Salivary Levels of Interleukin-17 in Iranian Patients With Systemic Sclerosis

Ali Tadayon[1], Javad Moayedi[2], Mohamad Ali Nazarinia[3], Mahyar Malekzadeh[4], Sara Kazemi[5], Maryam Mardani[6]

[1] *Department of Surgery, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

[2] *Central Research Laboratory, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

[3] *Department of Internal Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

[4] *Shiraz Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

[5] *Department of Oral and Maxillofacial Medicine, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran*

[6] *Department of Oral and Maxillofacial Medicine, School of Dentistry, Oral and Dental Disease Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

Received: 18 Jan. 2024; Accepted: 10 Jul. 2024

Abstract- Systemic sclerosis (SSc) is a rare immune-mediated rheumatic disease in which the skin, muscles, blood vessels, and internal organs are damaged through chronic inflammation. Interleukin-17 (IL-17) is a potent pro-inflammatory cytokine produced by T helper 17 (Th17) cells, and plays a critical role in many inflammatory conditions. This study aims to assess the salivary IL-17 levels in Iranian patients with SSc. In this cross-sectional study, unstimulated saliva samples were collected from patients with SSc (n=80) and age- and sex-matched healthy individuals (n=80). The salivary levels of IL-17 in all samples were measured using a commercially available enzyme–linked immunosorbent assay (ELISA) kit. The mean salivary levels of IL-17 in patients with SSc were significantly higher than the control group (199.6±38.9 pg/mL *vs*. 112.7±39.4 pg/mL, *P*<0.0001). IL-17 in the patient group had a significant positive correlation with anticentromere antibody (ACA) concentration (r=0.875, *P*<0.0001). The salivary levels of IL-17 showed no significant differences between males and females. Based on the results, salivary levels of IL-17 could be considered a good marker to differentiate patients with SSc from healthy subjects. Considering the role of this inflammatory cytokine in tissue inflammation and its association with ACA concentration, IL-17 might be involved in the pathogenesis of SSc; however, further comprehensive studies are needed to confirm our findings.

Acta Med Iran 2024;62(July-August):182-187.

Keywords: Interleukin-17 (IL-17); Saliva; Systemic sclerosis (SSc)

Introduction

Systemic sclerosis (SSc), also known as scleroderma, is one of the most complex and rare rheumatologic autoimmune diseases with high morbidity and mortality (1). It is characterized by inflammation, vasculopathy, and progressive fibrosis of the skin and internal organs. The peak incidence of the disease occurs in the fifth decade of life, and women tended to be more affected than men, depending on age and ethnicity. Although the exact etiology of SSc is not fully understood, genetic background, environmental stimuli, and infectious agents are thought to contribute to the development of the disease (2,3).

The activation of the innate and adaptive immune system also appears to play a prominent role in the pathogenesis of SSc; however, the precise mechanisms responsible for initiating autoimmunity remain unclear (4,5). Inflammation as a part of the natural biological response to harmful stimuli involves the upregulation of pro-inflammatory signals. Properly controlled inflammation is essential for maintaining normal tissue and organ homeostasis; however, excessive and uncontrolled inflammation contributes to the overproduction of several cytokines and chemokines, autoimmunity, and persistent tissue damage (6,7). The

Corresponding Author: M. Mardani
Department of Oral and Maxillofacial Medicine, School of Dentistry, Oral and Dental Disease Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 7136263193, E-mail address: mardanim@sums.ac.ir

American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria include three SSc-associated autoantibodies: anti-centromere antibodies (ACA), anti-topoisomerase I antibodies (ATA), and anti-RNA-polymerase III antibodies (ARA). These autoantibodies can be detected using a wide variety of immuno-assays with appropriate sensitivity and specificity (8). Among these autoantibodies, ACA is typically associated with limited cutaneous involvement (lcSSc) and pulmonary arterial hypertension (PAH). It is useful in classifying different variants of SSc and often remains stable throughout the course of the disease (9,10).

Overall, CD4+ T cells are considered the main regulators of adaptive immunity. Under the influence of a network of inflammatory cytokines, T helper 17 (Th17) cells, (a distinct class of effector T cells), differentiate from naïve CD4+ T cells. Accumulating evidence suggests that Th17 cells and their associated cytokines can participate in the pathogenesis of chronic inflammatory conditions, autoimmune diseases, tissue destruction, and even malignancies (11-13). Interleukin-17 (IL-17) is a key pro-inflammatory cytokine predominantly produced by Th17 cells to regulate the expression of several inflammatory mediators including cytokines, chemokines, adhesion molecules, and growth factors (14,15). This cytokine is a disulfide-linked homodimeric glycoprotein with a molecular weight of about 30-35 kDa. IL-17 exists in six isoforms from A to F and has five receptors (IL-17RA to IL-17RE); however, Th17 cells are only able to produce IL-17A and IL-17F. Numerous publications have shown that both IL-17A and IL-17F can stimulate chronic inflammation in human systemic and organ-specific autoimmune disorders (16-18). An increase in IL-17 levels (now synonymous with IL-17A) has been reported in patients with rheumatoid arthritis (19,20), rheumatic heart disease (21), systemic lupus erythematosus (22), Sjögren syndrome (23), multiple sclerosis (24,25), inflammatory bowel disease (26,27), psoriasis (28), and other autoimmune diseases (29).

The literature on salivary expression of IL-17 is limited; however, several biomarkers can be successfully detected in saliva to identify a range of diseases, from autoimmune disorders to infections and cancers. SSc also plays a crucial role in impairing saliva production, salivary flow rate, and pH values (9,30-32). To our knowledge, IL-17 salivary levels have not yet been studied in SSc. Therefore, the aim of the current study is to compare the salivary levels of IL-17 in Iranian patients with SSc and healthy subjects.

Materials and Methods

Ethics

The protocol of this study was approved by the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Approval ID: IR.SUMS.DENTAL.REC.1399.070). Before donating saliva, all participating subjects signed a written informed consent in accordance with the Declaration of Helsinki and its later amendments.

Study design

This cross-sectional study was conducted on patients diagnosed with SSc between January 2020 and January 2022. To confirm the disease, all cases referred to the Rheumatology Clinic at Hafez Hospital affiliated with Shiraz University of Medical Sciences, Shiraz, Iran were initially visited by a rheumatologist. Evidence of active disease was then assessed in all patients according to the 2013 ACR/EULAR classification criteria (33). The time between symptom onset and the initial rheumatological evaluation was documented based on the patients' history. All patients had a disease duration of less than one year. Clinical data were also collected from the patients' medical records. Ultimately, 80 newly diagnosed patients of both genders who were over 18 years old at the time of diagnosis were included. None of the patients had previously received any medications for SSc. The exclusion criteria were patients with infectious diseases, pregnancy, poor general health, other autoimmune diseases other than SSc, and any conditions that could interfere with the results. The control group of this study consisted of 80 healthy individuals without any systemic and/or autoimmune disorders who were matched by age and gender to each case.

Evaluation of salivary IL-17 levels

Each study participant self-collected a 5 cc unstimulated whole saliva sample. Before collecting saliva, subjects were requested to brush their teeth and refrain from eating, drinking, or smoking for at least two hours. They were also instructed to mentally stimulate salivary flow as much as possible during collection. The saliva samples were then centrifuged at 2000 RPM for 10 minutes. The clear supernatant was transferred to a clean tube and stored at -70° C until needed. A commercially available ELISA kit (Human IL-17, DY317-05, R&D Systems, USA) was used to measure the salivary levels of IL-17. Briefly, all samples, reagents, and standard solutions were prepared and added to respective wells, following the manufacturer’s instructions. The working

solution of Streptavidin-HRP was then added to all wells, except the blank control well. The plate was incubated at 37º C for 60 minutes. After several washes to remove excess enzyme conjugate, substrate solutions were added to each well, and the plate was incubated at 37º C for 10 minutes in the dark. Finally, the enzymatic reaction was terminated by adding the stop solution and the optical density (absorbance) in each well was measured at 450 nm using a microplate reader (Biochrom Anthos 2020, Cambridge, UK).

Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics for Windows version 22 (IBM, Armonk, NY, USA). The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. Categorical variables were reported as counts and percentages, and compared using Pearson's chi-square test ($\chi 2$) or Fisher's exact test, where appropriate. Continuous variables were expressed as means with standard deviations and compared between groups using independent samples t test. Correlation analysis between salivary levels of IL-17 and continuous variables was performed using Pearson's correlation coefficient. All reported probabilities (*P*) less than 0.05 were considered statistically significant.

Results

The patient group (n=80) consisted of 16 (20%) males and 64 (80%) females with a mean age of 43.3±12.1 years. The control group in this study (n=80) was matched for age and sex distribution with the patient group, consisting 20 (25%) males and 60 (75%) females with a mean age of 42.5±10.1 years. There were no statistically significant differences between the study groups in terms of gender (*P*=0.570) and age (*P*=0.643) distribution.

The salivary levels of IL-17 were significantly elevated in patients with SSc compared to the control group (199.6±38.9 pg/mL vs. 112.7±39.4 pg/mL, *P*<0.0001). There were no statistically significant differences in the salivary levels of IL-17 between males and females, neither in the patient group (190.2±38.2 pg/mL vs. 193.8±43.1 pg/mL, *P*=0.696) nor in the control group (109.5±42.4 pg/mL vs. 113.7±38.6 pg/mL, *P*=0.683).

After conducting a correlation coefficient test, it was found that there were no significant correlations between the salivary levels of IL-17 and the duration of the disease (r=0.003, *P*=0.978) or the age of the patients (r=0.074, *P*=0.354). The mean concentration of ACA in the patient group was 45.1±4.4 ng/mL. Figure 1 illustrates a significant positive correlation between salivary levels of IL-17 and ACA concentration (r=0.875, *P*<0.0001). In other words, as the ACA concentration increased in the patient group, the salivary level of IL-17 also increased.

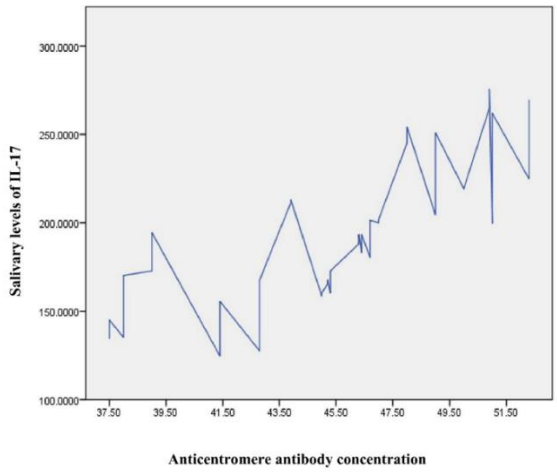

Figure 1. The correlation between salivary levels of IL-17 and the concentration of ACA in SSc patients

Discussion

Immunological abnormalities of the innate and adaptive immune system, including inflammation, dysregulation of cytokines, and production of autoantibodies, have long been recognized in SSc (4,5). Since its identification, IL-17 signaling pathways and its biological functions have been extensively studied.

Accumulating evidence indicates that IL-17, as the founder member of the IL-17 family of inflammatory cytokines, is one of the key players in local inflammation and is involved in the pathogenesis of a diverse group of immune-mediated diseases, including psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma (4,5,34,35). However, data on IL-17 in patients with SSc are scarce, with controversy in their results. Some studies have reported abnormal (increased) levels of IL-17 in peripheral blood and fibrotic lesions of the skin and lungs of patients with SSc, while others found no significant differences between the patient and control groups (1,11,12,36-39). A previous study also stated that the serum levels of IL-17 in patients with SSc are generally low and near the detection level of the assays (40), which might in part explain the variability of the results. However, to the best of our knowledge, the salivary levels of this inflammatory cytokine in SSc have not been studied yet.

The findings of this study, for the first time, showed a significant increase in the salivary levels of IL-17 in patients with SSc compared to the healthy control group. Our study also revealed that salivary IL-17 levels were strongly associated with ACA concentration. The pathological hallmark of SSc is excessive collagen deposition and microvascular injury. Chronic inflammation persistently activates interstitial fibroblasts, leading to irreversible fibrosis of multiple organs. Fibroblast growth and collagen overproduction are related to Th17 cell-derived IL-17 (4). Additionally, IL-17 enhances the proliferation of fibroblasts and induces the expression of adhesion molecules in endothelial cells (1). Therefore, the progression of SSc might be linked to the expansion of circulating Th17 cells and overproduction of IL-17 cytokine, especially in the early stages of the disease (1,4).

Saliva is a heterogeneous biological fluid constantly produced by salivary glands and secreted into the oral cavity. It contains various molecules present in the bloodstream. Collecting saliva is noninvasive, safe, and easy, making it a valuable tool for disease diagnosis and prognosis. Salivary biomarkers are increasingly important for monitoring disease progression and management (31,32,41). IL-17 is mainly expressed in the periductal and perivascular infiltrates of salivary glands. The secretion of IL-17 by salivary gland epithelial cells leads to the sequestration of neutrophils and monocytes to the glands, but the level of expression correlated with the severity of glandular inflammation (41-43). Studies on patients with primary Sjögren syndrome (42,43) and oral lichen planus (44,45) have demonstrated a significant increase in salivary IL-17 levels, which is consistent with our findings. Salivary IL-17 levels have also been used as a biomarker to identify patients at risk of developing severe COVID-19 (32). Patients with oral squamous cell carcinoma have also shown significantly higher levels of this cytokine in their saliva compared to the control group (31). Currently, there are no options to reverse, stop, or even slow the natural progression of SSc. Therefore, the goal of management is to improve the patient's quality of life by monitoring signs, reducing symptoms, and minimizing functional disabilities (5,46,47). IL-17 inhibitors including Ixekizumab, Secukinumab, and Brodalumab are widely used to treat many chronic inflammatory diseases. Hence, neutralization of IL-17 may be a useful tool for intervention in the fibrotic course of SSc (48,49).

This study has several limitations. The overall sample size was relatively small to generalize the results to the overall population. Secondly, the disease stage was not considered in the analysis. Circulating Th17 cells have been shown to increase only in patients with moderate to high systemic disease activity, but not in patients with low systemic disease activity (34). These findings, along with our observations that salivary levels of IL-17 had a significant positive correlation with ACA concentration, indicate that numbers of circulating Th17 cells and levels of IL-17 are associated with certain stages of the disease. Therefore, future studies should investigate a sufficient number of patients in both genders with similar disease duration and severity; however, the enrollment of such patients is difficult.

IL-17 is an important T cell-derived cytokine that contributes to the development of SSc. Our findings indicate that IL-17 levels were notably elevated in the saliva samples of SSc patients and were associated with ACA concentration. Therefore, understanding its functions and developing strategies to block the harmful effects of IL-17 could be beneficial for treating SSc patients. However, further comprehensive studies with larger sample sizes and longer follow-ups are needed to determine the role of Th17 cells and excessive IL-17 production in SSc.

Acknowledgments

This study was financially supported by grant No. 98-01-03-21841 from the Vice-Chancellor for Research Affairs of Shiraz University of Medical Sciences, Shiraz, Iran. This manuscript is based on a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Dental Medicine by Sara Kazemi.

References

1. Kurasawa K, Hirose K, Sano H, Endo H, Shinkai H, Nawata Y, et al. Increased interleukin-17 production in patients with systemic sclerosis. Arthritis Rheum 2000;43:2455-63.
2. Hashempour A, Moayedi J, Musavi Z, Ghasabi F, Halaji M, Hasanshahi Z, et al. First report of HHV-8 viral load and seroprevalence of major blood-borne viruses in Iranian patients with systemic sclerosis. Mult Scler Relat Disord 2021;51:102872.
3. Stern EP, Denton CP. The pathogenesis of systemic sclerosis. Rheum Dis Clin North Am 2015;41:367-82.
4. Yang X, Yang J, Xing X, Wan L, Li M. Increased frequency of Th17 cells in systemic sclerosis is related to disease activity and collagen overproduction. Arthritis Res Ther 2014;16:1-11.
5. Fuschiotti P. Current perspectives on the immunopathogenesis of systemic sclerosis. Immunotargets Ther 2016;5:21-35.
6. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med 2019;18:121-6.
7. Wu B, Sodji QH, Oyelere AK. Inflammation, fibrosis and cancer: Mechanisms, therapeutic options and challenges. Cancers (Basel) 2022;14:552-89.
8. Damoiseaux J, Potjewijd J, Smeets RL, Bonroy C. Autoantibodies in the disease criteria for systemic sclerosis: the need for specification for optimal application. J Transl Autoimmun 2022;5:1-5.
9. Najafi S, Mardani M, Motamedifar M, Nazarinia MA, Hadadi M. Salivary Streptococcus mutans and Lactobacilli Levels as Indicators of Dental Caries Development in Iranian Patients with Systemic Sclerosis. Iran J Med Microbiol 2022;16:350-6.
10. Santos CS, Morales CM, Castro C, Álvarez ED. Clinical phenotype in scleroderma patients based on autoantibodies. Rheumatol Adv Pract 2023;7:26-33.
11. Sierra-Sepúlveda A, Esquinca-González A, Benavides-Suárez SA, Sordo-Lima DE, Caballero-Islas AE, Cabral-Castañeda AR, et al. Systemic sclerosis pathogenesis and emerging therapies, beyond the fibroblast. Biomed Res Int 2019;2019:4569826.
12. Qu N, Xu M, Mizoguchi I, Furusawa JI, Kaneko K, Watanabe K, et al. Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases. Clin Dev Immunol 2013;2013:968549.
13. O'Reilly S, Hügle T, Van Laar JM. T cells in systemic sclerosis: a reappraisal. Rheumatology (Oxford) 2012;51:1540-9.
14. Xu S, Cao X. Interleukin-17 and its expanding biological functions. Cell Mol Immunol 2010;7:164-74.
15. Park SJ, Lee YC. Interleukin-17 regulation: an attractive therapeutic approach for asthma. Respir Res 2010;11:1-11.
16. Tabarkiewicz J, Pogoda K, Karczmarczyk A, Pozarowski P, Giannopoulos K. The role of IL-17 and Th17 lymphocytes in autoimmune diseases. Arch Immunol Ther Exp 2015;63:435-49.
17. Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. J Invest Dermatol 2013;133:17-26.
18. de Morales JMGR, Puig L, Daudén E, Cañete JD, Pablos JL, Martín AO, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: an updated review of the evidence focusing in controversies. Autoimmun Rev 2020;19:102429.
19. Liu Y, HO RCM, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. Int J Rheum Dis 2012;15:183-7.
20. Rosu A, Margaritescu C, Stepan A, Musetescu A, Ene M. IL-17 patterns in synovium, serum and synovial fluid from treatment-naive, early rheumatoid arthritis patients. Rom J Morphol Embryol 2012;53:73-80.
21. Bilik MZ, Kaplan I, Polat N, Akil MA, Akyüz A, Acet H, et al. Serum levels of IL-17 and IL-23 in patients with rheumatic mitral stenosis. Medicine (Baltimore) 2016;95:e3562.
22. Chen XQ, Yu YC, Deng HH, Sun JZ, Dai Z, Wu YW, et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. J Clin Immunol 2010;30:221-5.
23. Katsifis GE, Rekka S, Moutsopoulos NM, Pillemer S, Wahl SM. Systemic and local interleukin-17 and linked cytokines associated with Sjögren's syndrome immunopathogenesis. Am J Pathol 2009;175:1167-77.
24. Esendagli G, Kurne AT, Sayat G, Kilic AK, Guc D, Karabudak R. Evaluation of Th17-related cytokines and receptors in multiple sclerosis patients under interferon beta-1 therapy. J Neuroimmunol 2013;255:81-4.
25. Bălaşa R, Bajko Z, Huţanu A. Serum levels of IL-17A in patients with relapsing–remitting multiple sclerosis treated with interferon-β. Mult Scler 2013;19:885-90.
26. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003;52:65-70.
27. Nielsen O, Kirman I, Rüdiger N, Hendel J, Vainer B. Upregulation of interleukin-12 and-17 in active inflammatory bowel disease. Scand J Gastroenterol 2003;38:180-5.
28. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. Interleukin (IL)-22, IL-17, IL-23, IL-

8, vascular endothelial growth factor and tumour necrosis factor-α levels in patients with psoriasis before, during and after psoralen–ultraviolet A and narrowband ultraviolet B therapy. Br J Dermatol 2010;163:1282-90.
29. Ivanov S, Lindén A. Interleukin-17 as a drug target in human disease. Trends Pharmacol Sci 2009;30:95-103.
30. Parat K, Radić M, Perković D, Lukenda DB, Kaliterna DM. Reduced salivary flow and caries status are correlated with disease activity and severity in patients with diffuse cutaneous systemic sclerosis. J Int Med Res 2020;48:0300060520941375.
31. Abbas MJ, Al Rawi NA, Al-Duboni GI. The role of salivary interleukin 17 as a dependent positive predictive biomarker among iraqi patients with oral squamous cell carcinoma. J Pharm Sci Res 2018;10:3149-52.
32. Saheb Sharif-Askari F, Sharif-Askari NS, Hafezi S, Mdkhana B, Alsayed HAH, Ansari AW, et al. Interleukin-17, a salivary biomarker for COVID-19 severity. PloS One 2022;17:e0274841.
33. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747-55.
34. Verstappen GM, Corneth OB, Bootsma H, Kroese FG. Th17 cells in primary Sjögren's syndrome: pathogenicity and plasticity. J Autoimmun 2018;87:16-25.
35. Asano Y. The pathogenesis of systemic sclerosis: An understanding based on a common pathologic cascade across multiple organs and additional organ-specific pathologies. J Clin Med 2020;9:2687-714.
36. Robak E, Gerlicz-Kowalczuk Z, Dziankowska-Bartkowiak B, Wozniacka A, Bogaczewicz J. Serum concentrations of IL-17A, IL-17B, IL-17E and IL-17F in patients with systemic sclerosis. Arch Med Sci 2019;15:706-12.
37. Murata M, Fujimoto M, Matsushita T, Hamaguchi Y, Hasegawa M, Takehara K, et al. Clinical association of serum interleukin-17 levels in systemic sclerosis: is systemic sclerosis a Th17 disease? J Dermatol Sci 2008;50:240-2.
38. Dantas AT, de Almeida AR, Sampaio MCPD, Cordeiro MF, de Oliveira PSS, de Ataíde Mariz H, et al. Different profile of cytokine production in patients with systemic sclerosis and association with clinical manifestations. Immunol Lett 2018;198:12-6.
39. Rolla G, Fusaro E, Nicola S, Bucca C, Peroni C, Parisi S, et al. Th-17 cytokines and interstitial lung involvement in systemic sclerosis. J Breath Res 2016;10:046013.
40. Chizzolini C, Dufour AM, Brembilla NC. Is there a role for IL-17 in the pathogenesis of systemic sclerosis? Immunol Lett 2018;195:61-7.
41. Zian Z, Bakkach J, Barakat A, Ghailani Nourouti N, Bennani Mechita M. Salivary biomarkers in systemic sclerosis disease. Biomed Res Int 2018;2018:3921247.
42. Zhang LW, Zhou PR, Wei P, Cong X, Wu LL, Hua H. Expression of interleukin-17 in primary Sjögren's syndrome and the correlation with disease severity: A systematic review and meta-analysis. Scand J Immunol 2018;87:e12649.
43. Voigt A, Esfandiary L, Wanchoo A, Glenton P, Donate A, Craft WF, et al. Sexual dimorphic function of IL-17 in salivary gland dysfunction of the C57BL/6. NOD-Aec1Aec2 model of Sjögren's syndrome. Sci Rep 2016;6:38717.
44. Abdeldayem E, Rashed L, Ali S. Salivary expression of lncRNA DQ786243 and IL-17 in oral lichen planus: case–control study. BMC Oral Health 2022;22:240.
45. El-Refai I, Maged A, El-Saady D. Assessment of IL-17 in Oral Lichen Planus and in Pemphigus Vulgaris. Egypt Dent J 2019;65:343-50.
46. Wojeck RK, Bailey DE, Somers TJ, Knisely MR. Self-management interventions in systemic sclerosis: A systematic review. Res Nurs Health 2021;44:376-92.
47. Sherby NA, Sediq AM, Alsharawy AAO, Hammad MAH. Quality Of Life in Female Patients with Systemic Sclerosis. Egypt J Hosp Med 2022;87:1208-15.
48. Țiburcă L, Bembea M, Zaha DC, Jurca AD, Vesa CM, Rațiu IA, et al. The Treatment with Interleukin 17 Inhibitors and Immune-Mediated Inflammatory Diseases. Curr Issues Mol Biol 2022;44:1851-66.
49. Gao Q, Zhao Y, Wang X, Shi J, Wang H. Efficacy and safety of IL-17 inhibitors for patients with psoriatic arthritis: A systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2021;25:2958-70.