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Research Article

Circulating sTWEAK and its scavenger receptor sCD163 concentrations in patients with Behçet's disease

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Abstract

Objectives: Behçet's disease (BD) is a chronic multisystemic inflammatory disorder and is associated with many inflammatory processes. The present study aimed to examine the serum levels of proinflammatory cytokine soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) and its scavenger receptor soluble cluster of differentiation 163 (sCD163) simultaneously in patients with BD by considering their relationships with disease activity.

Methods: The study group included 53 patients with BD (29 females and 24 males) and 30 healthy individuals. Patients with a lesion or active organ involvement were defined as active (n=39) and those without were identified as inactive (n=14). Serum sTWEAK and sCD163 concentrations were determined by enzyme-linked immunosorbent assay.

Results: Serum sTWEAK and sCD163 levels were significantly increased in patients with BD compared with the healthy group (p=0.016 and p=0.003, respectively). Concentrations of these two molecules were also higher in active and inactive BD than the healthy individuals (p=0.043 for sTWEAK and p=0.010 for sCD163). Receiver operating characteristic curve analysis revealed that serum sCD163 and sTWEAK levels had a discriminating ability between patients with BD and healthy controls with area under the curve values of 0.706 and 0.661, respectively.

Conclusion: It was concluded that circulating sTWEAK and its scavenger receptor sCD163 levels were increased in BD, significantly predicted the disease, and might be significant molecules to assess inflammation.

Keywords: Apo3 ligand, BD, cytokines, inflammation, scavenger receptor cysteine-rich class B

Behçet's disease (BD) is a chronic multisystemic inflammatory disorder with major clinical manifestations including recurrent oral and genital aphthous ulcerations and eye and skin lesions [1]. BD shares some common features with autoinflammatory and autoimmune diseases and MHC-I-opathy [2]. Although its etiology and pathogenesis are not known precisely, several triggering factors such as infectious agents and/or immunological insults may induce inflammatory attacks in genetically predisposed individuals [2, 3]. It has been thought that inflammation, which is a hallmark of BD manifestations, involves the activation of several cell types like neutrophils, B cells, a variety of T cells, and production of cytokines, chemokines, and adhesion molecules, tissue factor expression, and microparticles [4-6]. Tumor necrosis factor (TNF)-alpha, interferon-gamma, and members of the interleukin family are among the major inflammatory cytokines investigated in this context [7-10]. Proinflammatory cytokine soluble TNF-like weak inducer of apoptosis (TWEAK), which belongs to the TNF superfamily, is associated with many different inflammatory disorders [11-15].

TWEAK (30 kD, 249 aa), which is synthesized as a membrane-bound protein in the endoplasmic reticulum, is processed

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with a furin protease found in the trans-golgi transmission network and transforms into small soluble fragment sTWEAK (18 kD, 156 aa) [16, 17]. TWEAK binding to its first characterized receptor Fn14 activates different signaling pathways and stimulates many biological responses [18]. TWEAK is expressed widely in many tissues [19] and performs many different functions depending on the cell types including stimulation of cell proliferation, differentiation, migration, growth, apoptosis, proangiogenic activity, and induction of proinflammatory cytokines [17, 19]. When TWEAK binding to Fn14 induces a proinflammatory response by activating the nuclear factor kappa B (NF-κB) signal transduction system [20, 21]. Circulating sTWEAK concentrations have been determined for approximately the past 15 years, and it has been suggested that sTWEAK concentrations can be used as a novel biomarker in a wide variety of diseases [13-15, 22-28].

Cluster of differentiation 163 (CD163), a member of the scavenger receptor cysteine-rich family class B, is found on the surface of the cells of the monocyte-macrophage lineage and is another recently identified receptor for TWEAK [29-33]. It has been demonstrated that protein-protein interaction occurs between TWEAK and CD163 on the human monocyte cell surface [33]. It has been proposed that CD163 either acts as a TWEAK scavenger in pathological conditions or serves as an alternate receptor for TWEAK in cells lacking Fn14/TweakR [33]. The extracellular domain of transmembrane glycoprotein CD163 is converted by ectodomain shedding to soluble form (sCD163), which is a normal constituent of plasma, and sCD163 is present in plasma and other tissue fluids [34]. There are studies showing that serum and other body fluid concentrations of sCD163 can be used as biomarkers for pathological conditions characterized by excessive macrophage expression and activation, cancer, infectious, acute, chronic inflammatory conditions, metabolic syndrome, type 2 diabetes, coronary artery disease, atherosclerosis, and many others as reviewed in the literature [34-36].

Upon the identification of CD163 as a TWEAK scavenger receptor, TWEAK/CD163 axis has also gained importance in addition to the TWEAK/Fn14 axis in the pathogenesis of diseases. In addition, the relationship of sCD163 with sTWEAK levels can be considered a potential biomarker of inflammatory activation. Therefore, it has been thought that it would be beneficial to evaluate the serum concentrations of soluble forms of TWEAK and CD163 molecules simultaneously [37-40].

In view of the above-mentioned data, we hypothesized that the concentrations of sTWEAK and/or sCD163 could be a marker of inflammation in BD. As far as we know, there have been no studies that examine the soluble form of TWEAK and CD163 together in BD for this purpose. Therefore, it was aimed to examine the serum levels of sTWEAK and sCD163 in patients with BD and also to evaluate the relationship between the levels of these two molecules and the clinical activity of BD.

Materials and Methods

The study group included 53 patients with BD who applied to the outpatient clinic of Karadeniz Technical University Faculty of Medicine, Department of Dermatology, and 30 sex- and age-matched healthy individuals. Patients were diagnosed with BD according to the criteria of the International Study Group for Behçet's Disease [41]. The activity status of the disease in our study was evaluated using BD current activity form [42] and having at least one mucocutaneous lesion or an active organ involvement at the time of blood collection. Patients without mucocutaneous lesion or systemic complaints were identified as inactive (n=14), while those with lesion or active organ involvement were defined as active (n=39). Chronic diseases, clinical infections, and using any medication were accepted as the exclusion criteria for the healthy control group. The study protocol was approved by the Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (Submission number; 2011/7, approval date; October 10, 2011) and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before their participation in the study.

Blood samples were obtained from both BD and control groups, and serum samples were separated. Then, centrifugation was done at 3000 rpm for 10 min and stored at -80°C until further analysis. Serum C-reactive protein (CRP) levels were assigned by latex-enhanced immunonephelometric method on Siemens Dade Behring, BN II nephelometer (Marburg, Germany). CBC was detected using the automatic blood counting device Beckman Coulter STKS (Brea, CA, USA). The levels of these variables were determined after daily quality control procedures completed in the clinical biochemistry laboratory of Karadeniz Technical University Faculty of Medicine.

Serum sTWEAK and sCD163 levels were determined using enzyme-linked immunosorbent assay kits (sTWEAK from BenderMedSystems GmbH, Vienna, Austria and sCD163 from R&D Systems, Minneapolis, USA). Concentrations of variables were analyzed in line with protocols of the manufacturer and the absorbance values were measured using Molecular Devices Versamax microplate reader (CA, USA). sTWEAK and sCD163 levels were expressed in pg/mL and ng/mL, respectively.

Statistical analysis

The distribution of variables was assessed by the Shapiro-Wilk test. The data not scattered normally were expressed as median with interquartile range (IQR) [Q1-Q3] values, and mean±SD values were given for normally distributed ones. The Chi-squared test was used to analyze the gender between the groups. Pairwise comparisons were made using the Mann-Whitney U test for nonnormal distribution and the independent t-test for normal distribution. The data comparison for control, active, and inactive BD was performed using the Kruskal-Wallis test. Correlation coefficients and statistical significance were evaluated using Spearman's correlation test. Statistical analysis was performed using SPSS version 22.0 software (SPSS, Inc., Chicago, USA). Re-

ceiver operating characteristic (ROC) curves were constructed using Medcalc version 9.6.4 software (Medcalc software BVBA, Belgium) to assess the cutoff value, sensitivity, specificity, and respective area under the curves (AUCs) with 95% CI. A p-value less than 0.05 was considered statistically significant.

Results

Clinical features of patients with BD (n=53) during the whole disease duration time are presented in Table 1. Recurrent oral aphthosis was present in all patients with BD among the clinical manifestations, and most patients had other mucocutaneous involvements. More than half of the patients had ocular involvement. In addition, 75.5% of the patients were on medication therapy. The median value and the IQR of average disease duration were 5 and [2-10] years.

Demographic features, findings of blood sample analysis, serum sTWEAK, and sCD163 levels of the healthy control group, total, active, and inactive BD patients are presented in Table 2. Fifty-three patients with BD with a mean age±SD value of 35±10 years were included in this study. Of these patients, 29 were female and 24 were male individuals with a female percentage of 54.7. There were no statistically significant differences in terms of age and gender between the groups. Neutrophil counts increased significantly in patients with BD in comparison with the control group (p=0.001); however, lymphocyte counts did not vary. The neutrophil/lymphocyte ratios of patients with BD were also significantly higher than the ratio of the control groups (p=0.001). In addition, there was a significant increase in serum CRP levels of patients with BD compared with the control group (p=0.001). However, a significant difference was not found between patients with BD in the active and inactive groups at the levels of these variables.

Table 1. Clinical characteristics of Behçet's disease patients during the course of the disease

Clinical characteristics	n	%
Oral aphthosis	53	100
Genital aphthosis	45	84.9
Papulopustular eruption	36	67.9
Erythema nodosum	32	60.4
Ocular involvement	31	58.5
Vascular involvement	12	22.6
Articular involvement	3	5.7
Gastrointestinal involvement	1	1.9
Neurologic involvement	1	1.9
Epididymitis	1	1.9
Positive pathergy test	13	24.5
Treatment	40	75.5

Serum sTWEAK and sCD163 levels in total, active, and inactive patients with BD and the control group are given in Table 2 and shown Figure 1. The median sTWEAK levels of control, total, active BD, and inactive BD groups were 587, 776, 776, and 762 pg/mL, respectively. Also, median sCD163 levels of control, total, active BD, and inactive BD groups were 486, 602, 637, 545 ng/mL, respectively. The increase in the serum sTWEAK and sCD163 levels of both total and active BD patients were significant according to the control group (p=0.016 and p=0.003 for total and p=0.043 and p=0.011 for active, respectively). However, sCD163/sTWEAK ratio did not change in groups. Moreover, no statistically significant alterations were found according to clinical manifestations in serum concentrations of sTWEAK and sCD163. Furthermore, variables did not correlate with sTWEAK and sCD163 in total, active, and inactive BD patients (p>0.05).

ROC curve analysis of sTWEAK and sCD163 in patients with BD was performed to assess their potential diagnostic value for BD (Fig. 2). In addition, the curve was also generated for CRP, which is a classical clinically used inflammatory marker. AUC values of CRP, sCD163, and sTWEAK are shown in Figure 2. Serum sCD163 and sTWEAK levels had a discriminating ability between patients with BD and healthy controls with AUC val-

Table 2. Demographic features and serum variable levels in the study groups

Variables	Control (n=30)	Behçet's disease (n=53)	p*	Active Behçet's disease (n=39)	Inactive Behçet's disease (n=14)	p**
Age (min-max) (years)	38±5 (29-47)	35±10 (14-58)	0.136	35±11 (14-58)	38±9 (22-52)	0.326
Female, n (%)	14 (46.7)	29 (54.7)	0.481	21 (53.8)	8 (57.1)	0.832
Neutrophils (10^3 μL^{-1})	3.40 [2.50-4.23]	4.20 [3.40-5.40][a]	0.001	3.80 [3.10-5.83]	4.50 [4.05-5.10]	0.503
Lymphocytes (10^3 μL^{-1})	2.20 [1.90-2.50]	2.00 [1.50-2.50]	0.054	2.00 [1.50-2.53]	2.00 [1.50-2.20]	0.530
Neutrophils/lymphocytes	1.49 [1.21-1.85]	2.27 [1.65-2.94][a]	0.001	2.18 [1.64-2.95]	2.47 [2.02-2.80]	0.552
CRP (mg/dL)	0.11 [0.05-0.19]	0.45 [0.33-0.92][a]	0.001	0.45 [0.33-0.95]	0.46 [0.33-0.88]	0.787
sTWEAK (pg/mL)	587 [493-787]	776 [606-987][a]	0.016	776 [607-1000]	762 [462-986]	0.559
sCD163 (ng/mL)	486 [396-564]	602 [465-764][a]	0.003	637 [459-772]	545 [468-735]	0.468
sCD163/sTWEAK ($\times 10^3$)	0.75 [0.53-1.08]	0.77 [0.59-1.10]	0.691	0.77 [0.60-1.05]	0.89 [0.55-1.15]	0.856

Age is given as mean±SD. The remaining variables are given as median with IQR [Q1-Q3]. Statistical analyses used: independent t-test for age, Pearson's Chi-squared test for gender, and the Mann-Whitney U test for the remaining variables. [a]: Different from the control group; *: For comparison between control and BD; **: For comparison between active and inactive BD. CRP: C-reactive protein; sTWEAK: Serum tumor necrosis factor-like weak inducer of apoptosis.

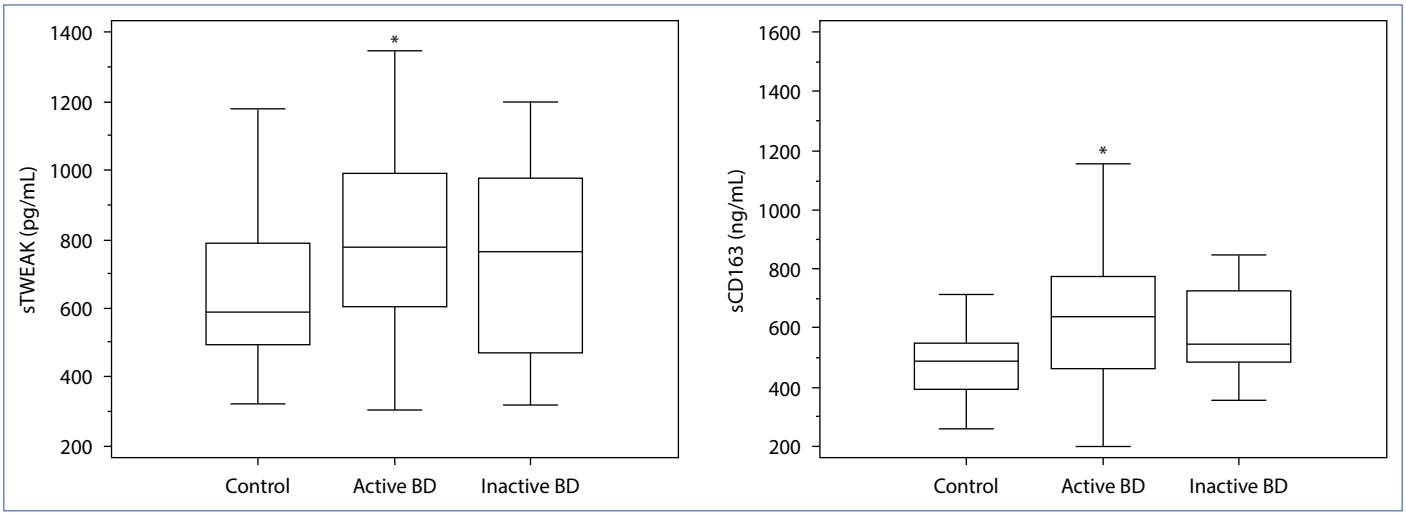
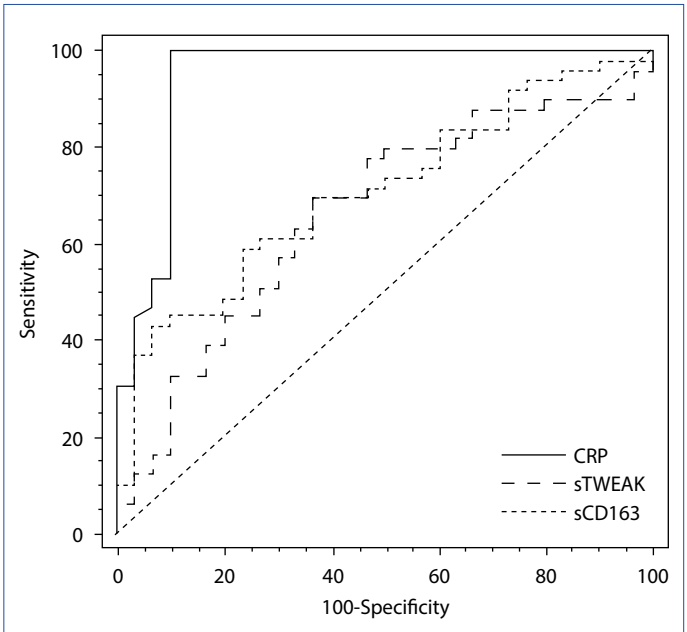


Figure 1. sTWEAK and sCD163 levels in control, active Behçet's disease, and inactive Behçet's disease groups.

Statistical analyses used: the Kruskal-Wallis test and post hoc Mann-Whitney U test. *: Significantly different from the control group, p<0.043 for sTWEAK and p<0.010 for sCD163. sTWEAK: Serum tumor necrosis factor-like weak inducer of apoptosis; BD: Behçet's disease; sCD163: Soluble cluster of differentiation 163.



	AUC	SE	95% CI	p
CRP (mg/dL)	0.943	0.0254	0.867 to 0.982	0.0001
sCD163 (ng(mL)	0.706	0.0581	0.593 to 0.803	0.0008
sTWEAK (pg/mL)	0.661	0.0614	0.545 to 0.763	0.0083

Figure 2. Recevier operating characteristic curve of CRP, sTWEAK, and sCD163 levels in patients with Behçet's disease.

CRP: C-reactive protein; sTWEAK: Serum tumor necrosis factor-like weak inducer of apoptosis; sCD163: Soluble cluster of differentiation 163.

ues of 0.706 and 0.661, respectively. However, these variables did not reach the AUC value that was observed in CRP. Moreover, serum cutoff points corresponding to the maximum of the Youden index for sCD163 and sTWEAK were 672 ng/mL (43.4% sensitivity, 93.3% specificity) and 636 pg/mL (67.9% sensitivity, 63.3% specificity), respectively.

Discussion

The primary finding of this study is increased concentrations of serum sTWEAK and sCD163 in patients with BD. Our results suggested that serum sTWEAK and sCD163 levels could distinguish patients with BD from healthy individuals. In addition, sTWEAK and sCD163 levels were observed to be high in patients with active complaints, and serum sCD163 levels increased in parallel to the clinical activity of the disease.

There are limited studies of sTWEAK in patients with BD. Icli et al. [43] evaluated the relationship between carotid artery intima-media thickness (cIMT) and serum sTWEAK levels as a marker for subclinical atherosclerosis in patients with BD [43]. They found serum sTWEAK levels higher in patients with BD than in the healthy control group. This result is in agreement with our present study, albeit no differences were observed between active and inactive patients. The reason for the increase in the serum sTWEAK level could be due to BD being a systemic inflammatory disease. Moreover, they showed a positive correlation between serum TWEAK levels and both disease activity and cIMT [43]. Study group differences mainly resulted from low heterogeneity of clinical activity of the current study may be responsible for why we could not find a relationship with disease activity.

The second main finding of the current study is that serum sCD163 concentrations were found to be significantly higher in total, active, and inactive BD patients compared with the control group, and it had the highest value in active patients (Table 2, Fig. 1). Two studies investigated the concentration of sCD163 in patients with BD. Abu El-Asrar et al. [44] analyzed the soluble cytokine receptors including sCD163 in the aqueous humor samples from patients with active uveitis associated with four systemic inflammatory diseases containing 13 male

patients with BD with the use of multiplex assays [44]. Unlike our study, they determined aqueous humor sCD163 levels and observed that aqueous humor sCD163 levels were significantly higher in all patients with active uveitis, inclusive of BD, compared with healthy controls (n=9). Based on the knowledge that sCD163 can be used as a marker for macrophage activation, they hypothesized that increased macrophage activation in active uveitis might be related to this elevation [44]. However, in another study, 25 serum cytokines including sCD163 and TWEAK were quantified simultaneously using cytokine bead arrays in 46 patients with BD and 19 healthy individuals, both of them were Caucasians of Italian origin [45]. No differences between patients with BD and the control group were observed in serum levels of sCD163 and sTWEAK. However, they did not present findings on the circulating levels of the sCD163 in active and inactive patients [45]. The current study differs from these two studies in that it is the first to demonstrate higher serum concentrations of sCD163 in patients with BD when compared with the control group. This finding is consistent with the literature. Many studies have shown that the serum sCD163 level increases in various pathological conditions other than BD, such as atherosclerosis, gaucher, hemophagocytic syndrome, macrophage activation syndrome, and rheumatoid arthritis [34-36].

Our proposal about the mechanism for the increase in the circulating amount of TWEAK and CD163 in BD is as follows: TWEAK expression is increased in BD being a systemic inflammatory disease. TWEAK exerts its proinflammatory effect by binding to the Fn14 receptor and activates the NF-κB signaling pathway. Scavenger receptor CD163 expression is increased in response to increased expression of the proinflammatory cytokine TWEAK because the receptor mediates endocytic uptake and degradation of TWEAK. It has been observed that TWEAK involves the upregulation of a disintegrin and metalloprotease ADAM17 and other sheddases in keratinocytes [46]. ADAM17 is shown to cleave CD163 ectodomain and leads to the generation of sCD163, and this shedding downregulates the surface expression of CD163 but increases the circulating levels of sCD163 [47]. The increase in both circulating TWEAK and CD163 concentrations suggests that the expression of both molecules may be increased in patients with BD. To prove this hypothesis, future studies are needed in patients with BD with a wide range of clinical manifestations.

We also determined the sCD163/sTWEAK ratio as a possible candidate biomarker in patients with BD. This is another different aspect of our research from the literature about these molecules in BD. However, sCD163/sTWEAK ratio did not change significantly in groups. Moreno et al. [30] were the first researchers to propose using the sCD163/sTWEAK ratio to assess the relationship between sTWEAK and its scavenger receptor sCD163 concentrations. In this study, it was shown that CD163 and TWEAK were expressed in the opposite direction in human carotid atherosclerotic plaques, and at the same time, sCD163 plasma level was negatively related to sTWEAK. They argued that the sCD163/sTWEAK ratio could be a potential biomarker of clinical and subclinical atherosclerosis.

To examine the diagnostic values of serum sTWEAK and sCD163 levels in BD, ROC curve was constructed. ROC curve analyses of sTWEAK and sCD163 for BD showed discriminating powers, but their values were not as good as CRP. Although CRP was a stronger discriminating ability between patients with BD and healthy controls than serum sTWEAK and sCD163 levels, the levels of CRP were not different both in active and inactive BD. While CRP, being a conventional biomarker, is commonly used to assess disease activity in daily clinical practice of BD, clinical experience has shown that this marker may not be sufficient to monitor disease activity. In fact, no diagnostic marker has been found so far to evaluate disease activity. The concentrations of sCD163 in active patients were higher than those in inactive patients in our study despite not being statistically significant. This finding suggests that sCD163 may be a potential determinant to evaluate the disease activity of BD.

The main limitation of our study are the number of inactive patients with BD and the low heterogeneity of clinical activity. The small number of the inactive patient group and the low heterogeneity of clinical activity may result in the low distinguishing power of active patients with BD from inactive patients. Also, this could be a reasonable explanation for the discrepancy of results seen in the present literature data in BD. Moreover, we could see the correlation with involvement by increasing the number. For example, it is worth noting that the sample size of patients with vascular involvement in this study was small. Determine the circulating amount of these cytokines would be useful, by increasing the number of patients with vascular involvement, as a further study.

It was concluded that circulating sTWEAK and its scavenger receptor sCD163 levels were increased in BD, significantly predicted the disease, and might be significant molecules to assess inflammation.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (No: 7, Date: 10/10/2011).

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