Behçet’s syndrome and relationship with the ratio of insulin-like growth factor-1 (IGF-1)/IGF-binding protein-3 (IGFBP-3)

Özlem Doğan¹, Emine Ünal², Üçler Kisa³, Nurkan Aksoy⁴

¹Department of Biochemistry, Medical School, Ankara University, Ankara, Turkey
²Department of Dermatology, Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Ankara, Turkey
³Department of Biochemistry, Medical School, Kırıkkale University, Kırıkkale, Turkey
⁴Department of Biochemistry, Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Ankara, Turkey

Abstract

Introduction: Behçet's syndrome (BS) is a chronic inflammatory disease with unknown aetiology. Insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3) have important metabolic properties such as anabolic, cytoprotective and anti-inflammatory effects. Circulating IGF-1 and IGF-1/IGFBP-3 concentrations are associated with adiposity and insulin resistance.

Aim: To determine whether serum IGF-1 and IGFBP-3 levels or IGF-1/IGFBP-3 ratio were associated with the presence or activity of BS.

Material and methods: Forty patients with BS (mean age: 39.6 ±10), and 20 healthy volunteers (mean age: 37 ±10.4) were enrolled. Serum IGF-1, IGFBP-3, and high sensitive C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR) levels were measured in all subjects.

Results: Mean IGF-1 levels were low in both active BS and remission BS compared to the control group and mean IGF-1 levels were similar in active BS and remission BS. In active BS, mean IGFBP-3 levels were higher than in the control group and remission BS. There were positive correlations between these inflammatory cytokines and IGFBP-3 levels. IGF-1/IGFBP-3 ratio was lower in patients with BS compared to the healthy volunteer group, which was statistically significant. IGF-1/IGFBP-3 ratio was lower in BS than in the control group independently of ESR and hs-CRP.

Conclusions: IGF-1 may play a diagnostic role to present itself in BS. IGF-1/IGFBP-3 ratio is not useful as an activation or remission criterion. The ratio may be a useful marker to predict the risk of BS presence in the critical population.

Key words: Behçet’s syndrome, insulin like growth factor-1, IGF-binding protein-3, inflammation.
Indeed important in the regulation of glucose homeostasis [11, 12]. IGF-1 and its primary binding protein IGFBP-3 have important metabolic properties such as anabolic, cytoprotective, and anti-inflammatory effects, and have a role in the apoptosis of many tumors [13–15]. IGF-1 is decreased in rheumatoid arthritis and juvenile idiopathic arthritis because its synthesis is inhibited by inflammation [16]. IGFBPs may present biological functions with IGF-dependent and IGF-independent action. The underlying mechanisms mediating these biological actions of IGFBPs are largely unknown. IGFBPs may be mediated through cell surface receptors.

The molar IGF-1/IGFBP-3 ratio as an index for IGF-1 availability is used to investigate different conditions such as predicting the ovarian cancer risk, predicting the initiation of colorectal cancer, breast cancer risk, providing additional non-invasive markers in HCV-related liver injury and insulin sensitivity in patients with type 2 diabetes, and cardiovascular events in recent studies [17–24]. IGFBP-3 may have therapeutic potential in RA [16]. It has been concluded that patients with BS exhibit peripheral insulin resistance; and this could be explained as diverse consequences of inflammation and endothelial dysfunction [6, 7, 25].

**Aim**

In the present study, we have investigated the role of IGF-1, IGFBP-3, and IGF-1/IGFBP-3 ratio in BS.

**Material and methods**

Forty patients (20 active and 20 remission criteria), who were diagnosed with BS, according to Japanese criteria were enrolled in this study. The patients were recruited from the Yıldırım Beyazıt University Yenimahalle Training and Research Hospital. Smoking and alcohol consumption, chronic disease (primary/secondary hypertension, diabetes mellitus, coronary arterial disease, heart/liver/renal failure, B12, and folic acid deficiency), history of trauma in last 15 days, acute and chronic inflammatory disease, and drug abuse were considered as exclusion criteria.

Age and sex of the patients were recorded. Physical examination was performed and BS patients were divided into 2 subgroups of active and remission. Active or remission criteria were used according to criteria defined by Bayazıt et al. Active criteria were as follows: one or more oral aphthae presented in the last week, genital aphthae presented in the last 2 weeks, erythema nodosum like skin lesions presented in the last 2 weeks, and specific eye and organ involvement in the last week [1, 2].

**Ethical status**

The approval of the Yıldırım Beyazıt University ethics committee was obtained (2017-07-02).

**Blood samples**

Blood samples were collected and separated sera were stored in –80°C until processed.

**Biochemistry analyses**

IGF-1 DRG (DRG International Inc., USA) and IGFBP-3 DiAsource (DiAsource ImmunAssays S.A, Belgium) Elisa Kit, a solid phase enzyme-linked immunoabsorbent assay based on the principle of competitive binding, were used. ESR levels were estimated using an automated method (Alifax, Padova, Italy).

**Statistical analysis**

Kolmogorov Smirnov test was used to determine, whether the distribution of continuous variables were normal or not. Levene test was used for the evaluation of the homogeneity of variances. The continuous variables were shown as mean ± SD or median (25th–75th) percentiles, and the number of cases and percentages were used for categorical data.

While the mean differences between the control and Behçet’s disease groups were compared by Student’s t test, Mann Whitney U test was applied for the comparison of data with non-normal distribution. The comparison of more than two independent groups was analysed by one-way ANOVA or Kruskal Wallis test, where appropriate. When the p-value from One-Way ANOVA or Kruskal Wallis test statistics were statistically significant, post-hoc Tukey HSD or Conover’s multiple comparison test were used to determine which group was different from others. Categorical data were evaluated by Pearson’s χ² or continuity corrected χ² test, where applicable. Degrees of association between continuous variables were evaluated by Spearman’s Rank Correlation analyses.

The continuity of the differences in laboratory measurements (i.e. IGFBP-3, IGF-1 and IGF-1/IGFBP-3) between control and patient groups was evaluated by multiple linear regression analyses after adjusting for all possible confounding factors. Any variable with a p-value of <0.10 in univariable test was accepted as a candidate for the multivariable model along with all variables with known clinical importance. Coefficient of regression and 95% confidence interval for each independent variable were also calculated.

Data analysis was performed by using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). P value of less than 0.05 was considered statistically significant.

**Results**

There were no differences between the control and BS groups as to mean age and gender distribution (p = 0.347 and p = 1.000, respectively). The mean body mass index (BMI) levels were also similar between the two groups (p = 0.249). Half of the patients had active dis-
ease and the other half were in remission. There were no statistical differences between the control group, active BS and remission BS according to average age, gender, and BMI, respectively (p = 0.642, p = 0.932, p = 0.313). These results are summarized in Table 1.

Results of blood levels belonging to active and remission Behçet’s groups and comparison with the control group are shown in Table 1.

There were no statistical differences between active and remission BS as to mean disease duration, lipid profiles, active organ involvement, and administration of therapy (p > 0.05). In the Behçet’s group, the erythrocyte sedimentation rate (ESR) and high sensitive C-reactive protein (hs-CRP) levels were statistically higher compared to the control group (p < 0.001).

The ESR levels were statistically higher in active and remission Behçet’s groups compared to the control group (p = 0.004 and p < 0.001). The ESR levels were statistically higher in active Behçet’s group compared to the remission Behçet’s group (p < 0.001). Hs-CRP levels were higher in the active Behçet’s group and the remission Behçet’s group compared to the control group (p < 0.001 and p < 0.001, respectively). Hs-CRP levels were higher in the active Behçet’s group than the remission Behçet’s group (p < 0.001). The levels of mean IGFBP3 were higher in BS than in the control group, and mean IGF-1 and molar IGF-1/IGFBP3 ratio was lower in BS in a statistically significant manner compared to the control group (p < 0.001).

In Figure 1, IGF-1 and IGFBP-3 levels in control and active-remission BS groups are given.

**IGF-1 levels**

Mean IGF-1 levels were low in both active BS (p < 0.001) and remission BS (p = 0.030), compared to the control group (Figure 1) and mean IGF-1 levels were similar between active BS and remission BS (p = 0.467).

IGF-1 levels were lower than the healthy controls both in the active BS (B = –168.546, 95% CI: –300.120 – –36.972 and p = 0.013) and the remissions BS (B = –107.475, 95% CI: –192.580 – –22.370 and p = 0.014) that IGF-1 level was an independent factor in BS of both ESR and hs-CRP (B = –108.98, 95% CI: –193.508 – –22.687 and p = 0.014) (Tables 2, 3).

**IGFBP-3 levels**

The levels of mean IGFBP3 were not statistically different between the control group and the remission group of BS (p = 0.453). In active BS, mean IGFBP-3 levels were higher in active BS (B = –168.546, 95% CI: –300.120 – –36.972 and p = 0.013) and the remissions BS (B = –107.475, 95% CI: –192.580 – –22.370 and p = 0.014).

The ESR levels were statistically higher in active and remission Behçet’s groups compared to the control group (p = 0.004 and p < 0.001). The ESR levels were statistically higher in active Behçet’s group compared to the remission Behçet’s group (p < 0.001). Hs-CRP levels were higher in the active Behçet’s group and the remission Behçet’s group compared to the control group (p < 0.001 and p < 0.001, respectively). Hs-CRP levels were higher in the active Behçet’s group than the remission Behçet’s group (p < 0.001). The levels of mean IGFBP3 were higher in BS than in the control group, and mean IGF-1 and molar IGF-1/IGFBP3 ratio was lower in BS in a statistically significant manner compared to the control group (p < 0.001).

In Figure 1, IGF-1 and IGFBP-3 levels in control and active-remission BS groups are given.

Table 1. Clinic (ESR, hs-CRP, IGF-1, IGFBP-3, IGF-1/IGFBP-3 values for all groups) and demographic values of all groups

| Parameter            | Controls (n = 20) | Patients (n = 40) | P-valuea | Remission (n = 20) | Active (n = 20) | P-valueb |
|----------------------|------------------|------------------|----------|-------------------|----------------|----------|
| Age [years]          | 37.0 ±10.4       | 39.6 ±10.0       | 0.347    | 39.4 ±10.0        | 39.8 ±10.2     | 0.642    |
| Female gender        | 12 (60.0%)       | 25 (62.5%)       | 1.000    | 13 (65.0%)        | 12 (60.0%)     | 0.932    |
| BMI [kg/m$^2$]       | 25.8 ±3.7        | 27.1 ±4.2        | 0.249    | 26.5 ±4.2         | 27.8 ±4.3      | 0.313    |
| Duration of disease  | –                | 60.0 (36.0–148.5)| –        | 84.0 (37.0–192.0) | 54.0 (18.7–114.0)| 0.114    |
| [months]             |                  |                  |          |                   |                |          |
| Organ involvement    | –                | 25 (62.5%)       | –        | 10 (50.0%)        | 15 (75.0%)     | 0.191    |
| Treatment receiving  | –                | 30 (75.0%)       | –        | 13 (65.0%)        | 17 (85.0%)     | 0.273    |
| ESR                  | 7.6 ±5.3$^{A,B}$ | 24.0 ±11.4       | < 0.001  | 15.3 ±8.2$^{C}$  | 30.7 ±9.7$^{C}$| < 0.001  |
| hs-CRP               | 0.83 ±0.14$^{A,B}$ | 3.66 ±1.3        | < 0.001  | 3.32 ±1.1$^{C}$  | 5.77 ±1.2$^{C}$| < 0.001  |
| IGFBP-3              | 2427.4 ±431.1$^{A}$ | 3044.1 ±961.4   | < 0.001  | 2729.4 ±513.0$^{C}$ | 3358.9 ±1193.9$^{B,C}$ | 0.002 |
| IGF-1                | 404.0 ±106.3$^{A,B}$ | 285.3 ±122.3    | < 0.001  | 307.2 ±109.8$^{A}$ | 263.4 ±132.8$^{B}$ | < 0.001  |
| IGF-1/IGFBP-3        | 0.17 ±0.063$^{A,B}$ | 0.10 ±0.046     | < 0.001  | 0.12 ±0.041$^{A}$ | 0.08 ±0.047$^{A}$ | < 0.001  |

*aThe comparison between the control and patient group, bthe comparison among the control, remission and active disease groups, ccontrol vs. remission (p < 0.05), dcontrol vs. active (p < 0.001), remission vs. active (p < 0.05). ESR – erythrocyte sedimentation rate, hs-CRP – high sensitive C-reactive protein, IGFBP-3 – insulin-like growth factor binding protein-3, IGF-1 – insulin-like growth factor-1, IGF-1/IGFBP-3 – insulin-like growth factor-1/insulin-like growth factor binding protein-3 ratio.*
were statistically higher than in the control group and the remission BS \( (p < 0.001) \) and the remission BS \( (p = 0.014) \) (Figure 1). There was a statistical and positive correlation between levels of ESR and IGFBP-3 \( (r = 0.440 \) and \( p < 0.001) \) and there were similar correlations between the hs-CRP levels and IGFBP-3 levels \( (r = 0.430 \) and \( p < 0.001) \) (Table 4).

IGFBP-3 levels were not a useful marker for predicting the activation and remission of BS according to multiple linear regression analyses after being adjusted for all possible confounding factors \( (p = 0.631 \) and \( p = 0.221) \).

IGF-1/IGFBP-3 ratio

According to the control group, mean IGF-1/IGFBP-3 levels were lower in the active BS \( (p < 0.001) \) and the remission BS \( (p = 0.002) \), and mean IGF-1/IGFBP-3 levels were similar between the active BS and the remission BS \( (p = 0.146) \). IGF-1/IGFBP-3 ratio was a predictive factor for BS and it was an independent factor in BS both in inactive \( (B = 0.056, 95\% \text{ CI: } -0.094 \rightarrow -0.018 \) and \( p = 0.004) \) and active patients \( (B = 0.086, 95\% \text{ CI: } -0.144 \rightarrow -0.028 \) and \( p = 0.005) \). IGF-1/IGFBP-3 ratio was lower in BS than in the control group and it was an independent factor with respect to ESR and hs-CRP \( (B = -0.056, 95\% \text{ CI: } -0.094 \rightarrow -0.018 \) and \( p = 0.004) \) (Table 3).

There were no differences with regard to sex, BS treatment, and systemic organ involvement in the levels of IGFBP3 and IGF-1, and IGF-1/IGFBP-3 ratio \( (p > 0.05) \) as shown in Table 5.

Discussion

Behçet’s syndrome is a chronic recurrent systemic inflammatory disease. The symptoms are observed concurrently or in different time periods. The site and timing of activation periods could not be predicted. Behçet’s syn-
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Table 5. IGF-1, IGFBP-3 and IGF-1/IGFBP-3 levels according to gender, organ involvement and treatment receiving

| Parameter                     | N   | IGF-1       | IGFBP-3    | IGF-1/IGFBP-3 |
|-------------------------------|-----|-------------|------------|---------------|
| Gender:                       |     |             |            |               |
| Female                        | 37  | 318.2 ±137.4| 2973.1 ±983.0| 0.12 ±0.064   |
| Male                          | 23  | 335.6 ±117.2| 2622.1 ±607.3| 0.14 ±0.059   |
| P-value                       | 0.616| 0.130       | 0.246      |               |
| Organ involvement:            |     |             |            |               |
| No                            | 15  | 273.7 ±110.9| 2725.7 ±555.2| 0.11 ±0.044   |
| Yes                           | 25  | 292.3 ±130.4| 3235.2 ±1104.8| 0.10 ±0.048   |
| P-value                       | 0.648| 0.105       | 0.619      |               |
| Treatment receiving:          |     |             |            |               |
| No                            | 10  | 272.4 ±123.4| 2779.8 ±602.8| 0.10 ±0.044   |
| Yes                           | 30  | 289.6 ±123.8| 3132.3 ±1047.8| 0.10 ±0.048   |
| P-value                       | 0.705| 0.322       | 0.965      |               |

IGFBP-3 levels were associated with a shorter stature. These findings are consistent with a model of inflammation driving hepatic resistance to GH signalling as noted in preclinical studies. Similarly, reduction in serum IGF-1 by dietary restriction in animal models slows tumour progression and increases apoptosis in tumour cell effects that are both reversed by infusions of recombinant IGF-1 [15].

IGF-1 levels were lower in BS and it was an independent factor of ESR and hs-CRP (a diagnostic predictive factor) (B = −108.098, 95% CI: −193.508 – −22.687 and p = 0.014).

There was an increase in inflammatory markers such as ESR and hs-CRP in both the active and the remission patients. In active patients, these levels were also higher than in the remission patients as expected. There was a positive correlation between these inflammatory cytokines and IGFBP-3 levels, respectively (ESR r = 0.44, p < 0.001), and hs-CRP (r = 0.43 and p < 0.001). There was a statistically significant negative correlation between IGF-1 and ESR (r = −0.291 and p = 0.024) and there was no statistically significant correlation between IGF-1 and hs-CRP (p > 0.05). During the regression analyses, it was found that the levels of IGF-1 were lower in BS and independent of ESR and hs-CRP (B = −108.098, 95% CI: −193.508 – −22.687 and p = 0.014). The reason may be that the levels of ESR and hs-CRP increase in BS, and these inflammatory markers directly induce (not affect IGF-1) the production of IGFBP-3. Subsequently, IGFBP-3 binds to the free IGF-1 and the level of IGF-1 decreases in the bloodstream. Another mechanism may be due to insulin resistance in BS. IGFBP-3 may be mediated by an unknown trigger through impaired cell surface re-

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ceptors in BS. Insulin also up-regulates IGFBP-3 levels, as known. Otherwise, it may be an unknown immunological mechanism.

In active BS, mean IGFBP-3 levels were statistically higher than in the control group and the remission BS (ρ < 0.001 and p = 0.038, respectively). The levels of mean IGFBP-3 were not statistically different (were similar) between the control group and the remission group of BS (ρ = 0.453). In the active BS, inflammatory markers such as IL-1, TNF-α, TGF-β1 were increased, as known, and this inflammatory response might induce the production of IGFBP-3 and its subsequent increase. Therefore, the levels of IGF-1 may decrease in the bloodstream. Nevertheless, during the regression analyses, the effects of IGFBP-3 were not statistically different in the active (p = 0.221) and the remission BS (p = 0.631). IGF-1 levels were lower than in the healthy controls and IGFBP-1 was an independent factor in BS for both ESR and hs-CRP, both in the active BS (B = –168.546, 95% CI: –300.120 – –36.972 and p = 0.013) and the remission BS (B = –107.475, 95% CI: –192.580 – –22.370 and p = 0.014) according to multiple linear regression analyses after being adjusted for all possible confounding factors. It may be due to inflammation in BS and possible insulin resistance that up-regulates the production of IGFBP-3 and its subsequent increase.

The findings suggest that reduced levels of IGF-1 in circulation and increased blood levels of IGFBP-3 in BS may result in suppression of its anti-inflammatory functions, and therefore IGF-1 may play a diagnostic role to present itself.

The IGF-1/IGFBP-3 ratio was lower in BS in a statistically significant manner as compared to the healthy control group, and the ratio was independent of ESR and hs-CRP.

Conclusions

We have found that the IGF-1/IGFBP-3 ratio was lower in BS and it was an independent factor of ESR and hs-CRP according to multivariate regression analyses. The IGF-1/IGFBP-3 ratio may be a useful parameter for predicting the presence of BS; however, further studies are required on this subject.

Conflict of interest

The authors declare no conflict of interest.

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