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ORIGINAL ARTICLE – OPEN ACCESS

Level of Serum Adiponectin in Sjögren's Syndrome

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ABSTRACT

Objective: To evaluate the serum adiponectin level and determine the association between adiponectin and various clinical and laboratory findings in patients with primary Sjögren's syndrome (pSS).

Materials and Methods: A total of 50 patients and 30 healthy volunteers were enrolled in the present study. Serum adiponectin levels were detected by colorimetric enzyme-linked immunosorbent assay. The medical history of patients including complete blood count analysis; high sensitive C-reactive protein; erythrocyte sedimentation rate (ESR); complement component 3; complement component 4; low density lipoprotein cholesterol; triglyceride; immunoglobulin G (IgG), IgA, and IgM levels; and the status of Ro 60, Ro 52, Sjögren's syndrome A, Sjögren's syndrome B, and rheumatoid factor were obtained from laboratory information system.

Results: Serum adiponectin levels were 2.34 (0.77–4.95) ng/mL and 1.73 (0.01–7.76) ng/mL in patients and controls, respectively (p=0.316). Positive correlation was observed between the values of serum adiponectin, ESR (p=0.013, rho=0.362), and body mass index (p=0.018, rho=0.362) in patients.

Conclusion: These findings indicate that adiponectin does not play a crucial role in the immunological and clinical patterns of pSS.

Keywords: Sjögren's syndrome, adiponectin, serum

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INTRODUCTION

The adipose tissue has various functions such as storage of energy and secretion of bioactive proteins. Adiponectin is one of the main bioactive molecules secreted by the adipose tissue (1, 2). It is also secreted by the salivary glands, skeletal and cardiac myocytes, airway epithelial cells, and lymphocytes (3). This molecule modulates insulin sensitivity, glucose utilization, and fatty acid oxidation. Besides, it participates in different physiological and biological processes, including inflammation and immunity (4). Till date, the anti-inflammatory and protective effects of adiponectin have been shown in the case of cardiovascular disease (5), and recent evidence has shown that high adiponectin levels are associated with severe inflammation and cytokine expression in rheumatologic diseases. Therefore, it is thought that adiponectin acts as a proinflammatory factor in rheumatologic disease (5–7).

Primary Sjögren's syndrome (pSS) is a chronic systematic autoimmune disease characterized by exocrine gland dysfunction and periepithelial lymphocytic infiltration in the lungs, kidneys, and liver (8). The disease typically affects middle-aged women and its estimated range of incidence is 0.9–6 per 1,000 individuals (9). The underlying pathophysiologic mechanism of pSS is unclear, but the production of interferons (IFNs), lymphocyte activation induced by TNF family cytokines, and the increased levels of immunoglobulins and autoantibodies are widely accepted as the contributing factors of pSS (9–11). Although adiponectin levels are extensively evaluated in rheumatologic disease (12), little is known about the adiponectin levels in pSS.

Therefore, the present study aims to determine serum adiponectin levels of pSS patients. The study provides an important opportunity to improve upon our existing knowledge about the relationship between adipocytokines and pSS.

MATERIALS and METHODS

Patients

This prospective study was performed from August 2017 to June 2018 at the Department of Biochemistry, School of Medicine and University of Sivas Cumhuriyet, Sivas, Turkey. The diagnosis of primary Sjögren's syndrome (pSS) was made according to the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria (13). We included patients with a focus score of 1 and above in the study; the focus score

Table 1. Basic clinical and laboratory findings of patients

ESR (sec)	30.38±16.04
CRP (mg/L)	5.00 (2.55–8.00)
Hb (g/dL)	13.23±1.37
Plt (x10^3 mcL)	252±78
C3 (g/L)	104.63±21.24
C4 (g/L)	20.47±6.08
LDL-C (mg/dL)	132.94±33.17
TG (mg/dL)	160.18±97.83
BMI (kg/m^2)	28±3.38
AMA (p/n)	3/47
AntiCCP (p/n)	6/44
IgG (g/L)	1432±572
IgA (g/L)	258.6±103.5
IgM (g/L)	148±68.3
Sicca symptoms (present/absent)	46/4
Schirmer test (positive/negative)	37/13
Arthralgia (present/absent)	7/43
Cytopenia (present/absent)	8/42

p/n: Positive/negative; AntiCCP: Anti-cyclic citrullinated peptide; AMA: Anti-Mitochondrial antibody; BMI: Body mass index; C3: Complement component 3; C4: Complement component 4; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LDL-C: Low density lipoprotein cholesterol; Plt: Platelet; TG: Triglyceride. Values are expressed as n (%), mean±SD or median (1^{st}–3^{rd} quartiles)

defines the number of inflammatory cells in the minor labial salivary glands (14). Basic laboratory and clinical findings are given in Table 1. Out of the total subjects, 2 patients received both hydroxychloroquine sulfate and cyclophosphamide, 2 patients received both hydroxychloroquine sulfate and methylprednisolone sodium succinate, 4 patients received both hydroxychloroquine sulfate and methotrexate, 7 patients received both hydroxychloroquine sulfate and azathioprine, and the remaining 35 patients received only stable doses of hydroxychloroquine sulfate. Exclusion criteria consisted of the presence of diabetes mellitus, liver disease, malignancy, musculoskeletal disease, skin diseases, pregnancy, impaired renal and thyroid function, and other rheumatologic diseases. The presence of clinical suspicion of pregnancy, kidney disease, infections, malignancy, liver disease, rheumatic disease, and smoking was accepted as the exclusion criteria in the controls. Samples were sent by physicians from the Department of Rheumatology, University of Cumhuriyet. The protocol was approved by the local ethics committee with the approval number: 2017-07/23.

Samples and Laboratory Analysis

Red top tubes (Becton Dickinson, UK) were used to collect fasting venous blood samples from all participants for clot formation before centrifugation. Centrifugation was performed at the following conditions: 4°C for 10 minutes at 4000 rpm. The serum was aliquoted and immediately stored at –80°C. Enzyme-linked immunosorbent assay technique was used for the measurement of adiponectin levels (Thermo Fisher Scientific, Waltham, USA), and tests were performed according to the manufacturer's recommendations. The full personal medical history of patients was recorded and information about complete blood count (CBC); erythrocyte sedimentation rate (ESR); high sensitive C-reactive protein (hsCRP), complement component 3 (C3), complement component 4 (C4), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), immunoglobulin G (IgG), IgA, and IgM levels; and the status of Ro 60, Sjögren's syndrome A (ssA), Sjögren's syndrome B (ssB), Ro 52 antigen, and rheumatoid factor (Rf) were obtained from the laboratory system.

CBC analysis was performed using the hematology system (Min-

Table 2. Comparisons of adiponectin levels in patients grouped according to different clinical and laboratory findings

Variable	Adiponectin levels (ng/mL)	p
Laboratory findings		
SSa		
Positive (n=26)	2.33 (0.7–7.02)	0.798
Negative (n=24)	2.74 (1.09–3.30)	
SSb		
Positive (n=14)	3.90 (1.33–9.50)	0.119
Negative (n=36)	1.89 (0.64–3.28)	
Rf		
Positive (n=19)	2.9 (1.12–8.04)	0.267
Negative (n=31)	2.56 (0.66–3.37)	
ANA		
Positive (n=39)	2.56 (0.82–5.08)	0.967
Negative (n=11)	2.9 (1.00 3.76)	
ro52		
Positive (n=28)	2.6 (1.19–7.91)	0.174
Negative (n=22)	2.11 (0.65–3.22)	
Schirmer's test		
Positive (n=37)	2.85 (0.90–4.64)	0.763
Negative (n=13)	1.64 (0.83–4.99)	
Clinical findings		
Arthrit		
Present (n=12)	1.76 (1.02–6.87)	0.968
Absent (n=38)	2.74 (0.78–4.95)	
Neurologic involvement		
Present (n=10)	1.20 (0.23–3.36)	0.156
Absent (n=40)	2.89 (1.12–5.41)	
Pulmoner invlovement		
Present (n=8)	1.75 (0.83–2.81)	0.422
Absent (n=42)	2.87 (0.94–5.19)	
Renal involvement		
Present (n=10)	4.44 (0.19–9.14)	0.491
Absent (n=40)	2.33 (1.03–3.28)	

ANA: Anti-nuclear antibody; Rf: Rheumatoid factor; ro52: Ro antigen 52; ssA: Sjögren's syndrome A antigen; ssB: Sjögren's syndrome B antigen; TG: Triglyceride. Results were expressed as median (1^{st}–3^{rd} quartiles)

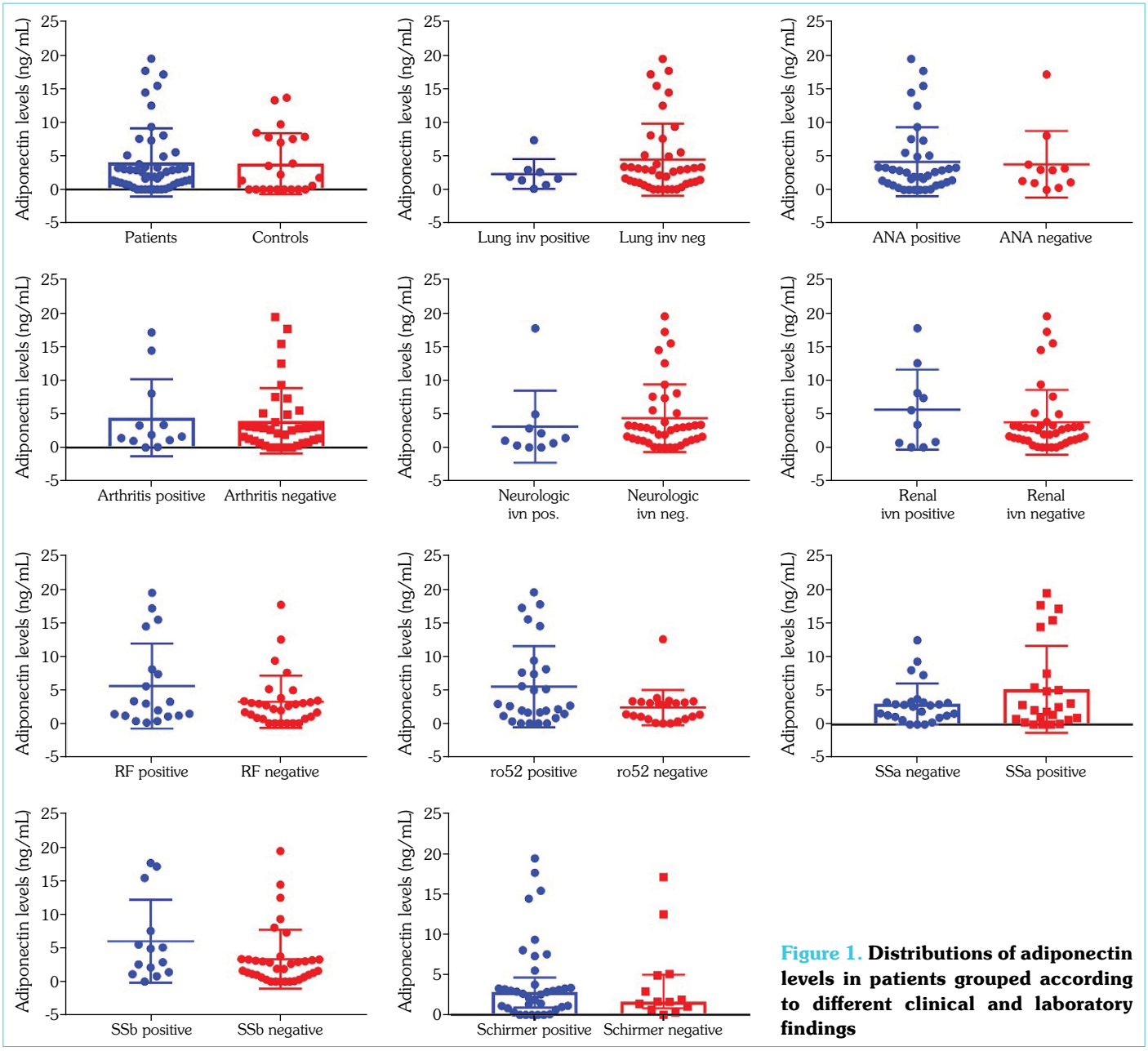

Figure 1. Distributions of adiponectin levels in patients grouped according to different clinical and laboratory findings

dray BC6800, China). ANA (Allegria, Orgentec, Germany) and Anti-CCP (Abbott Architect Plus 1200 SR, USA) levels were determined using immunoassay method. Measurements of Anti-Microbial Antibody (AMA), Sjögren's syndrome A (ssA), and Sjögren's syndrome B (ssB) were performed using immunofluorescence technique (Euroimmun, Germany). Ro 52 and Ro 60 measurements were performed using the immunoblotting technique (Euroimmun, Germany). LDL-C and TG levels were measured using enzymatic colorimetric method (Mindray BC 2000, PRC). Serum C3, C4, Rf, IgG, IgM, IgA, hsCRP concentrations were measured using nephelometry (Beckman Coulter, Image 800, USA). ESR was measured using the Westergren method (Sistat ESR 100, Ankara, Turkey). Schirmer's test was performed according to Stevens' study (15).

Statistical Analysis

Conformity of the data to normal distribution was evaluated using a histogram, q-q graphs, and the Shapiro Wilk test. Comparison of body mass index values between groups was performed using student's t-test. The Mann-Whitney U test was used for group comparisons in terms of serum adiponectin levels. The correlation between quantitative data was assessed using the Spearman test. Comparison of the categorical variable was performed using Chi-square test. Data analysis was conducted using R software (https://www.r-project.org/) and figures were obtained using the GraphPad Software (GraphPad Prism version 7.00, Windows). A value of $p<0.05$ was considered statistically significant.

RESULTS

Study subjects comprised 50 pSS patients [4 males and 46 females; with ages 22–72 years (mean age: 48±11)] and 30 controls [(3 males and 27 females; with ages 19–65 years (mean age:

38±11)]. No differences were detected between patients and controls in terms of age (p=0.057) and gender (p=0.094). Mean BMI values of the patients and controls were 28±3.38 and 26±2.54, respectively (p=0.157). BMI index values were calculated as follows: patient weight in kg/height (m^2). Median adiponectin levels were 2.34 (0.77–4.95) and 1.73 (0.01–7.76) ng/mL in patients and controls, respectively (p=0.316).

We compared adiponectin levels between patients with and without the presence of pulmonary, neurologic and renal involvement. Neurologic involvement is defined by the presence of headache, paresthesia, and numbness; pulmonary involvement is defined by the presence of findings in the high resolution computed tomography evaluation, and renal involvement is defined by the presence of either proteinuria or renal tubular acidosis.

Median serum adiponectin levels were 1.75 (0.83–2.81) ng/mL, 1.20 (0.23–3.36) ng/mL, and 4.44 (0.49–9.14) ng/mL in pulmonary, neurologic, and renal involvement-positive patients, respectively. Median serum adiponectin levels were 2.87 (0.94–5.19) ng/mL, 2.89 (1.12–5.41) ng/mL, and 2.33 (1.03–3.28) ng/mL in pulmonary, neurologic, and renal involvement-negative patients, respectively.

Comparisons and distributions of adiponectin levels in patients are grouped according to different clinical and laboratory findings in Table 2 and Figure 1, respectively. We found a positive, weak, and statistically significant correlation between the values of serum adiponectin, ESR (p=0.013, rho=0.361) and BMI (p=0.018, rho=0.362). We also found a positive, weak, and statistically significant correlation between C3 and BMI (p=0.007, rho=0.378) and TG levels (p=0.007, rho=0.379). No correlations were found between serum adiponectin, C3 (p=0.774, rho=0.042), and C4 (p=0.850, rho=0.027) levels in patients.

DISCUSSION

There are two different properties of adiponectin; its protective role in cardiovascular disease and its proinflammatory effect in rheumatologic diseases (16). Previous studies have already reported higher adiponectin levels in rheumatoid arthritis (RA) patients. Besides this, a positive correlation was observed between the severity of RA and adiponectin levels (7). Rho et al. found higher serum adiponectin levels in RA patients than in controls (17). Tan et al. reported higher adiponectin levels and adiponectin-1 receptor expressions in synovial fluids of RA patients (18). In our study, we did not find any significant difference between controls and patients in terms of serum adiponectin levels. We also did not find any difference between patients grouped according to the presence of lung, renal, neurologic involvement, ssA and ssB, and Ro52 positivity.

Little is known about the adiponectin levels in pSS. Toussirof et al. investigated serum adiponectin levels in 15 female patients with different autoimmune diseases including pSS (19), where higher serum adiponectin levels were reported. In the study conducted by Erbasan et al., higher expressions levels of leptin, an adipocytokine, and leptin receptor were not found in patients with pSS (20). The difference between previous studies and our study in terms of serum adiponectin levels may be because of the difference in nature of the disease, patients and study characteristics. We also speculated that serum adiponectin levels in patients might be influenced by drug therapy.

In the present study, we found a positive correlation between serum adiponectin levels and BMI in patients. It is a well-known fact that the proinflammatory effects of adiponectin (21). Previous studies reported that adiponectin could induce the expression of IL-8, IL-1β, IL-6, and MMP-1 (22–25). Recently, investigators have examined the effects of metabolic syndrome on rheumatologic diseases. It was reported that RA activity was correlated with metabolic syndrome parameters (26–29). Ramos Casals et al. reported that there was a correlation between metabolic alterations and clinical findings of pSS (26). Thus, we speculated that metabolic alterations such as the increase of fat mass might be related to the levels of adiponectin in patients with pSS.

CONCLUSION

These findings indicate that adiponectin does not play an important role in the immunological and clinical patterns of pSS. However, further research should be done to investigate the adipokine levels in pSS patients.

Ethics Committee Approval: The protocol was approved by the local ethics committee with the approval number: 2017-07/23.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Designed the study: KD, AŞ, HOD. Collected the data: ŞY, MEU, ED, AŞ, HOD. Analyzed the data: KD, HOD, ŞY, ED, AŞ. Wrote the paper: KD, HOD, ED. All authors have read and approved the final manuscript.

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REFERENCES

1. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrinol Metab 2000;11(8):327–32. [CrossRef]
2. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3(12):716–24. [CrossRef]
3. Fantuzzi G. Adiponectin in inflammatory and immune-mediated diseases. Cytokine 2013;64(1):1–10. [CrossRef]
4. Riis JL, Bryce CI, Ha T, Hand T, Stebbins JL, Matin M, et al. Adiponectin: Serum-saliva associations and relations with oral and systemic markers of inflammation. Peptides 2017;91:58–64. [CrossRef]
5. Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jørgensen A, Tarp U, et al. Plasma adiponectin in patients with active, early, and chronicrheumatoid arthritis who are steroid- and disease-modifyingantirheumatic drug-naive compared with patients with osteoarthritisand controls. J Rheumatol 2009;36(9):1885–91. [CrossRef]
6. Filková M, Lisková M, Hulejová H, Haluzík M, Gatterová J, Pavelková A, et al. Increased serum adiponectin levels in female patients with erosivecompared with non-erosive osteoarthritis. Ann Rheum Dis 2009;68(2):295–6. [CrossRef]

7. Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gómez-Reino JJ, et al. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65(9):1198–201. [CrossRef]
8. Goules AV, Tzioufas AG. Primary Sjögren's syndrome: clinical phenotypes, outcome and the development of biomarkers. Immunol Res 2017;65(1):331–44. [CrossRef]
9. Nocturne G, Mariette X. Advances in understanding the pathogenesis of primarySjögren's syndrome. Nat Rev Rheumatol 2013;9(9):544–56.
10. Mavragani CP, Moutsopoulos HM. Sjögren's syndrome. Annu Rev Pathol 2014;9:273–85. [CrossRef]
11. Maślińska M, Przygodzka M, Kwiatkowska B, Sikorska-Siudek K. Sjögren's syndrome: still not fully understood disease. Rheumatol Int 2015;35(2):233–41. [CrossRef]
12. Abella V, Scotece M, Conde J, López V, Lazzaro V, Pino J, et al. Adipokines, metabolic syndrome and rheumatic diseases. J Immunol Res 2014;2014:343746. [CrossRef]
13. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM,et al. 2016 American College of Rheumatology/European LeagueAgainst Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology InvolvingThree International Patient Cohorts. Arthritis Rheumatol 2017;69(1):35–45. [CrossRef]
14. Mariette X, Criswell LA. Primary Sjögren's Syndrome. N Engl J Med 2018;378(10):931–9. [CrossRef]
15. Stevens S. Schirmer's test. Community Eye Health 2011;24(76):45.
16. Scotece M, Conde J, López V, Lago F, Pino J, Gómez-Reino JJ, et al. Adiponectin and leptin: new targets in inflammation. Basic Clin Pharmacol Toxicol 2014;114(1):97–102. [CrossRef]
17. Rho YH, Solus J, Sokka T, Oeser A, Chung CP, Gebretsadik T, et al. Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. Arthritis Rheum 2009;60(7):1906–14. [CrossRef]
18. Tan W, Wang F, Zhang M, Guo D, Zhang Q, He S. High adiponectin and adiponectin receptor 1 expression in synovial fluids and synovial tissues of patients with rheumatoid arthritis. Semin Arthritis Rheum 2009;38(6):420–7. [CrossRef]
19. Toussirot E, Gaugler B, Bouhaddi M, Nguyen NU, Saas P, Dumoulin G. Elevated adiponectin serum levels in women with systemicautoimmune diseases. Mediators Inflamm 2010;2010:938408. [CrossRef]
20. Erbasan F, Alikanoğlu AS, Yazısız V, Karasu U, Balkarlı A, Sezer C, et al. Leptin and leptin receptors in salivary glands of primarySjögren's syndrome. Pathol Res Pract 2016;212(11):1010–4. [CrossRef]
21. Kang YE, Kim JM, Joung KH, Lee JH, You BR, Choi MJ, et al. The Roles of Adipokines, Proinflammatory Cytokines, and Adipose Tissue Macrophages in Obesity-Associated Insulin Resistance in Modest Obesity and Early Metabolic Dysfunction. PLoS One 2016;11(4):e0154003. [CrossRef]
22. Katano M, Okamoto K, Arito M, Kawakami Y, Kurokawa MS, Suematsu N, et al. Implication of granulocyte-macrophage colony-stimulating factorinduced neutrophil gelatinase-associated lipocalin in pathogenesis of rheumatoid arthritis revealed by proteome analysis. Arthritis Res Ther 2009;11(1):R3. [CrossRef]
23. Lee YA, Choi HM, Lee SH, Yang HI, Yoo MC, Hong SJ, et al. Synergy between adiponectin and interleukin-1β on the expression of interleukin-6, interleukin-8, and cyclooxygenase-2in fibroblast-like synoviocytes. Exp Mol Med 2012;44(7):440–7. [CrossRef]
24. Gómez R, Scotece M, Conde J, Gómez-Reino JJ, Lago F, Gualillo O. Adiponectin and leptin increase IL-8 production in humanchondrocytes. Ann Rheum Dis 2011;70(11):2052–4. [CrossRef]
25. Ehling A, Schäffler A, Herfarth H, Tarner IH, Anders S, Distler O, et al. The potential of adiponectin in driving arthritis. J Immunol 2006;176(7):4468–78. [CrossRef]
26. Ramos-Casals M, Brito-Zerón P, Sisó A, Vargas A, Ros E, Bove A, et al. High prevalence of serum metabolic alterations in primarySjögren's syndrome: influence on clinical and immunologicalexpression. J Rheumatol 2007;34(4):754–61.
27. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD, et al. Metabolic syndrome is common among middle-to-older agedMediterranean patients with rheumatoid arthritis and correlateswith disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis 2007;66(1):28–33. [CrossRef]
28. Ferraz-Amaro I, González-Juanatey C, López-Mejias R, Riancho-Zarrabeitia L, González-Gay MA. Metabolic syndrome in rheumatoid arthritis. Mediators Inflamm 2013;2013:710928. [CrossRef]
29. Medina G, Vera-Lastra O, Peralta-Amaro AL, Jiménez-Arellano MP, Saavedra MA, Cruz-Domínguez MP, et al. Metabolic syndrome, autoimmunity and rheumatic diseases. Pharmacol Res 2018;133:277–88. [CrossRef]