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Original Article

Differential Expression of Visfatin, Sirtuin-1, and Interleukin-18 in Ankylosing Spondylitis Patients: A Comparative Study of Etanercept-Treated versus Newly Diagnosed Patients

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Abstract

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the axial joints. In response to inflammation, sirtuin-1 *(SIRT-1)* plays a regulatory role by modulating inflammatory signaling pathways and protecting against further tissue damage. Interleukin-18 (IL-18) is a potent pro-inflammatory cytokine released predominantly by pyroptotic immune cells. Visfatin, an adipokine secreted by lymphocytes and other immune cells, is increasingly recognized as a pro-inflammatory mediator implicated in various rheumatologic disorders. This study aimed to evaluate the expression levels of *SIRT-1, IL-18*, and visfatin genes in immune cells of AS patients.

Methods: In 2022, this cross-sectional study was conducted in Gorgan, Iran. Peripheral blood mononuclear cells (PBMCs) were isolated from a total of 49 AS patients, including patients undergoing treatment with three doses of etanercept and the newly diagnosed, treatment-naïve patients. Total RNA was extracted from PBMCs, and complementary DNA (cDNA) was synthesized. Gene expression levels of *SIRT-1*, *IL-18*, and visfatin were quantified using real-time PCR, and data were analyzed using SPSS v16 and GraphPad Prism 9 with Student's *t* test. A significant difference was considered as $P<0.05$.

Results: *SIRT-1* expression was significantly lower in newly diagnosed AS patients than in the etanercept-treated group ($P=0.041$). Visfatin expression was significantly higher in the new case group than in the treated group ($P=0.021$). Similarly, *IL-18* expression was significantly higher in new cases than in etanercept-treated patients ($P=0.028$).

Conclusion: Etanercept significantly upregulates SIRT-1 expression while suppressing IL-18 and visfatin levels in AS patients, highlighting its pleiotropic anti-inflammatory mechanisms beyond TNF-α blockade. These findings provide novel insights into the molecular pathways modulated by anti-TNF therapy, particularly the interplay between *SIRT1*-mediated epigenetic regulation and adipokine-driven inflammation.

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Keywords ● Ankylosing spondylitis ● Etanercept ● *IL-18* ● *SIRT-1* ● Visfatin

What's Known

- The visfatin, *SIRT-1*, and *IL-18* genes play important roles in maintaining cellular homeostasis under conditions of oxidative stress and inflammation.

What's New

- Etanercept significantly upregulates SIRT-1 expression while suppressing IL-18 and visfatin levels in AS patients, highlighting its pleiotropic anti-inflammatory mechanisms beyond TNF-α blockade.

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Introduction

Ankylosing spondylitis (AS) is an autoimmune disorder along with systemic inflammation that primarily affects the spine joints, such as the sacroiliac joints and adjacent soft tissues.[1] The incidence of AS is approximately 0.03–1.8% in the world.[2] Men are influenced around twice as often as women.[3] Although the main cause of this disease is still unknown, genetic and environmental factors are effective in causing this disease.[4, 5] Environmental factors could include age, gender, smoking, and infection.[6] Genetics is also important. One of the most important genetic factors is the HLA-B27 class I allele of the major histocompatibility complex (MHC) that has been associated with the prevalence of AS in different populations around the world.[1] Studies show that IL (interleukin)-23-17-IL axis and more generally type 17 immune responses have a particular connection to the pathogenesis of AS. A hyperactive IL-23-17 signaling pathway could explain both the key inflammatory aspects of the disease (including enthesitis) and the paradoxical feature of systemic bone loss with pathological bone neogenesis.[7] Since this disease is associated with inflammation, it is important to examine the genes involved in this process for its treatment.

Visfatin is an adipokine expressed and secreted by lymphocytes.[8] Visfatin also plays a role in osteoarthritis. The basal level of visfatin increases, especially in serum and synovial fluid of people with osteoarthritis.[9] In rheumatological diseases, visfatin is known as a pro-inflammatory peptide, and this pro-inflammatory marker increases in the serum level of patients with rheumatoid arthritis.[10] Sirtuins mediate the deacetylation of histone and non-histone proteins. Deacetylation of SIRT-1 affects multiple biological processes. These processes include cellular aging, apoptosis, glucose and lipid metabolism, oxidative stress, and inflammation. Even small changes in SIRT-1 expression and function can have significant effects on cellular responses.[11] Cells involved in the inflammatory response include macrophages, mast cells, and endothelial cells. Sirtuins, particularly SIRT-1, can influence the secretion of inflammatory mediators and play a central role in regulating dendritic cell differentiation and macrophage activation.[12] IL-18, a member of the IL-1 family, is a pro-inflammatory and cancer-suppressing cytokine.[13] Various cytokines, including IL-18, IL-2, IL-12, and IL-15, affect the activity of natural killer (NK) cells. Cytokines derived from NK cells and their cytotoxic function are effective in regulating immune responses through the induction of apoptosis and are involved in the pathogenesis of many diseases caused by the immune system, such as AS, rheumatoid arthritis, and others.[14]

Therefore, the importance of these genes in inflammation, the lack of comprehensive information about the expression of these genes in AS disease, and the expression of these genes in PBMC samples led to the investigation of the relationship between these three important genes in the regulation of inflammatory pathways in the present study.

Materials and Methods

Subjects and Study Protocol

This experimental study was conducted in 2022 in Gorgan, Iran. After diagnosis by a rheumatologist, blood samples were collected from women and men aged 20–60 with AS.

The sample size was obtained based on the standard deviation, according to the study by Hu[16] with a confidence level of 95% and a statistical test power of 80%. Thus, patients were divided into two groups, as described below:

Anti-tumor necrosis factor (anti-TNF) users: 25 patients in whom anti-TNF treatment is indicated, so they receive three doses of etanercept.

New cases: 24 patients in whom anti-TNF treatment is not allowed.

Exclusion criteria: Patients who are in the final stage of the disease and have developed spine bamboo, other inflammatory diseases, malignancies and cancers, and diabetic patients. Patients with AS who have received etanercept in the past. Inclusion criteria: Patients with a definitive diagnosis of AS, without other inflammatory or underlying diseases, who were receiving etanercept. In new cases, patients with a definitive diagnosis of AS, without other inflammatory or underlying diseases, and without a history of anti-TNF therapy were included in the study.

Ethics Approval

Before collecting data, the researchers obtained written informed consent from the participants.

At the first visit by the physician and after explaining the purpose and objective of the study, written informed consent was obtained from the patients. This study was approved by the Ethics Committee of Golestan University of Medical Sciences (IR.GOUMS.REC.1401.195). All procedures performed were in accordance with the principles of the Declaration of Helsinki and its later amendments (World Medical Association, 2013).[15]

Table 1: Sequence of primers used for Real-Time Polymerase Chain Reaction (RT-PCR)

Gene names	Forward primer sequences (5'→ 3')	Reverse primer sequences (5'→ 3')
SIRT1	GACGTCTTATCCTCTAGTTCTTGTGGC	ATCATCTCCATCAGTCCCAAATCCAGC
Visfatin	GGTTCTTGGTGGAGGTTTGCTAC	GAAGACGTTAATCCCAAGGCC
IL18	GATAGCCAGCCTAGAGGTATGG	CCTTGATGTTATCAGGAGGATTCA
GAPDH	5′- GGGAAGGTGAAGGTCGGAGT-3′	TCCACTTTACCAGAGTTAAAAGCAG

Table 2: Demographic characteristics of ankylosing spondylitis patients

Characteristics		Anti-TNF group (n=25)	New case group (n=24)	P value
Age (years, mean±SD)		43.1±8.3	42.67±9.76	0.093
Sex	Male	17	15	-
	Female	8	9	

Laboratory Assessment

First, we collected 10 mL of the individual's peripheral blood in tubes containing appropriate anticoagulants. Then, 4 mL of the blood samples was diluted with an equal volume of phosphate-buffered saline (PBS). In the next step, 4 mL of diluted blood was added to an equal volume of Ficoll in a sterile tube, and finally, we centrifuged it to extract PBMCs. They were stored at -80 °C till RNA extraction. Total RNA from PBMCs was extracted using the RNX plus kit (Cinnagen, Tehran, Iran). Total RNA quantification was determined using the NanoDrop spectrophotometer (Denovix, DE, USA). The complementary DNA (cDNA) was produced from 1 µg of total RNA by using a cDNA synthesis kit (Yekta Tajhiz Azma, Tehran, Iran) with random and oligo (dT) primers (table 1) at a 1:1 ratio according to the kit instructions. Then, Cyber Green dye was added to the synthesized cDNAs and the gene expression was checked using the real-time PCR technique.

Statistical Analysis

The data obtained was subjected to statistical analysis by SPSS 16 software (IBM, USA), GraphPad Prism (GraphPad, USA). The normality distribution of quantitative data was evaluated using the Shapiro–Wilk test. The data distribution in the present study was normal. Mean values were compared using *t* student statistical tests in the new case and anti-TNF groups. The demographic information results were reported as Mean±SD. The average is the result of at least two repetitions of the experiment. A significant difference was considered as P<0.05.

Results

Demographic Information

In the present study, we measured visfatin, *SIRT-1,* and cytokine *IL-18* gene expression in PBMCs in the two groups. The participants, aged 20–60 years, were divided into two groups, with age and sex matched between the groups. The mean age in the anti-TNF user group was 43.1±8.3 and 42.67±9.76 years in the new case group. The demographic characteristics of the study participants are summarized in table 2.

Relative Gene Expression of SIRT-1 in PBMCs of AS Patients

SIRT-1 gene expression was significantly lower in newly diagnosed AS patients than in those receiving etanercept treatment (P=0.041), indicating higher *SIRT-1* expression levels in the etanercept-treated group (figure 1).

Relative Gene Expression of Visfatin in PBMCs of AS Patients

Visfatin gene expression was significantly higher in newly diagnosed AS patients than in those treated with etanercept (P=0.021), demonstrating elevated Visfatin levels in the patients not yet receiving etanercept (figure 2).

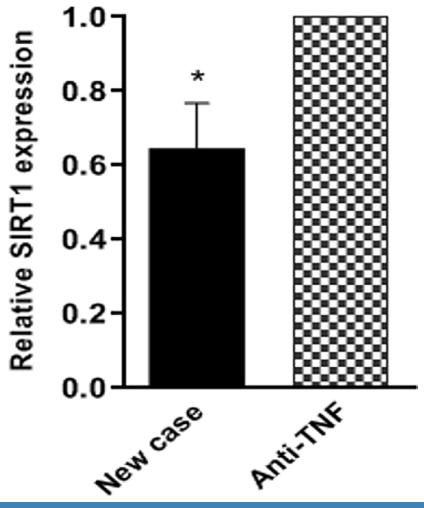

Figure 1: The gene expression levels of Sirtuin-1 in peripheral blood mononuclear cells of ankylosing spondylitis patients with anti-TNF-treated (etanercept) were significantly higher than newly diagnosed patients (new case) (P=0.041). *, **, *** mean P<0.05, P<0.01, P<0.001, respectively.

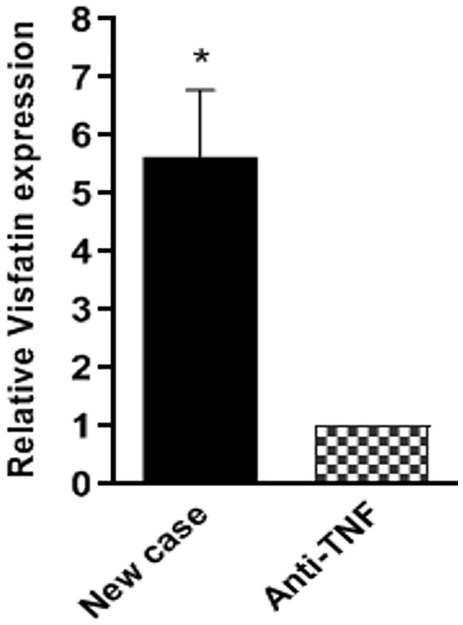

Figure 2: Visfatin expression was significantly elevated in newly diagnosed ankylosing spondylitis patients (new case) in comparison with patients receiving etanercept treatment (anti-TNF) (P=0.021). *, **, *** mean P<0.05, P<0.01, P<0.001, respectively.

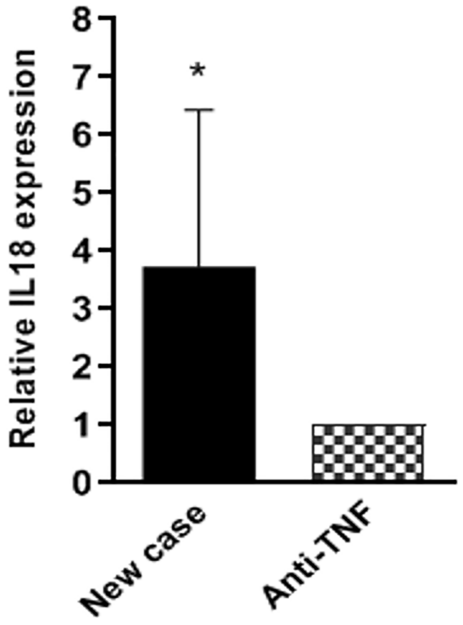

Figure 3: The etanercept-treated (anti-TNF) group showed a significant reduction in IL-18 mRNA levels compared to the treatment-naïve new cases (P=0.028). *, **, *** mean P<0.05, P<0.01, P<0.001, respectively.

Relative Gene Expression of IL-18 in PBMCs of AS Patients

IL-18 gene expression, similar to visfatin, was significantly higher in new case AS patients than in patients treated with etanercept (P=0.028), indicating an increased level of expression of this gene in patients who had not yet received etanercept (figure 3).

Discussion

Totally, our results demonstrated that patients receiving etanercept exhibited significantly higher *SIRT1* expression, whereas the expression levels of visfatin and *IL-18* were significantly lower than those of newly diagnosed untreated patients.

Our results showed the high expression of visfatin in the PBMCs of new case patients and a significant decrease in its expression under the influence of anti-TNF treatments. In 2024, in a study aimed at measuring visfatin serum levels in patients with AS and non-radiographic axial spondyloarthritis (nr-axSPA), found that serum visfatin concentration was elevated in the patients and was accompanied by disease activity.[17] It has also been determined that treatment of patients with rheumatoid arthritis with biological disease-modifying antirheumatic drug (bDMARD) adalimumab reduced visfatin levels in the serum of these patients.[18-20] In this study, we investigated the effect of etanercept on visfatin gene expression in PBMCs, and the results were the same as the effect of adalimumab on visfatin levels in serum. Visfatin is one of the genes related to inflammation. Production of visfatin is increased by inflammatory stimulation. This adipokine stimulates pro-inflammatory reactions by acting as a particular immunomodulatory factor. Visfatin increases the synthesis of cytokines that are both pro- and anti-inflammatory. By influencing the production of matrix metalloproteinases (MMPs), a disintegrin with thrombospondin motifs (ADAMTS), and prostaglandin E2 (PGE2) in chondrocytes, as well as pro-inflammatory cytokines and MMPs in synovial fibroblasts, visfatin has pro-inflammatory and matrix-degrading effects in joint inflammation.[8]

The result of the present study demonstrated a low expression level of *SIRT-1* in the PBMCs of new case patients and a significant increase in its expression in patients treated with etanercept. In a study aimed at examining the SIRT-1 auto-antibodies profiles in AS patients, it was found that anti-SIRT1 auto-antibodies levels in AS patients were significantly higher than those who were not affected by AS.[16] Recent experimental evidence has shown that activation of *SIRT1* suppresses TNF-α-induced inflammatory responses by inhibiting NF-κB signaling and reducing the production of downstream proinflammatory cytokines.[11] Overexpression of SIRT-1 in the body can slow the aging process, reduce cell death, counteract inflammation, and regulate metabolic processes.[21]

Furthermore, the results showed the high expression of this gene in new case patients and a significant decrease in its expression in patients treated with etanercept, which showed the prominent effect of etanercept treatment in the reduction of inflammation. Elevated IL-18 levels have been consistently reported in patients with ankylosing spondylitis and other autoimmune disorders, suggesting its role in enhancing Th1 and Th17-mediated inflammatory responses.[22, 23] Given the central role of TNF-α in inflammation and the regulatory interaction between TNF-α and IL-18, suppression of TNF signaling may play a role in reducing IL-18-induced responses.[22] IL-18 has the potential to trigger inflammatory and cytotoxic responses in immune cells, which could ultimately result in the development of autoimmunity.[22]

As a result, investigating the genes involved in the inflammatory pathways is effective for more accurate identification of the process of this disease. Additionally, evaluating their changes in order to measure the efficacy of drug treatments and monitoring patients is a big step in the direction of fighting inflammatory diseases and improving the quality of life of patients. Furthermore, research on these genes is helpful in designing newer treatments or improving the efficiency of existing therapies. The limitations of the present study include the small number of patients with a confirmed diagnosis of AS and the multiple pharmacological interventions these patients were receiving, which limited patient enrollment in the study.

Conclusion

The results of this study showed that etanercept treatment significantly upregulates SIRT-1 expression while suppressing IL-18 and visfatin levels in AS patients, highlighting its pleiotropic anti-inflammatory mechanisms beyond TNF-α blockade. These findings suggest that etanercept therapy may exert additional anti-inflammatory effects beyond TNF-α inhibition, potentially modulating key regulatory genes involved in the inflammatory cascade of AS and providing novel insights into the molecular pathways modulated by anti-TNF therapy, particularly the interplay between SIRT1-mediated epigenetic regulation and adipokine-driven inflammation. The decreased expression of IL-18 and visfatin may suggest them as potential biomarkers for monitoring treatment response or disease activity in AS. However, higher numbers of patients are needed for confirmation.

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Authors' Contribution

A.A: Data gathering, performing the experiments, data analysis, drafting, K.SS: Study design, and reviewing the manuscript; M.A: Data gathering and drafting; Z.F: Data gathering and reviewing the manuscript; R.M: data interpretation and drafting; S.B: Data analysis, and reviewing the manuscript; Z.H: Study design, and reviewing the manuscript, All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of AI

All scientific content, analysis, and interpretations were performed by the authors.

Conflict of Interest: None declared.

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