups was not significantly different, making the detected increased FPG, plasma insulin level, and HOMA-IR in BD patients than control group reliable measures. This result was consistent with the results of Erdem et al.[20], Oğuz et al.[21], and Kim et al.[22] who detected increased incidence of insulin resistance in patients with BD as compared with the control group; however, in Oğuz study, BMI values were significantly different in both groups which makes it an unreliable comparison. Moreover, Sahin study [23] detected higher HOMA-IR values in one control subject and in four BD patients, however, there was insignificant difference between the two groups.

In our study, HOMA-IR values were not correlated with BD activity and severity. This was not in agreement with Kim et al [24], and Sahin et al, 2012 who found that HOMA-IR measurements were significantly different between inactive and active patients. [23]

In the present study, one of the major pro-inflammatory (IL-6) was detected to be higher in serum of patients with BD than healthy controls and was correlated with disease severity and activity. This result goes in line with another study that detected higher CSF IL-6 level in patients with neurological Behçet disease than controls. It has been shown that cytokines make a pivotal role in pathogenesis of BD as IL-6 has a crucial role in antibody production by B-cells, and T-cell and macrophage differentiation. [3] Increased interleukin-6 level has been also shown in patients with neuro-Behcet. [4] IL-6 level was significantly different between active, inactive BD and control subjects, thus, it appears to be related to disease activity. [24]

Among the important risk factors for atherosclerotic cardiovascular disease are higher hs-CRP and dyslipidemia. CRP is believed to be a major systemic indicator of inflammation and participates in endothelial dysfunction. [25] Our results revealed that CRP levels were higher in Behçet's patients compared to those in the control group and were correlated with disease severity and activity. Similar results were obtained by Kose et al. [26] and Sahin et al study [23]; serum CRP levels were found higher in Behçet's patients compared to the control group. Moreover, higher CRP levels were detected in active BD cases in Kose et al study. [26] In contrast, Gullu et al. [27] study showed similar serum hsCRP levels in Behçet's patients and controls.

Our study exhibited higher TGs in male Behçet patients than controls, however, TC, HDL-c, and LDL were similar in both BD and control groups according to gender. Sahin study [23] , and found that serum levels of TC, TGs, HDL-c, and LDL-c were similar in both groups. In addition, Yalcin [8] showed no significant differences in lipid profiles between Behçet and control group according to gender.

BD patients with Met S showed statistically significant higher disease activity and severity. Moreover, TC, TGs, HDL-c, and LDL-c measurements of Met S were positively correlated with disease severity and activity. These findings were inconsistent with Nakhjavani and his collaborators who detected no differences in disease

activity among Behçet patients with and without Met S. [9]

For the explanation of higher disease severity and activity in Behçet patients with Met S, it is not clear whether an increased Behçet activity is a factor in the development of Met S or whether Met S is contributing to disease activity. Inflammation is not only a triggering factor of the Met S but also a consequence. In this study, patients with Met S showed statistically significant higher levels of IL-6, hsCRP. The adipocyte secretes several bioactive molecules such as leptin, TNF-α, IL-6, adiponectin, resistin, and others. [28] Insulin resistance was closely associated with many inflammatory markers as leukocyte count, fibrinogen level, and CRP [18], and their chronic elevation may directly affect aspects of beta-cell function, including insulin synthesis and secretion, insulin cell survival and apoptosis [29], decreased glucose uptake in the muscle, increased glucose formation by the liver and, therefore decreased glucose tolerance. [30] Furthermore, it is thought that increased circulating adipocytokines such as TNF-α, IL-6, leptin, resistin, plasminogen activator inhibitor-1, and acute-phase reactants such as C-reactive protein could have an important role in the development of Met S and/or its components in SLE patients. [31]

However, Met S seems to be more prevalent in Behcet disease patients than controls, several important limitations of this cross sectional study are present. First, this study is a cross sectional study measuring only the prevalence of Met S among BD patients and did not evaluate whether exercise, diet-induced weight loss, and using drugs for decreasing serum cholesterol and LDL may improve the incidence of Met S among this category of patients. Second, the sample size is too small. Thus, larger prospective multicenter studies are needed to confirm this finding in different populations and to find out if exercise, diet-induced weight loss, and using drugs for decreasing serum cholesterol and LDL may improve the incidence of Met S by raising glucose tolerance, lowering insulin resistance, and lowering blood pressure.

## CONCLUSIONS

BD male patients are more susceptible to develop Met S compared with controls. Moreover, females in general were more prone to develop Met S. On the other hand, the BD severity and activity were positively correlated with fasting insulin, HOMA-IR, and lipid profile. Thus, BD patients, specially females, should be encouraged to follow a healthier lifestyle, as choosing healthy food, decreased calorie intake and more exercise and physical activity. All BD patients should be followed up regularly for diabetes mellitus, hyperlipidemia, and hypertension to prevent Met S development.

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