Journal of
Kerman University of Medical Sciences

https://jkmu.kmu.ac.ir
10.34172/jkmu.2024.24
Vol. 31, No. 3, 2024, 148-152

Original Article

Salivary Levels of Interleukin-23 in Iranian Patients with Systemic Sclerosis

Ali Tadayon[1], Javad Moayedi[2], Mohamad Ali Nazarinia[3], Zahra Baghayifar[4], Maryam Mardani[5*]

[1]Department of Surgery, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Center of Comparative and Experimental Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Internal Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Undergraduate Student, Department of Oral and Maxillofacial Medicine, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Oral and Dental Disease Research Center, Department of Oral and Maxillofacial Medicine, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran

*Corresponding Author: Maryam Mardani, Email: mardanim@sums.ac.ir

Abstract

Background: Systemic sclerosis (SSc) is a rare chronic inflammatory disorder characterized by diffuse fibrosis and vascular abnormalities in the skin and internal organs. Interleukin-23 (IL-23) is a pro-inflammatory cytokine that can enhance the expansion of T helper 17 (Th17) cells and thus plays a critical role in many inflammatory autoimmune diseases. This study aimed to assess the salivary IL-23 levels in Iranian patients with SSc compared to healthy individuals.

Methods: In this cross-sectional study, unstimulated saliva samples (5 cc) were collected from 88 SSc patients and 88 age- and sex-matched healthy individuals. The salivary levels of IL-23 in the saliva samples were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit.

Results: The mean salivary levels of IL-23 in the patient group were significantly higher than in the control subjects (164.5 ± 22.1 ng/L vs. 95.8 ± 15.7 ng/L, $P < 0.0001$). In SSc patients, the salivary IL-23 levels were significantly elevated in ACA-positive compared to ACA-negative participants (179.8 ± 11.2 ng/L vs. 144.3 ± 15.7 ng/L, $P < 0.0001$). However, IL-23 was not associated with gender or age ($P > 0.05$).

Conclusion: The results suggest that IL-23 is associated with the pathogenesis of SSc; therefore, this pro-inflammatory cytokine is not only a valuable supportive biomarker for monitoring the disease progression but also blocking IL-23 could be considered a potential therapeutic target, especially in early SSc. Further comprehensive studies are needed to confirm our findings.

Keywords: IL-23, Saliva, Systemic sclerosis

Citation: Tadayon A, Moayedi J, Nazarinia MA, Baghayifar Z, Mardani M. Salivary levels of interleukin-23 in Iranian patients with systemic sclerosis. *Journal of Kerman University of Medical Sciences*. 2024;31(3):148–152. doi: 10.34172/jkmu.2024.24

Received: July 11, 2023, **Accepted**: September 4, 2023, **ePublished**: June 29, 2024

Introduction

Systemic sclerosis (SSc) is a rare, chronic, and complex rheumatologic disease in which several pathogenic pathways lead to diffuse proliferative vascular modifications and widespread fibrosis of the skin and visceral organs. It has a worldwide distribution, with extensive patient-to-patient variability (1,2). This autoimmune disease can occur in people of any age. However, the peak incidence is in the fifth decade of life, and it preferentially affects women, with a female-to-male ratio of 4:1–10:1, depending on age and ethnicity. Endogenous or exogenous environmental triggers/risk factors, particularly immunological abnormalities of the innate and acquired immune systems, are thought to be involved in the pathogenesis of SSc; however, the precise mechanisms remain elusive (3-5).

T-cell-mediated immune responses and the abnormal production of autoantibodies are the most recognized evidence of the participation of the immune system in the initiation and progression of chronic inflammatory skin diseases, such as SSc (6,7). The pathologic hallmark of SSc is fibroblast growth and excessive collagen deposition, which is related to cytokines derived from a distinct class of effector T cells called T helper 17 (Th17) cells. Th17 cells are one of the primary triggers of tissue inflammation (8,9). Inflammation is a biological response of the immune system to harmful stimuli, and adequately controlled inflammation is essential for maintaining tissue/organ homeostasis. However, excessive and uncontrolled inflammation can persistently activate interstitial fibroblasts, leading to irreversible fibrosis of multiple organs. By producing specific chemokines and

cytokines, Th17 cells can promote the development of chronic inflammatory conditions, autoimmune diseases, tissue destruction, and even malignancies (10-12).

Interleukin-23 (IL-23) is a pro-inflammatory cytokine composed of the unique IL-23A (IL-23p19) and the common IL-23B (IL-23p40) subunits, the latter of which is shared with IL-12. It is secreted by various cell types, such as antigen-presenting dendritic cells, macrophages, and the epithelium. Increasing evidence suggests that IL-23 signaling pathways are involved in the development of inflammation and autoimmunity, playing a crucial role in a wide array of immune-mediated disorders, and they have garnered much attention in recent years (12-14). IL-23 is essential for stabilizing Th17 cells and regulating the maturation of IL-17-producing T cells. The powerful signals generated by IL-23 can stimulate Th17 cells to produce IL-17, which is elevated in the tissue and peripheral blood of patients, activating different cells such as epithelial and endothelial cells, fibroblasts, chondrocytes, osteoblasts, and macrophages to produce a network of inflammatory molecules (12,15,16).

There are few conflicting data concerning the role of IL-23 in the pathogenesis of SSc. Although some studies have reported elevated levels of IL-23 in sera of SSc patients, others have found no significant differences between the patient and control groups or higher levels of this pro-inflammatory cytokine in the control group (12,17-21). To the best of our knowledge, the literature investigating salivary levels of IL-23 is limited; therefore, this study aimed to investigate the salivary levels of IL-23 in Iranian patients with SSc and compare them with those of healthy subjects.

Methods

Study design

From January 2020 to January 2022, a total of 88 patients with a confirmed diagnosis of SSc according to the criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) were enrolled in this cross-sectional study. Participants were of both genders, aged over 18 years at diagnosis, and had received no prior medications for SSc. Patients with other autoimmune diseases apart from SSc, as well as those with infectious diseases (patients with HBV, HCV, or HIV infections), pregnancy, cancer, and any conditions that could interfere with the results were excluded. Eighty-eight healthy individuals without evidence of autoimmune diseases, infectious diseases, pregnancy, and cancer who were matched by age and gender distribution to each case were considered as the control group.

Evaluation of salivary IL-23 levels

All participants included based on the inclusion/exclusion criteria were requested not to eat, drink, or brush their teeth 1 hour before saliva collection. Whole unstimulated saliva samples (5 cc) were self-collected by the participants and then centrifuged at 3500 RPM for 10 minutes. The clear supernatant was transferred to a clean tube and stored at -70 °C until further use. A commercially available Human Interleukin-23 ELISA kit (Cat. No. E0074Hu, Bioassay Technology Laboratory, China) was used to measure the salivary levels of IL-23.

Statistical analysis

All statistical analyses were done 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 expressed 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 mean ± standard deviation and compared across the study groups using the independent samples *t* test. All reported probabilities (*P* values) less than 0.05 were considered statistically significant.

Results

The patient group in this research comprised 88 cases, 21 men (23.9%) and 67 women (76.1%), with a mean age of 42.7 ± 10.6 years. The control group, which consisted of healthy participants matched for age and sex distribution with the patient group, comprised 21 men (23.9%) and 67 women (76.1%), with a mean age of 42.2 ± 10.1 years. There were no statistically significant differences between the study groups regarding age ($P = 0.751$) and gender ($P = 1.000$) distribution.

The mean salivary levels of IL-23 were significantly higher in SSc patients compared to the healthy control group (164.5 ± 22.1 ng/L vs. 95.8 ± 15.7 ng/L, $P < 0.0001$). As shown in Figure 1, a receiver operating characteristic curve (ROC curve) was constructed to evaluate the

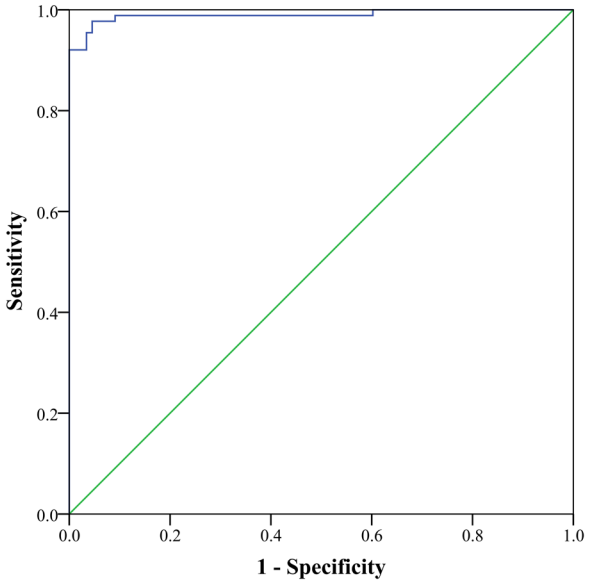

Figure 1. ROC curve analysis for the diagnostic value of salivary IL-23 levels

diagnostic value of IL-23 based on the area under the curve (AUC). The ROC curve analysis showed excellent diagnostic potential for the salivary levels of IL-23 (AUC = 0.990, 95%CI = 0.976–1.000, $P < 0.0001$).

There were no statistically significant differences in the salivary levels of IL-17 between men and women, neither in the patient (166.8 ± 21.5 ng/L vs. 163.7 ± 22.4 ng/L, $P = 0.580$) nor in the control groups (95.3 ± 14.6 ng/L vs. 96.1 ± 16.7 ng/L, $P = 0.873$). Additionally, the mean salivary levels of IL-23 were similar between participants aged below and over 40 years in both the patient (167.4 ± 17.3 ng/L vs. 162.4 ± 24.8 ng/L, $P = 0.298$) and control (97.9 ± 14.8 ng/L vs. 94.1 ± 16.2 ng/L, $P = 0.265$) groups. The patient group was further divided into two subgroups of anticentromere antibody (ACA)-positive ($n = 50$) and ACA-negative ($n = 38$) subjects. The salivary levels of IL-23 were significantly higher in the ACA-positive than the ACA-negative patients (179.8 ± 11.2 ng/L vs. 144.3 ± 15.7 ng/L, $P < 0.0001$).

Discussion

SSc is a complex autoimmune disease with no known way to reverse, stop, or slow its natural progression. Immunological abnormalities, such as inflammation, dysregulation of immune responses, and autoantibody production, are often associated with the development and progression of SSc, particularly during earlier stages (2,8,9,12). IL-23 is a pro-inflammatory cytokine, a heterodimeric molecule, which helps Th17 cells expand and maintain their lineage while promoting the production of IL-17. The IL-23–IL-17 axis is a significant player in developing chronic inflammation and autoimmunity, vascular injury, and fibrosis in SSc patients (18,19,22-24). Previous studies have indicated that IL-23 plays a role in many inflammatory- and autoimmune-related diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, Sjögren's syndrome, and SSc (18,25-30). Anti-IL-23-targeted therapy has become a potential therapeutic strategy for these diseases (28,31,32).

This study showed a significant increase in the salivary levels of IL-23 in SSc patients compared to the healthy control group for the first time. Additionally, our study revealed that salivary IL-23 levels were associated with ACA concentration. Several studies have suggested that IL-23 may play a role in the pathogenesis of SSc due to its potent pro-inflammatory capacity. To the best of our knowledge, the salivary level of IL-23 has not been studied in SSc patients, and the current study is the first. However, some studies in the literature confirm the elevation of IL-23 levels in the serum of SSc patients compared to the healthy control group (17-19).

In contrast, Gourh et al (20) and Olewicz-Gawlik et al (21) observed decreased levels of IL-23 in the serum of SSc patients compared to healthy subjects. Celal et al (12) also found that the mean serum IL-23 levels of the healthy control group and SSc patients were similar. These discrepancies can be attributed to the small sample size of SSc patients, the duration of the disease, differences in treatment and stages of the disease, the heterogeneity among SSc patients, the pattern of internal organ involvement, and the presence of SSc-associated autoantibodies (12,17-21).

This report used whole unstimulated saliva samples. Saliva is a heterogeneous biological fluid, constantly produced by salivary glands and secreted into the oral cavity. Its collection is non-invasive, safe, and easy. This body fluid includes many molecules circulating in the blood, making it an ideal site for biomarkers to be reflected. It should be noted that SSc has a crucial role in the impairment of saliva production, secretion, and pH values; hence, saliva has become an essential part of diagnosing, prognosticating, and managing local and systemic diseases (33-37).

The present study was the first to investigate the salivary levels of IL-23 in SSc patients. We adjusted variables such as gender and age, which can influence cytokine levels in SSc patients and healthy controls. Although the number of patients in this study can be considered sufficient compared to similar studies in the literature, there are some limitations due to methodological flaws and potential unmeasured confounding factors, including the lack of assessment of immunosuppressive medications and the effects of such treatments on IL-23 levels. Furthermore, the disease stage was not considered in the analysis. The role of IL-23 on the etiopathogenesis of SSc in a sufficient number of treated and untreated patients of both genders with similar disease duration and severity should be investigated to eliminate the differences between studies.

Conclusions

This study showed that the salivary levels of IL-23 had good potential to differentiate SSc patients from healthy control participants. The signals generated by this pro-inflammatory cytokine may play an essential role in the pathogenesis of SSc; thus, measuring IL-23 levels in combination with other laboratory tests could assist in diagnosing patients with SSc. Moreover, defining IL-23 functions and targeting its producing cell types and release pathways could be a potential therapeutic approach for these patients. Although this preliminary study supports the clinical value of IL-23, further comprehensive studies, including a larger number of patients with clinically active disease, are still necessary to clarify the association between IL-23 and SSc. Serial measurements of IL-23 levels during the disease are necessary to elucidate this issue.

Acknowledgments

This study was financially supported by grant No. 98-01-03-21840 from the Vice-Chancellor for Research of Shiraz University of Medical Sciences, Shiraz, Iran. Hereby, the authors would like to thank Mr. Malekzadeh at Shiraz Institute for Cancer Research,

School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. This manuscript is based on a thesis submitted in partial fulfillment of the requirements for the Doctor of Dental Medicine degree by Zahra Baghayifar.

Authors' Contribution

Conceptualization: Ali Tadayon, Maryam Mardani.
Data curation: Mohamad Ali Nazarinia, Zahra Baghayifar.
Formal analysis: Javad Moayedi.
Funding acquisition: Maryam Mardani.
Investigation: Zahra Baghayifar.
Methodology: Ali Tadayon, Mohamad Ali Nazarinia, Zahra Baghayifar.
Project administration: Maryam Mardani.
Software: Javad Moayedi.
Supervision: Maryam Mardani.
Writing–original draft: Javad Moayedi.
Writing–review & editing: Ali Tadayon, Maryam Mardani.

Competing Interests

None declared.

Ethical Approval

Before saliva donation, all participating subjects signed a written informed consent in accordance with the Declaration of Helsinki and its later amendments. 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.1399.069).

Funding

This study was financially supported by grant No. 98-01-03-21840 from the Vice-chancellor for Research Affairs of Shiraz University of Medical Sciences, Shiraz, Iran.

References

1. 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. doi: 10.1016/j.msard.2021.102872.
2. Fuschiotti P. Current perspectives on the immunopathogenesis of systemic sclerosis. Immunotargets Ther. 2016;5:21-35. doi: 10.2147/itt.s82037.
3. 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. doi: 10.1155/2019/4569826.
4. Stern EP, Denton CP. The pathogenesis of systemic sclerosis. Rheum Dis Clin North Am. 2015;41(3):367-82. doi: 10.1016/j.rdc.2015.04.002.
5. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol. 2012;24(2):165-70. doi: 10.1097/BOR.0b013e32834ff2e8.
6. Coondoo A. The role of cytokines in the pathomechanism of cutaneous disorders. Indian J Dermatol. 2012;57(2):90-6. doi: 10.4103/0019-5154.94272.
7. Liu T, Li S, Ying S, Tang S, Ding Y, Li Y, et al. The IL-23/IL-17 pathway in inflammatory skin diseases: from bench to bedside. Front Immunol. 2020;11:594735. doi: 10.3389/fimmu.2020.594735.
8. 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):R4. doi: 10.1186/ar4430.
9. Truchetet ME, Brembilla NC, Chizzolini C. Current concepts on the pathogenesis of systemic sclerosis. Clin Rev Allergy Immunol. 2023;64(3):262-83. doi: 10.1007/s12016-021-08889-8.
10. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019;18(3):121-6. doi: 10.4103/aam.aam_56_18.
11. Wu B, Sodji QH, Oyelere AK. Inflammation, fibrosis and cancer: mechanisms, therapeutic options and challenges. Cancers (Basel). 2022;14(3):552. doi: 10.3390/cancers14030552.
12. Demir C, Şahin A, Küçükşahin O, Turgay T, Türkçapar N, Erten Ş, et al. Comparison of serum IL-23 and IL-17 levels in patients with systemic sclerosis and healthy subjects. J Clin Anal Med. 2015;6(1):83-7. doi: 10.4328/jcam.1709.
13. Yen D, Cheung J, Scheerens H, Poulet F, McClanahan T, McKenzie B, et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin Invest. 2006;116(5):1310-6. doi: 10.1172/jci21404.
14. Qu N, Xu M, Mizoguchi I, Furusawa J, 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. doi: 10.1155/2013/968549.
15. Lu R, Zeng X, Han Q, Lin M, Long L, Dan H, et al. Overexpression and selectively regulatory roles of IL-23/IL-17 axis in the lesions of oral lichen planus. Mediators Inflamm. 2014;2014:701094. doi: 10.1155/2014/701094.
16. O'Reilly S, Hügle T, van Laar JM. T cells in systemic sclerosis: a reappraisal. Rheumatology (Oxford). 2012;51(9):1540-9. doi: 10.1093/rheumatology/kes090.
17. Radstake TR, van Bon L, Broen J, Hussiani A, Hesselstrand R, Wuttge DM, et al. The pronounced Th17 profile in systemic sclerosis (SSc) together with intracellular expression of TGFbeta and IFNgamma distinguishes SSc phenotypes. PLoS One. 2009;4(6):e5903. doi: 10.1371/journal.pone.0005903.
18. Komura K, Fujimoto M, Hasegawa M, Ogawa F, Hara T, Muroi E, et al. Increased serum interleukin-23 in patients with systemic sclerosis. J Rheumatol. 2008;35(1):120-5.
19. Hammad GA, Eltanawy RM, Fawzy RM, Gouda TMA, Eltohamy MA. Serum interleukin-23 and its associations with interstitial lung disease and clinical manifestations of scleroderma. Egypt J Bronchol. 2018;12(1):69-75. doi: 10.4103/ejb.ejb_22_17.
20. Gourh P, Arnett FC, Assassi S, Tan FK, Huang M, Diekman L, et al. Plasma cytokine profiles in systemic sclerosis: associations with autoantibody subsets and clinical manifestations. Arthritis Res Ther. 2009;11(5):R147. doi: 10.1186/ar2821.
21. Olewicz-Gawlik A, Danczak-Pazdrowska A, Kuznar-Kaminska B, Gornowicz-Porowska J, Katulska K, Trzybulska D, et al. Interleukin-17 and interleukin-23: importance in the pathogenesis of lung impairment in patients with systemic sclerosis. Int J Rheum Dis. 2014;17(6):664-70. doi: 10.1111/1756-185x.12290.
22. Stritesky GL, Yeh N, Kaplan MH. IL-23 promotes maintenance but not commitment to the Th17 lineage. J Immunol. 2008;181(9):5948-55. doi: 10.4049/jimmunol.181.9.5948.
23. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;441(7090):235-8. doi: 10.1038/nature04753.
24. Nakayama W, Jinnin M, Tomizawa Y, Nakamura K, Kudo H, Inoue K, et al. Dysregulated interleukin-23 signalling contributes to the increased collagen production in scleroderma fibroblasts via balancing microRNA expression. Rheumatology (Oxford). 2017;56(1):145-55. doi: 10.1093/rheumatology/kew336.
25. Stamp LK, Easson A, Pettersson L, Highton J, Hessian PA. Monocyte derived interleukin (IL)-23 is an important

determinant of synovial IL-17A expression in rheumatoid arthritis. J Rheumatol. 2009;36(11):2403-8. doi: 10.3899/jrheum.081304.
26. Fransen K, van Sommeren S, Westra HJ, Veenstra M, Lamberts LE, Modderman R, et al. Correlation of genetic risk and messenger RNA expression in a Th17/IL23 pathway analysis in inflammatory bowel disease. Inflamm Bowel Dis. 2014;20(5):777-82. doi: 10.1097/mib.0000000000000013.
27. Hollis-Moffatt JE, Merriman ME, Rodger RA, Rowley KA, Chapman PT, Dalbeth N, et al. Evidence for association of an interleukin-23 receptor variant independent of the R381Q variant with rheumatoid arthritis. Ann Rheum Dis. 2009;68(8):1340-4. doi: 10.1136/ard.2008.090142.
28. Nakae S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. J Immunol. 2003;171(11):6173-7. doi: 10.4049/jimmunol.171.11.6173.
29. McKenzie BS, Kastelein RA, Cua DJ. Understanding the IL-23-IL-17 immune pathway. Trends Immunol. 2006;27(1):17-23. doi: 10.1016/j.it.2005.10.003.
30. Nguyen CQ, Hu MH, Li Y, Stewart C, Peck AB. Salivary gland tissue expression of interleukin-23 and interleukin-17 in Sjögren's syndrome: findings in humans and mice. Arthritis Rheum. 2008;58(3):734-43. doi: 10.1002/art.23214.
31. Toussirot E. The IL23/Th17 pathway as a therapeutic target in chronic inflammatory diseases. Inflamm Allergy Drug Targets. 2012;11(2):159-68. doi: 10.2174/187152812800392805.
32. Ratsimandresey RA, Duvallet E, Assier E, Semerano L, Delavallée L, Bessis N, et al. Active immunization against IL-23p19 improves experimental arthritis. Vaccine. 2011;29(50):9329-36. doi: 10.1016/j.vaccine.2011.09.134.
33. 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(4):350-6. doi: 10.30699/ijmm.16.4.350.
34. 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(12):3149-52.
35. Saheb Sharif-Askari F, Saheb Sharif-Askari N, Hafezi S, Mdkhana B, Alsayed HA, Ansari AW, et al. Interleukin-17, a salivary biomarker for COVID-19 severity. PLoS One. 2022;17(9):e0274841. doi: 10.1371/journal.pone.0274841.
36. 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(10):300060520941375. doi: 10.1177/0300060520941375.
37. Zian Z, Bakkach J, Barakat A, Ghailani Nourouti N, Bennani Mechita M. Salivary biomarkers in systemic sclerosis disease. Biomed Res Int. 2018;2018:3921247. doi: 10.1155/2018/3921247