Medical Journal of Europe

ISSN: 2995-7907 doi: 10.5281/zenodo.10706940

# Interleukin-27 in Takayasu Arteritis: Serum Levels and Relationship with Disease Activity

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**Article Info**

Received: 20 February 2024

Accepted: 22 February 2024

Published: 26 February 2024

**Keywords:**

Takayasu, IL-27, inflammation, vasculitis.

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**ABSTRACT**

This study aimed to investigate the serum levels of interleukin-27 (IL-27) in patients with Takayasu arteritis (TA) and evaluate its role in determining disease activity. A total of 34 patients with TA (32 female, 2 male) and 34 healthy controls (32 female, 2 male) were enrolled. Patients with TA were divided into two groups: active and inactive, according to Kerr scores. Twenty-one patients were in active group (mean age; 27.1 ± 6.9 years, mean disease duration 7.2±2.8 years) and 13 patients were in inactive group (mean age; 32.7 ± 5.3 years, mean disease duration; 8.7±4.1 years). Serum IL-27 levels were determined by ELISA. The mean serum IL-27 levels were 19.7±4.8 pg/ml in healthy controls, 128.3±11.7 pg/ml in active group, and 45.2±9.5 pg/ml in inactive group. Serum IL-27 levels in patients with TA were significantly higher than in healthy controls ($p<0.001$). Serum IL-27 levels were significantly higher in active group compared with inactive group ($p<0.001$). Both in active and inactive groups, there was a statistically significant correlation between serum IL-27 and serum CRP and ESR ($r=0.588$, $p<0.001$, $r=0.503$, $p<0.001$ and $r=0.474$, $p<0.01$, $r=0.446$, $p<0.01$, respectively). Biomarker studies in TA are mainly focused on differentiating active stage from inactive stage. The serum level of IL-27 may be a potential biomarker, which is associated with disease activity in patients with TA.

**Cite as:** Altıner S, Çolak S, Çerçi P, Inal A, Keskin K. Interleukin-27 in Takayasu Arteritis: Serum Levels and Relationship with Disease Activity. Med J Eur. 2024;2(2):41-45. doi: 10.5281/zenodo.10706940

## INTRODUCTION

Takayasu arteritis (TA) is a chronic idiopathic inflammatory and obliterative granulomatous arteritis characterized by large-vessel vasculitis affecting the aorta and its major branches (1). TA occurs most commonly in young females and is more common among Asian populations. The mean age at diagnosis is between 20 and 30 years. The incidence of the disease is reported between 1-2 per million in Japan and 0.4-1.5 per million in Europe (2-4).

The pathogenesis of TA is poorly understood. Cell-mediated mechanisms involving T cells and antigen-presenting cells take part in TA and there is no role of autoantibodies. Several studies have demonstrated an association with human leukocyte antigens, suggesting a genetic predisposition for the immune-mediated process1. Histopathologically granulomatous inflammation has been observed in the media and mononuclear cells and giant cells are present in the media-intima border (5,6).

IL-27 is a member of the IL-6/IL-12 family of cytokines composed of Epstein-Barr virusinduced gene 3 (EBi3) and IL-27p28 heterodimers. IL-27 receptor (IL-27R) comprises two chains, IL-27Rα (WSX-1) and gp130 which are expressed by a large variety of immune and non-immune cells (7). Upon secretion by activated antigen-presenting cells, IL-27 has both pro and anti-inflammatory properties because of its shared receptors. IL-27 has proinflammatory effects by Jak/STAT signaling which promotes the expansion of naive CD4+ T cells and drives Th1 differentiation. IL-27R signaling promotes IFN-γ production, the key inflammatory mediator in autoimmune disorders, by induction of T-bet, a Th-1 specific transcription factor. IL-27 has also been shown to act as a negative regulator of ongoing autoimmune inflammation via inhibiting pro-

inflammatory Th17 cells by different STAT 1signaling pathways (8-10).

Despite correlation between TA and serum/plasma levels of cytokines being less clear, higher IL-6 serum levels and association with disease activity in TA is reported in many studies (11-13). But there are no studies examining the relationship between TA and IL-27 in the literature. The assessment of IL-27 may provide a better understanding of its pathophysiology and circulating levels of IL-27 may act as biomarker of disease activity. Therefore, the aim of the study was to investigate the serum IL-27 levels in patients with TA compared to healthy controls (HC). Also, we aimed to investigate the utility of serum IL-27 in order to assess disease activity in patients with TA.

## METHODS

Thirty-four patients with TA (32 female, 2 male; mean age 29.9 ± 6.1 years, mean disease duration 7.9 ± 3.4 years) were enrolled in this study. Thirty-four age and sex matched healthy persons (32 female, 2 male; mean age 29.3 ± 4.1 years) who had no acute or chronic diseases were enrolled to serve as served as HCs. The patients were attending Medical School of Ankara University and Ministry of Health Dışkapı Yıldırım Beyazıt Research and Educational Hospital, Department of Immunology. Patients were diagnosed according to the diagnostic criteria of the American College of Rheumatology 1990 criteria for the classification of Takayasu Arteritis.14 Patients with TA were divided into active and inactive groups according to Kerr scores.15 Kerr's criteria were used to define active disease when at least two criteria were positive. Also, patients were classified according to their angiographic site of involvement.16 Blood erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) and serum IL-27 levels were studied for all patients. Serum IL-27 levels were determined by ELISA.

The statistical Package for Social Sciences (SPSS) version 17.0 for windows was used to analyze the data. The Kolmogorov-Smirnov test was used to assess the assumption of normality. Normally distributed continuous variables are expressed as mean±standard deviation. In all the groups, nonparametric tests were utilized for the statistical analysis. The Kruskal-Wallis test was used to analyze the variance between the groups. P values below 0.05 were considered statistically significant.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the ethics committee of Ministry of Health Dışkapı Yıldırım Beyazıt Research and Educational Hospital, Department of Immunology. Written informed consents were obtained from all participants.

## RESULTS

Twenty-one patients had active disease (mean age; 27.1±6.9 years, mean disease duration 7.2±2.8 years) and 13 patients had inactive disease (mean age; 32.7±5.3 years, mean disease duration; 8.7±4.1 years) according to their clinical status. All inactive patients had been treated with glucocorticoids and immunosuppressive agents, but newly diagnosed active patients had no medication at the time of the study. All inactive patients were treated with corticosteroids, 10 patients received methotrexate (15–25 mg/week) and 3 patients received IV cyclophosphamide. Ten patients who did not achieve remission with corticosteroids and immunosuppressive agents were replaced by biological drugs (8 tocilizumab, 2 adalimumab, and 1 infliximab).

The mean ESR (mm/h) of active, inactive patients, and HCs were 54.3 ± 18.2, 20.7 ± 11.4, and 13.3 ± 6.6 respectively. The mean serum CRP levels (mg/dl) of active, inactive patients, and HCs were 57.3± 28.7, 14.9± 8.5, and 1.9±1.7, respectively. The mean serum IL-27 levels were 19,7 ± 4.8 pg/ml in healthy controls, 128,3 ± 11.7 pg/ml in active patients with TA and 45.2 ± 9.5 pg/ml in inactive patients with TA and 86.7 ± 10.6 pg/ml in all patients with TA (Table 1). Clinical and angiographic findings of patients are presented on Table 2.

According to these results; serum IL-27 levels in all patients with TA were significantly higher than in healthy controls ($p<0.001$). Both in active and inactive patients with TA, serum IL-27 levels were significantly higher when compared with healthy controls ($p<0.001$, $p<0.01$ respectively). Also, serum IL-27 levels were significantly higher in active patients with TA compared to inactive patients with TA ($p<0.001$) (Figure-1). In patients with active Takayasu arteritis, ESR and CRP levels were significantly higher, when compared with the healthy controls. We evaluated whether the serum IL-27 could be correlated to other serologic parameters (ESR and CRP) in patients with TA. Both in active and inactive groups, there was a statistically significant positive correlation between serum IL-27 and serum CRP and ESR ($r=0.588$, $p <0.001$, $r=0.503$, $p<0.001$ and $r=0.474$, $p<0.01$, $r=0.446$, $p<0.01$ respectively).

**Table 1**: Clinical and laboratory findings in patients with Takayasu arteritis and healthy controls.

| | All TA patients (n=34) | Active TA (n=21) | Inactive TA (n=13) | HCs (n=34) | p |
|---|---|---|---|---|---|
| ***Clinical features*** | | | | | |
| **Age*** | 29.9±6.1 | 27.1±6.9 | 32.7±5.3 | 29.3±4.1 | NS |
| **Female/Male** | 32/2 | 19/2 | 13/0 | 32/2 | NS |
| **Disease duration*** | 7.9±3.4 | 7.2±2.8 | 8.7±4.1 | - | NS |
| ***Laboratory features*** | | | | | |
| **ESR(mm/h)*** | 37.6±14.8 | 54.3±18.2 | 20.7±11.4 | 13.3±6.6 | <0.001** |
| **CRP(mg/dl)*** | 36.1±18.6 | 57.3±28.7 | 14.9±8.5 | 1.9±1.7 | <0.001** |
| **IL-27 (pg/ml) *** | 86.7±10.6 | 128.3±11.7 | 45.2±9.5 | 19.7±4.8 | <0.001** |

*:mean±standart deviation. **All patients with TA and active TA compared to HCs. TA: Takayasu arteritis, HC: Healthy control, NS: not significant, ESR: Erytrocyte sedimentation rate, CRP:C-reactive protein

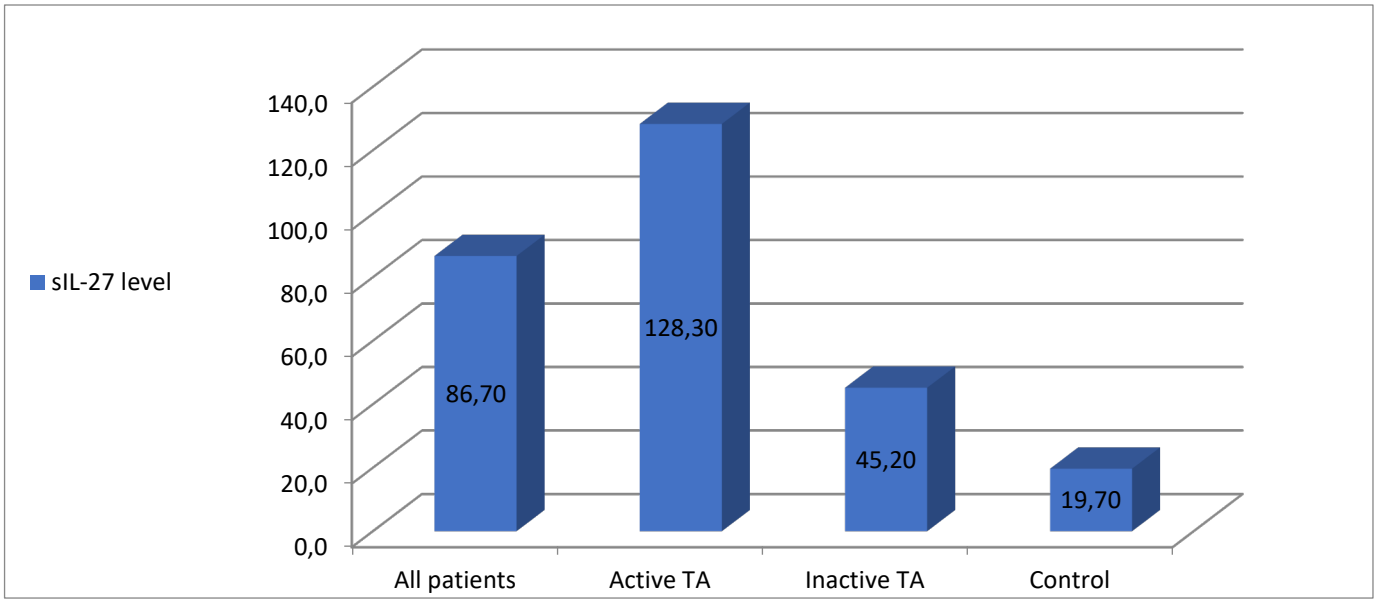


**Figure 1.** Serum IL-27 (pg/ml) levels in groups. *p<0.001 when all patients with TA and active TA compared to HC. **p<0.01 when inactive TA compared to HC. ***p<0.001 when active TA compared to inactive TA. TA: Takayasu arteritis

## DISCUSSION

In our study we found out that serum IL-27 levels were significantly higher in patients with TA compared to HCs. Also, active TA patients had higher IL-27 levels compared to inactive patients. As expected, active TA patients had higher serum CRP and ESR levels and these levels were positively correlated with serum IL-27 levels.

Associations between TA and serum levels of some cytokines are studied before. Of these, IL-6 is the main focus of proinflammatory cytokines involved in TA. Many studies have suggested that IL-6 levels were positively related to TA disease activity (11-13). This proinflammatory cytokine, mainly synthesized by activated mononuclear cells, has an important role in the Th17 pathway and contributes to vascular lesions through the recruitment of infiltrating neutrophils. Numerous case reports and a randomized trial showed that IL-6 receptor blockade with tocilizumab is effective for TA patients (14-21). IL-8 is another cytokine of interest in elucidating the pathogenesis of TA. As a potent chemoattractant and activating factor for neutrophils, IL-8 is found to be increased in patients with TA compared to healthy controls (11,22). Other than IL-6 and IL-8; IL-18 was also considered as a potential biomarker for disease activity evaluation in TA.17 Alibaz et al demonstrated that IL-18 level was significantly higher in active patients and it was correlated with CRP.11 Also, Misra et al found a significant expansion of Th17 cells and elevated serum IL-17 and IL-23 levels in TA patients compared to healthy controls (23).

Recent data strongly support the mechanism that the extravascular and vascular components of TA have independent trajectories and the acute phase response may lie downstream of arterial wall inflammation. In patients with TA, vasculitis is frequently associated with a systemic inflammatory syndrome, easily detected by acute phase response (24). On the other hand, the discordance between systemic and vascular wall inflammation may lead to normal serum ESR and CRP levels despite the active disease. Therefore, evaluating only systemic inflammation may be misleading. So, more reliable biomarkers are needed to reflect vascular wall inflammation and overall disease activity in patients with TA (17).

**Table 2**. Clinical and angiographic findings of patients with Takayasu arteritis.

| **Clinical findings (n=34)** | **n ( %** | **Angiographic findings** | **n ( %)** |
|---|---|---|---|
| Lassitude | 30 (88) | Type 1 | 14 (41) |
| Claudication | 23 (67) | Type 2a | 8 (23) |
| Carotidynia | 8 (23) | Type 2b | 10 (29) |
| Pulselessness | 22 (64 | Type 3 | 6 (17) |
| Skin manifestation | 4 (12) | Type 4 | 6 (17) |
| Respiratory system involvement | 4 (12) | Type 5 | 16 (47) |
| Neurological symptoms | 10 (29) | | |
| Cardiac/coronary involvement | 10 (29) | | |

Although limited, there are some studies examining the relationship between IL-27 and inflammatory diseases. Different studies reveal controversial results about the effect of IL-27 on experimental arthritis models and rheumatoid arthritis. IL-27 inhibits the differentiation of Th-17 cells and may suppress autoimmune arthritis (25). On the contrary, other studies support its proinflammatory effects on arthritis, and IL-27 neutralization results in suppression of inflammation (25,26). It is estimated that increased serum IL-27 levels may cause peripheral B cell dysfunction via the mTOR signaling pathway in RA patients (27). It is reported that IL-27 signaling contributes to disease development in patients with systemic sclerosis (28). Pre-disease lupus-prone mice models express higher levels of IL-27 upon stimulation. IL-27 gene expression is significantly higher in SLE patients than in healthy controls (29).

In many studies conducted in different diseases, it has been determined that serum Il-27 level may be associated with disease activity. Recently this association has been demonstrated in ANCA-associated vasculitis and Crohn's disease (30,31). In another study on the experimental Sjögren model, it was argued that IL-27 deficiency exacerbates Sjögren's Syndrome by affecting the regulation of CD4+ IL-10+ T cells (32). Gene polymorphisms of IL-27 have been studied too and some variants were found to be associated with Behcet's Disease and SLE (33,34). All these new studies point out that IL-27 has an important role in the pathogenesis of proinflammatory diseases, which has not yet been clarified.

The association between serum IL-27 levels and disease activity in Takayasu arteritis has not been studied before. Our findings show that serum IL-27 levels are significantly higher in patients with TA compared to HCs. Serum IL-27 levels were positively correlated with serum CRP and ESR levels. The data that active TA patients have higher IL-27 levels compared to inactive patients can suggest that serum IL-27 levels decreased when the patients achieved remission. But we did not measure the level of IL27 in long term follow-ups of TA patients. This makes us unable to determine the possible changes of serum levels of these cytokines in a particular TA patient over time, regarding the activity of the disease. We believe that the small sample size of our study was an important limitation. IL-27 expression is enhanced upon response to a number of stimuli including cytokines, lipopolysaccharides, infections and smoke. Another limitation of our study is that these confounding factors were not evaluated. These results suggest that serum level of IL-27 may be a potential biomarker, which is associated with disease activity in patients with TA. Further prospective studies with higher numbers of patients are needed to clarify the role of serum IL-27 levels in the pathogenesis of TA and determine the disease activity of TA.

**Acknowledgements**

The patients enrolled in this study were followed by the Author Prof. Keskin, in his previous institution named Diskapi Training and Research Hospital, which has been permanently closed. Manuscript has been written at the author's final institution, Ankara University.

**Conflicts of Interest**

None to declare.

**Financial disclosure**

The authors did not receive support from any organization for the submitted work.

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