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ORIGINAL ARTICLE

# IL-38 serum levels in patients with Behcet's disease and the relationship with clinical features

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**ABSTRACT. Behcet's disease (BD) is a chronic multisystem autoimmune disorder. Various cytokines take part in the pathogenesis of this disease. Interleukin (IL)-38, a new member of IL-1 cytokine family, has been reported to have anti-inflammatory properties; however, its role in BD has not been investigated yet. In this study, we aimed to examine the probable role of IL-38 in the clinical context of BD. A total of 81 patients with BD and 81 age- and sex-matched healthy subjects as controls were included in this study. The serum levels of IL-38 were measured in patients and controls sera using enzyme-linked immunosorbent assay. The relationship between the serum levels of IL-38 and clinical and laboratory characteristics of the patients were determined. IL-38 serum levels were significantly lower in patients in comparison with healthy controls at P = 0.003. We found significant differences between IL-38 levels in BD patients with positive and negative pathergy tests (P = 0.048) and patients with and without eye involvement (P = 0.046). Despite the absence of significant differences in serum levels between male and female patients, IL-38 levels were higher in female patients with a positive pathergy test (P = 0.048) and those patients with eye involvement (P = 0.046). As healthy controls showed higher IL-38 serum levels than patients, a protective anti-inflammatory role of IL-38 in BD is suggested. Together, these results suggest that the positive relationship between IL-38 serum levels and eye involvement that IL-38 may play a role in this clinical feature of the disease.**

**Key words:** IL-38, Behcet's disease, autoimmune disease, cytokine

## INTRODUCTION

Behcet's disease (BD) is a chronic multisystem and auto-inflammatory disorder characterized by relapsing occurrence of oral aphthous ulcers, genital ulcers, skin and ocular lesions usually accompanied by vascular, gastrointestinal and neurological disturbances [1]. BD prevalence is more centralized in the Far East and Mediterranean basin with the highest prevalence in Turkey with 20-240 cases per 100,000 inhabitants [2]. Although etiopathogenesis of BD is not fully understood, the role of genetic susceptibility [1], bacterial and viral triggers [3] and immune-system abnormalities in the disease outbreak have been cleared [1]. A strong association between HLA-B51 inheritance and susceptibility to the disease has been reported since 1982 [4]. Furthermore, other MHC and non-MHC genes have come into consideration in this area [5].

In genetically susceptible cases, bacterial and viral infections (such as Streptococcus, Mycoplasma and Helicobacter pylori, Herpes simplex virus 1 and 2, Hepatitis virus, parvovirus B19) are considered among the main triggers of BD onset and progression [6]. Furthermore, various studies have cleared the principal role of both innate and adaptive immune responses in pathogenesis of BD; however, T cells and their cytokines are in the focus of attention. Th1 cells are supposed as the main executors of autoimmune inflammation in the BD context via secretion of cytokines such as IL-12, IL-18 and IFN-γ [7-9]. Th17 and Th22 cells also play roles in pathogenesis of the disease *via* the secretion of IL-17, IL-22 and IL-23 [9-13]. Other cytokines including IL-1, IL-6 and TNF-α are considered to be important pro-inflammatory cytokines in BD [1, 9].

IL-38, previously named as IL-1HY2, was discovered in 2001. This cytokine that is considered the tenth member of the 11-membered IL-1 cytokine family [IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-18, IL-36 receptor antagonist (IL-36Ra), IL-36α, IL-37, IL-36β, IL-36γ, IL-38 and IL-33], is expressed in numerous tissues such as heart, placenta, skin, spleen, thymus, fetal liver and proliferating B cells in the tonsil [14]. IL-38 gene is located in the IL-1 gene cluster on human chromosome 2p13, near the IL-1Ra and IL-

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36Ra genes [15]. It has been elucidated that IL-38 has 43% structural homology with IL-36Ra and 41% with IL-1Ra, *versus* significant lower homology (14-30%) with other members of IL-1 cytokine family [16]. The precise role and the biological characteristics of IL-38 have not been well characterized. However, because of its homology with IL-36Ra, it is suggested that this cytokine would function in inflammatory conditions via IL-36Ra downstream signaling pathways which is considered as nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK) inhibition [17, 18]. Along with the studies on the biological functions of IL-38, various findings about the possible role of this cytokine in inflammatory diseases have been achieved;IL-38 gene polymorphisms have been associated with rheumatoid arthritis (RA) [19], psoriatic arthritis [20], ankylosing spondylitis [21] and heart diseases [22]. On the other hand, elevated serum levels of IL-38 in patients with RA [23], systemic lupus erythematosus (SLE) [24], chronic hepatitis B [25], myocardial infarction [26], and childhood asthma compared to healthy controls have been reported [27]. Moreover, increased IL-38 mRNA levels in synovial membranes of RA patients and colons of Crohn's disease cases were detected [28, 29]. To the best of our knowledge, there is no report on the possible role of this newly identified cytokine in the pathogenesis of BD. Therefore, in the present study, we decided to measure the serum levels of IL-38 in BD patients and investigate its correlation with the clinical and paraclinical features of the patients.

## MATERIALS AND METHODS

### *Subjects*

Our study group was composed of 81patients with BD (57 females and 24 males) with mean age of 40.19 ± 10.87 years (range, 19-69 years)who referred to Motahari Outpatient Clinic, Shiraz, Iran. The disease was diagnosed by an expert rheumatologist (based on the BD criteria of Yazici, 2014) [30]. The control group consisted of 81 age- and sex-matched healthy individuals with no history of autoimmune diseases and signs of infection or other diseases. Patients' disease activity was determined based on the presence of two major symptoms at the time of blood sampling [31]. Among the patients, 18 and 63 individuals were diagnosed with active and inactive forms of the disease, respectively. Skin, eye and joint involvement was seen in 55%, 42.7% and 59.8% of the patients, respectively. Of patients, 42.1% had positive pathergy test. This test which is helpful for diagnosis of BD shows the overactivity of immune system to a minor injury by inserting a small needle into the skin and evaluating the reaction after 24 to 48 hours [4]. Informed consent approved by Ethical Committee of National Institute for Medical Research Development (NIMAD), Tehran, was obtained from all participants. The clinical and laboratory characteristics of the patients were extracted from their medical records and by a physician through asking questions (*table 1*).

**Table 1**
Demographic and characteristics of patients with Behcet's disease.

| **Patients characteristics** | |
|---|---|
| Number | 81 |
| Age (year) | 40.19 ± 10.87 |
| Gender: Female/Male | 57/24 (69.5/30.5) |
| Disease duration (month) | 107.9 ± 99.1 |
| Family history of autoimmune diseases | 12 (14.6) |
| Family history of Behcet's disease | 12 (14.6) |
| Smokers | 14 (17.1) |
| Disease activity | |
| – Active | 18 (23.2) |
| – Inactive | 63 (76.8) |
| Positive pathergy test | 24 (42.1) |
| Organ involvements | |
| – Skin | 44 (55) |
| – Eye | 35 (42.7) |
| – Joint | 49 (59.8) |
| – Renal | 10 (12.2) |
| – Vascular | 8 (9.8) |
| – Gastrointestinal | 8 (10.4) |
| – Others | 2 (2.9) |
| Laboratory data | |
| – Anti-dsDNA+ | 5 (11.6) |
| – CRP+ | 9 (13.8) |
| – ESR+ | 14 (17.2) |
| – HLA-B5 | 22 (64.7) |
| – HLA-B51 | 13 (56.5) |
| – HLA-B27 | 2 (9.1) |

Data are presented as mean ± SD, number (%). CRP: C-reactive protein (>6 mg/l as positive); ESR: erythrocyte sedimentation rate (>13 mm/h for males and >20 mm/h for females as positive); HLA: human leukocyte antigen.

### *Sample preparation*

In order to obtain the serum sample from each individual, 3 mL of whole blood was collected. After separation of the sera, they were kept at-70°C until use.

### *Enzyme-linked immunosorbent assay (ELISA) for measuring serum IL-38 levels*

The level of IL-38 in sera of the patients and healthy controls were measured using a specific ELISA kit which measured the natural human IL-38 (R&D Systems, USA, Cat. No. DY9110-05). According to the manufacturer's recommended protocol, anti-IL-38 monoclonal antibodies were precoated onto a microplate. Serum samples (100 µl) were added to each well. Afterward, 100 µl of the working solution of streptavidin-horseradish peroxidase (HRP) conjugated antibodies were added and then the substrate was added and finally stop solution. The optical density of each well was determined using a microplate reader (Biotech, USA) at 450 nm. IL-38 level of each sample was determined using a standard curve.

### *Statistical analysis*

Statistical analysis was performed using SPSS v. 25 software (SPSS, Inc., Chicago, IL, USA) and Graph

Pad Prism v.7 software (San Diego, CA, USA). Data were presented as mean ± SD. Evaluation of the differences in the serum IL-38 levels between every two groups was carried out *via* the Mann-Whitney U test. P value < 0.05 was considered statistically significant.

## RESULTS

### *IL-38 serum levels in BD patients and healthy controls*

According to the demographic data presented in Table 1, total number of 81 patients and 81 age and sex-matched healthy controls were evaluated for serum levels of IL-38. As shown in *figure 1*, the IL-38 serum levels in patients (163.0 ± 45.92pg/mL) were significantly lower than that in healthy controls (179.2 ± 63.5pg/mL, P = 0.003).

### *Relationship between IL-38 serum levels and patient characteristics*

IL-38 serum levels in patients were studied for any possible relationship with demographic, clinical and paraclinical features of the patients. As shown in *figure 2*, we found a statistically significant increase in IL-38 serum level of patients with positive pathergy test (188.9 ± 62.96pg/mL) in comparison with those with negative pathergy test (160.1 ± 37.52pg/mL) at P = 0.048.

We evaluated the probable relationship of IL-38 serum levels of patients with different organ-involvements including eye, skin, joints, renal and vascular involvement. *Figure 3* shows that, there was a statistically significant difference between patients with and without eye involvement based on their serum IL-38 levels. The serum levels of IL-38 in patients with eye involvement were 166.3 ± 34.82pg/mL compared to 161.7 ± 54.01 pg/mL in those without eye involvement (P = 0.046). We did not find any significant differences in IL-38 serum levels of patients with other organ involvements.

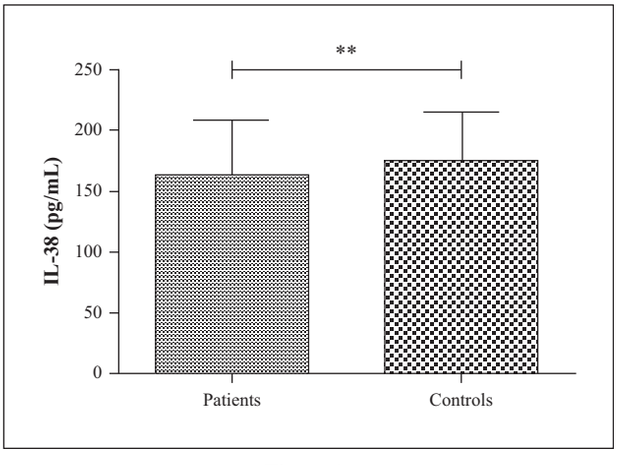


**Figure 1**
IL-38 serum levels in patients with Behcet's disease and healthy controls. Data are shown as mean ± SD. Asterisk** denotes statistical significance from normal controls. ** P < 0.01.

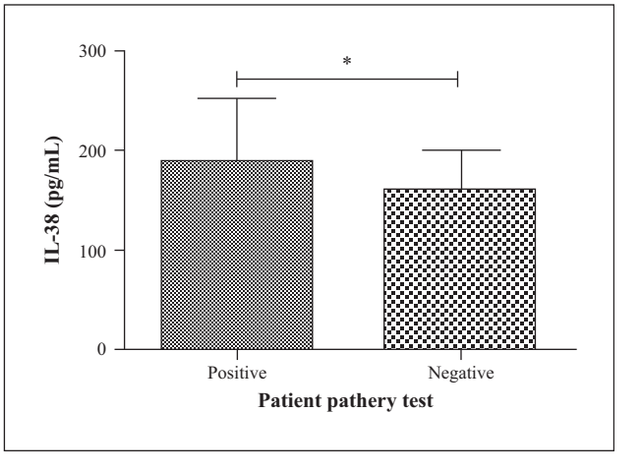


**Figure 2**
IL-38 serum levels in patients with positive and negative pathegry test. Data are represented as mean ± SD. Asterisk* denotes statistically significance.* P < 0.05.

### *Comparison of IL-38 serum levels between male and female patients*

The IL-38 serum levels in male patients (148.9 ± 27.9 pg/mL) were slightly lower than the female (169.5 ±51.03 pg/mL) patients, but the difference was not significant (P = 0.065). No significant difference in serum IL-38 levels of male (166.2 ± 22.43pg/mL) and female (177.4 ± 47.27pg/mL) controls was detected (P = 0.68).

### *Relationship between IL-38 serum levels and disease manifestations according to gender*

The serum level of IL-38 was evaluated in male and female patients for any correlation with disease characteristics. Of patients, 24 patients (16 female and 8 male) were positive for pathergy test. As shown in *figure 4*, we found a significantly higher level of IL-38 in female patients with positive pathergy test compared to those with negative pathergy test (213.2 ± 67.93 pg/mL *vs.* 160.7 ± 38.2 pg/mL, respectively, P = 0.009). Eye involvement was detected in 35

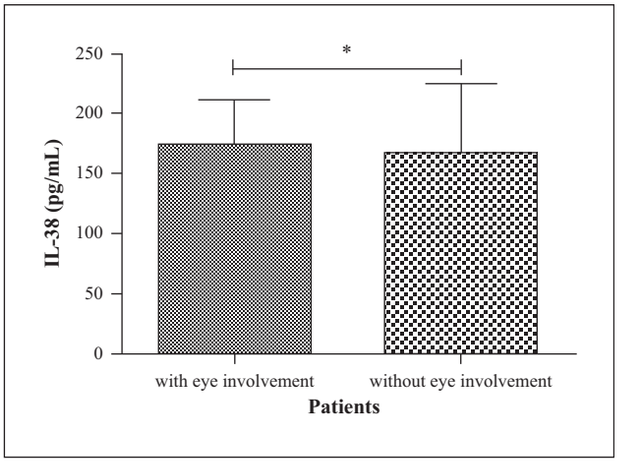


**Figure 3**
IL-38 serum levels in patients with and without eye involvement. Data are represented as mean ± SD. Asterisk* denotes statistical significance. * P < 0.05.

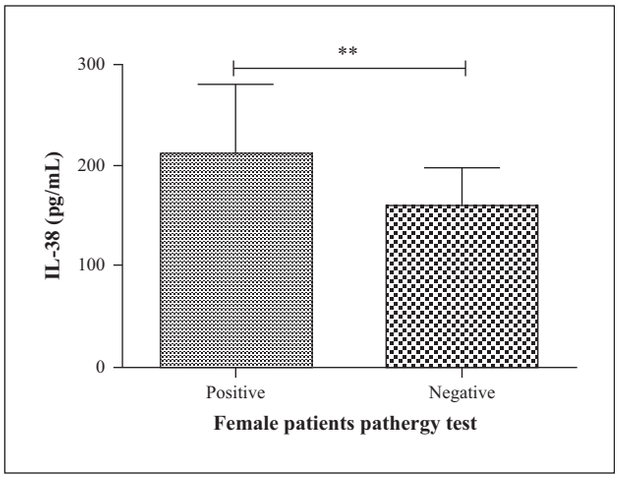


**Figure 4**
IL-38 serum levels in female BD patients with positive and negative pathegry tests. Data are represented as mean ± SD. Asterisk** denotes statistical significance. **P < 0.01.

patients (23 female and 12 male). The serum IL-38 level in female patients with eye involvement was significantly higher than that in females without this disturbance (173.6 ± 38.37 pg/mL *vs*. 166.5 ± 58.71, P= 0.048) (*figure 5*).
The data of HLA-typing in a limited number of patients was available. According to patient records, 22 of 34 patients and 2 of 22 patients were positive for HLA-B5 and HLA-27, respectively. The level of IL-38 in HLA-27-positive patients was lower than those HLA-B27 negative ones (126.6 ± 2.7*vs.* 185.5 ± 65.7, P = 0.022).

## DISCUSSION

IL-38, a member of IL-1 cytokine family, has been supposed to have anti-inflammatory properties because of its sequence homology with some inhibitors of inflammatory cytokines such as IL-36Ra and IL-1Ra [16-18]. An evidence for this effect has been reported in a study in which IL-38 inhibition of IL-17 production by *candida albicans*-stimulated peripheral blood mononuclear cells has been shown [32]. Growing evidence has cleared the role of IL-38 in inflammatory diseases of the joints such as RA [19] and ankylosing spondylitis [21]. Furthermore, the footprint of this cytokine has been found in some other disorder contexts including SLE [24], acute hepatitis B [25], myocardial infarction [26] and childhood asthma [27]. However, the probable role of IL-38 in BD has not been investigated and our study was the first one, evaluated the relationship between IL-38 cytokine and this chronic auto-inflammatory disease.
As the first step, we compared IL-38 serum level differences between patients and healthy control group. Unlike other studies reported the higher levels of this cytokine in some inflammatory diseases such as RA (23) and SLE (24), we detected lower level of IL-38 in patients sera compared to healthy subjects. Association of low level of IL-38 with BD, may suggest a protective role of IL-38 for BD which is compatible with the anti-inflammatory effects accounted for this cytokine. The differences between the levels of this cytokine in BD and other autoimmune diseases such as SLE may be attributed to the differences in the biology and pathogenesis of these diseases. Although both of these autoimmune inflammatory diseases are known to be induced by immune-regulatory defects, they have important differences. For example with SLE, there are various specific measurable antibodies such as anti-dsDNA, anti-Ro and antiphospholipid antibodies in sera of the patients, whereas with BD no known specific antibodies are detectable [33]. In BD usually the tests that are indicative of inflammation such as ESR are in the normal range, whereas in SLE low complement C3 and C4 levels often show a state of inflammation. The degree and type of ulcers and organ involvement are also different [34]. It has been suggested that immune hypersensitivity to certain antigens may trigger some of the BD manifestations [35]. T cells play a central role in the immune-pathogenesis of the disease. In a study by Shimizu et al., T cells producing IFN-γ were detected in erythema nodosum skin lesions of the patients [36]. Other studies have shown a Th1 dominance-related hypersensitivity due to loss of theTh1/Th2 balance [36]. With respect to Th17 cells, plasticity within this subset has been suggested in BD; There are IL-17 secreting cells, which express either transcription factors of regulatory T cells or of Th17 cells [37].
The second considerable difference in the IL-38 serum level that we found was in relation to the pathergy test. Various studies have focused on skin and mucocutaneous lesions as a hallmark of BD, but the specific pattern of cytokine expression in these areas has been rarely studied. The results of Shimizu et al. study (as mentioned above) and another study by Ben Ahmed et al. have shown that Th1-related cytokines, markedly IFN-γ and IL-12, are expressed in different types of mucocutaneous lesions, indicating the prominent role of Th1 in disease pathogenesis in BD [8]. However, to the best of our knowledge, the role of IL-38 in pathogenesis of skin lesions has not been studied yet. Based on our results, the expression of this cytokine is significantly higher in sera of patients with the positive pathergy test than those with the negative one.

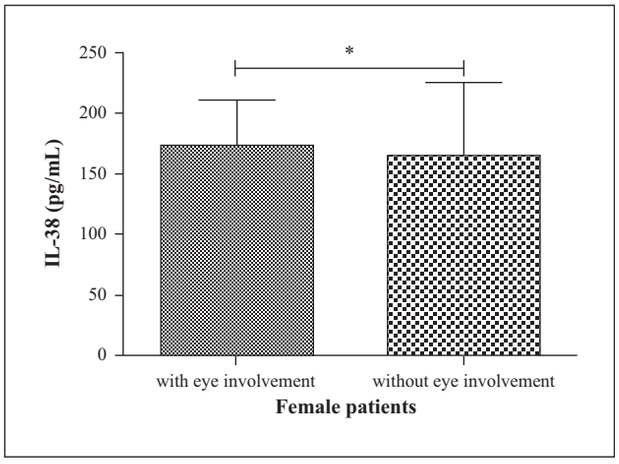


**Figure 5**
IL-38 serum levels in female BD patients with and without eye involvement. Data are represented as mean ± SD. Asterisk* denotes statistical significance.* P < 0.05.

Although the pathergy test is considered a minor criterion for BD diagnosis, it is a kind of hypersensitivity reaction. In a study by Man Chu et al. higher levels of IL-38 expression and secretion in the context of childhood asthma have been reported [27]. Moreover, several studies have considered the pathergy test as a skin reaction related to BD activity [31, 38]. In the present study, we found a positive relation between pathergy test positivity and patients disease activity ($P = 0.05$). However, IL-38 serum level did not show any association with disease activity; therefore, it is likely that IL-38 positive relation to pathergy test might be attributed to its reported raised level in hypersensitivity reactions, an issue that needs further studies.

Evaluation of the IL-38 relationship with clinical manifestations of the disease showed a significant relation of IL-38 serum level to eye involvement. These data imply that IL-38 may play a role in eye involvement in BD patients. It has been reported that the immune-pathogenesis of eye involvement in BD may be different from other autoimmune uveitis. Although the role of Th1/Th17 responses in BD uveitis has been shown by various studies [9, 39, 40], in a study by Yu et al., cytotoxic T cells have been reported as the main intraocular infiltrating cells in ocular BD [41]. Thus, the possible contribution of IL-38 with these cells and its role in ocular BD can be an interesting issue for more investigations. Moreover, BD uveitis has been associated with elevated production of reactive oxygen and nitrogen species [42]. It is possible that the presence of a positive pathergy test and ocular involvement may be marked by the activation/infiltration of phagocytes associated with the production of reactive oxygen and nitrogen species. These molecules are toxic and can lead to cell death. As IL-38 can be released from dying cells [43], the observed increase in the IL-38 level may also be associated with that phenomenon.

The relationship between IL-38 level with disease manifestations in male and female groups of patients was also studied. We found a significant difference in IL-38 serum levels in female patients with and without eye involvement, and those with positive and negative pathergy tests. We did not find this association in the male group, which may be due to the lower number of male patients.

The association of various HLA genotypes particularly HLA-B5 and HLA-B51 and in some cases HLA-B27 with BD has been reported [5, 44]. In this study, we had the result of HLA typing in a limited number of patients. The lower level of IL-38 in HLA-27-positive patients compared to that in HLA-B27-negative ones may be in favor of the IL-38 protective role in BD.

The relatively low number of patients and lack of clinical and laboratory data for all the patients were the limitations of this study.

As a conclusion, we should notify that our findings are in parallel with evidence about the probable anti-inflammatory role for IL-38. Although further studies are needed to firmly establish the anti-inflammatory action of IL-38, our results contribute to the elucidation of the exact role of IL-38 cytokine in the context of this chronic autoimmune disease.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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