Role of salivary caspase-1 and gasdermin D in the pathophysiology of rheumatoid arthritis in relation to salivary pH and flow rate of saliva

WASAN LAFTA ABDULLAH[1], ABBAS FADHIL AL-HASHIMY[2] and BATOOL HASSAN AL-GHURABI[3]

[1]Department of Basic Sciences, College of Dentistry, University of Baghdad, 89XH+47Q, Baghdad, Iraq;
[2]Department of Physiology, College of Medicine, Al-Nahrin University, 98HF+2R, Baghdad, Iraq;
[3]Department of Microbiology, College of Dentistry, University of Baghdad, 89XH+47Q, Baghdad, Iraq

Received June 8, 2024; Accepted October 8, 2024

DOI: 10.3892/wasj.2024.295

Abstract. Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting extra-articular organs, manifesting as symmetric polyarticular invasive joint inflammation. The disease pathogenesis involves cell death caused by lysis, known as pyroptosis, leading to the development of inflammation. Cytokines that promote inflammation, such as IL-18 and IL-1β, are released as a result of the NLRP3 inflammasome activating caspase (CASP)1, 3 and 4. Notably, the gasdermin D (GSDMD)-N-terminal allows substances to flow through the plasma membrane, and this protein is cleaved by CASP1 and other caspases. The present study aimed to evaluate the role of salivary CASP1 and GSDMD in the pathophysiology of RA, and determine the roles of the salivary flow rate and saliva pH. A control group and two groups of patients, including newly diagnosed and treated patients with RA, were enrolled in the present study. An independent rheumatologist rated the clinical disease activity score of each patient, and the saliva pH and salivary flow rate were also measured. In addition, ELISA was used to detect the expression levels of CASP1 and GSDMD. The results of the present study revealed that the CASP1 level was significantly increased in all patients with RA, compared with the control group. Notably, the levels of CASP1 differed between the treated patients with RA and those newly diagnosed with RA. The results also revealed that there were no significant differences in the levels of GSDMD between the groups. Moreover, there were significant differences in the mean saliva pH and salivary flow rate between all patients with RA and the control group. On the whole, the present study demonstrates that GSDMD and CASP1 may be required for the development of RA. Following the activation of CASP1, the development of RA is promoted via signals that amplify inflammatory responses. Understanding the specific roles of these signals may lead to the development of novel therapeutic approaches.

Correspondence to: Dr Wasan Lafta Abdullah, Department of Basic Sciences, College of Dentistry, University of Baghdad, 16 Bab Al-Moadam Road, 89XH+47Q, Baghdad, Iraq
E-mail: wasanlafta09@gmail.com

Key words: rheumatoid arthritis, caspase-1, gasdermin D, salivary flow rate

Introduction

Extra-articular organ involvement and symmetric polyarticular invasive joint inflammation are hallmarks of rheumatoid arthritis (RA), a chronic systemic inflammatory disorder. RA is characterized by synovitis (1). At present, 0.5-1.0% of patients present with RA worldwide, with greater prevalence rates observed in females and the elderly (2). RA involves immune cells and cytokines that trigger an inflammatory response, leading to damage in the arthritic joint (3,4). However, the pathophysiology of RA remains to be fully understood. At present, research is focused on the involvement of the inflammasome within rheumatic disorders. Pathogen pattern-recognition receptors (PRRs) form multimeric complexes on the inflammasome, and bind to damage-associated molecular patterns and pathogen-associated molecular patterns to facilitate host defense responses. In the majority of cases, pro-caspase (CASP)1, PRR and a protein adapter form the inflammasome (5). Following activation, CASP1 inhibits the binding between pro-IL-1, pro-IL-18 and gasdermin D (GSDMD), resulting in pyroptosis and in an inflammatory response (6). Moreover, following the activation of the inflammasome, GSDMD is cleaved into the GSDMD-N-terminal. Cleavage is promoted canonically or non-canonically via external stimuli or endogenous damage (7,8). GSDMD-induced pyroptosis protects the host from bacterial invasion (9). Numerous inflammatory diseases exhibit persistent inflammation mediated by abnormal GSDMD activation (10).

Temporomandibular joint disorders (11), and symptoms of dry mouth are oral complications associated with RA (12,13). In addition, patients with RA may experience extra-articular involvement of the skin, eyes, heart, lungs, kidneys, neurological system and gastrointestinal tract (14). Individuals with clinically diagnosed RA may also experience changes in salivary function (15). In the majority of the affected organs,

extra-articular symptoms of RA are caused by vascular vasculitis, which may be followed by arterial occlusion and vessel wall necrosis (14). The present study aimed to evaluate the role of salivary CASP1 and GSDMD in the pathophysiology of RA, and determine the potential associations between RA, saliva pH and salivary flow rate.

Subjects and methods

Subject information. Patients with RA (aged 20-60 years) were divided into two groups. The first group included 20 patients with a clinical diagnosis of RA who were not receiving any type of treatment from a rheumatologist (the newly diagnosed group). The second group included 40 patients with RA who had previously been treated with biological or non-biological Disease-modifying antirheumatic drugs (DMARD) in the Rheumatology Unit of the Baghdad Teaching Hospital (Baghdad, Iraq; treated group). Notably, rheumatologists in this unit evaluated the disease activity of all patients in each group using clinical disease activity score (CDAI).

Patient data was obtained, including name, age, sex, alcohol consumption, smoking history, family history, a history of systemic disorders and previous medications. In total, the control group included 16 male and 44 female participants. All patients in the control group were in good overall health, with no systemic disorders or immunological diseases and no previous medication. The age and sex of the individuals in the control group were matched to those of the RA groups. Patients were excluded from the present study according to the following criteria: An age >60 years, a history of smoking, alcoholism, or pregnancy at the time of the study.

All groups were examined between December, 2022 and mid-June, 2023. The present study was approved by the Institutional Review Board Ethics Committee at the College of Medicine, Al-Nahrain University, Baghdad, Iraq (ethics approval no. 20221029). The examination and collection of samples from patients with RA was approved by The Ministry of Health, Iraq. Written informed consent was obtained from all patients, and the Declaration of Helsinki was followed.

Assessment of disease activity using CDAI. In the Rheumatology Unit of The Baghdad Teaching Hospital, rheumatologists used CDAI to evaluate the disease activity of patients with RA (16).

Saliva collection. Unstimulated saliva collection was carried out according to the guidelines described by Tenovuo and Lagerlof (17). Samples were centrifuged for 10 min at 804.96 x g at room temperature (~20˚C), and divided into two groups for ELISA. Supernatants were stored at -200˚C until use in further experiments.

Calculation of salivary flow rate. All unstimulated saliva was collected from patients for 5 min. Volume was calculated and expressed as ml/min (18).

Determination of saliva PH. A digital pH meter with a single electrode was used to measure saliva pH (Jenway pH meter 3320) (19).

Detection of salivary CASP1. Salivary CASP1 was evaluated using ELISA, following the manufacturer's instructions (cat. no. ELK2076; ELK Biotechnology). Briefly, a microtiter plate was pre-coated with anti-CASP1 antibody (cat. no. ELK2076; ELK Biotechnology). Following the addition of samples, a biotin-conjugated anti-CASP1 antibody was added to the microtiter plate. Following incubation with primary antibodies for 50 min at 37˚C, the samples were incubated with horseradish peroxidase (HRP)-conjugated avidin (part number: ELK2076). TMB substrate solution (ELK Biotechnology, Co., Ltd.) was added to all wells, and color changes were observed in wells containing CASP1, biotin-conjugated antibody and enzyme-conjugated avidin. Changes in color were determined using a spectrophotometer (Thermo Fisher Scientific, Inc.) at 450±10 nm, and the enzyme-substrate reaction was terminated following the addition of sulphuric acid solution (ELK Biotechnology, Co., Ltd.). The optical density of the samples was read and compared with a standard curve to determine the concentration of CASP1.

Detection of salivary GSDMD. Salivary GSDMD was evaluated using ELISA, following the manufacturer's instructions (cat no. E6838Hu, Bioassay Technology Laboratory). Briefly, a plate was pre-coated with the anti-GSDMD antibody, and biotinylated human anti-GSDMD antibody was subsequently added. Following incubation with primary antibodies (provided with the kit) for 60 min at 37˚C, the samples were incubated with HRP-conjugated streptavidin, washed and substrate solution was added. Color development was indicative of human GSDMD. An acidic stop solution was added to all samples, and the absorbance was determined at 450 nm (using a spectrophotometer, Thermo Fisher Scientific, Inc.).

Statistical analysis. SPSS (version, 26; IBM Corp.) was used for statistical analysis. Differences between two groups were determined using unpaired Student's t-tests, and differences between multiple groups were determined using one-way ANOVA followed by a post hoc test (Duncan's multiple range comparisons). Percentage changes were determined using the Chi-squared test. Pearson correlation coefficient (r) was used to calculate the correlation between parameters. Receiving operating characteristics curve (ROC) analysis was used to determine the diagnostic capability of a binary discrimination system which plot the TPR (true positive rate) sensitivity against the false positive rate (1-specificity). A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographic characteristics of the study participants. The results of the present study revealed no significant differences in the age and sex of the participants between all groups. The mean disease duration in the treated RA group was 8.95±5.123 years. In addition, there was no significant difference in CDAI between the newly diagnosed and treated RA groups. The results of the present study demonstrated significant differences in the mean salivary flow rate and saliva pH between all patients with RA and the control group (Table I).

Table I. Demographic and clinical characteristics of the patients (treated and newly diagnosed patients) and the controls.

Variable	Treated group	Newly diagnosed group	Control group	P-value	P-value (treated group vs. newly diagnosed group)	P-value (treated group vs. control group)	P-value (newly diagnosed group vs. control group)
Age in years, median (IQR)	45.0000 (17.75)	42.0000 (19.25)	39.0000 (17.50)	0.099			
Sex, n (%)				0.200			
Male	12 (30%)	2 (10%)	16 (26.7%)				
Female	28 (70%)	18 (90%)	44 (73.3%)				
Duration of disease (years), mean ± SD	8.95±5.123	-	-	-			
CDAI, mean ± SD	16.95±8.748	19.55±8.858		0.200			
Salivary flow rate (ml/ min), mean ± SD	0.6518±0.42002	0.9105±0.70285	1.0402±0.48654	0.01	0.999	0.001[a]	0.756
pH of saliva, mean ± SD	7.5168±0.36498	7.3480±0.25345	7.1438±0.08501	0.01[a]	0.999	0.001[a]	**0**008[a]
Salivary CASP1 (ng/ml), mean ± SD	2.0134±0.74364	1.8665±0.89211	1.5183±0.37402	0.01[a]	0.457	0.002[a]	0.999
Salivary GSDMD (ng/ml), mean ± SD	3.1514±1.38895	3.4849±1.18221	3.2260±0.90858	0.50			

[a]Indicates a statistically significant difference (P<0.05). CASP1, caspase-1; GSDMD, gasdermin D; CDAI, clinical disease activity score.

Table II. Levels of CASP1 and GSDMD, and the disease activity score among treated and newly diagnosed patients.

Groups	Disease activity	Salivary CASP1, mean ± SD	Salivary GSDMD, mean ± SD
Treated	Low	2.0575±0.58939	2.9544±1.59425
	Moderate	2.1211±0.89705	3.1340±1.35189
	High	1.7050±0.53007	3.4509±1.27984
	P-value	0.4	0.7
Newly diagnosed	Low	1.6800±0.34496	3.4610±0.70885
	Moderate	1.7111±0. 50755	3.5117±1.40661
	High	2.1729±1.39582	3.4640±1.23875
	P-value	0.5	0.9

There were no statistically significant differences between all groups as regards disease activity. CASP1, caspase-1; GSDMD, gasdermin D.

Detection of salivary CASP1and GSDMD. The results of the present study revealed a significant difference in the mean salivary CASP1 levels between all three groups, with 2.0134, 1.8665 and 1.5183 ng/ml observed in the treated RA, newly diagnosed and control groups, respectively. In addition, the mean salivary CASP1 level was notably higher in the newly diagnosed group compared with the control group. However, there was no significant difference in the mean salivary CASP1 level between the treated RA and newly diagnosed groups (Table I).

In addition, the results of the present study revealed that the mean salivary GSDMD levels were 3.4849, 3.1514 and 3.2260 ng/ml in the treated RA, newly diagnosed and control groups, respectively; however, differences between groups were not significant. In addition, there were no notable differences in the means of GSDMD and CASP1 in the saliva of the two groups of RA when these were divided according to disease activity score to low, moderate and high activity (Table II). Moreover, the results demonstrated no notable correlation between CASP1, GSDMD, saliva pH or salivary flow rate (Table III).

Table III. Correlation between salivary biomarker and oral manifestation.

Parameter	GSDMD	pH of saliva	Flow rate
CASP1			
Pearson's correlation (r value)	0.095	0.090	.027
P-value (two-tailed)	0.380	0.404	0.803
GSDMD			
Pearson's correlation (r value)		0.012	-0.098
P-value (two-tailed)		0.907	.358
pH of saliva			
Pearson's correlation (r value)			-0.167
P-value (two-tailed)			0.117

CASP1, caspase-1; GSDMD, gasdermin D.

Diagnostic value of CASP1 and GSDMD. ROC analysis was used to determine the diagnostic value of CASP1 and GSDMD in patients with RA. CASP1 in the treated group revealed an area under the curve (AUC) of 0.7 (P=0.001), while GSDMD was not found to be efficient. At a 1.525 cut-off, CASP1 could predict the inflammation and disease activity in the treated RA group at a sensitivity of 78% and specificity of 63%. By contrast, the results of the ROC analysis demonstrated that CASP1 and GSDMD were not associated with disease activity in the newly diagnosed group (Fig. 1).

Discussion

The results of the present study demonstrated that RA often affects adults during their 40th decade of life, which is consistent with the results of the study by Ranade and Doiphode (20). The results of the present study revealed no significant differences in age or sex between the three study groups, which was comparable with the results of the study by Al Ghuraibawi *et al* (21). In the present study, the majority of patients with RA were female, which was also consistent with the study by Alkazzaz (22). The prevalence of RA may be higher among females due to gene silencing on the X chromosome, which plays a key role in the development of autoimmune disease. Notably, skewed inactivation may lead to differences in gene silencing in the maternal and paternal X chromosomes, resulting in distinct self-antigens that trigger a greater immune response. The reactions between self-antigens promote the development of auto-immune reactions, and the development of disease, such as RA (23).

The present study revealed that the salivary flow rate was significantly increased in patients with RA, compared with the control group. This outcome is consistent with the study conducted by Majid *et al* (24). This suggests that the salivary glands are one of the main target organs of RA, since RA is considered to be associated with the infiltration of lymphocytes of affected glands, leading to decreased chemical and salivary changes (25). In the present study, there were no appreciable changes between the newly diagnosed and treated patients with RA; however, the salivary pH increased significantly in the two patient groups compared with the control group. The

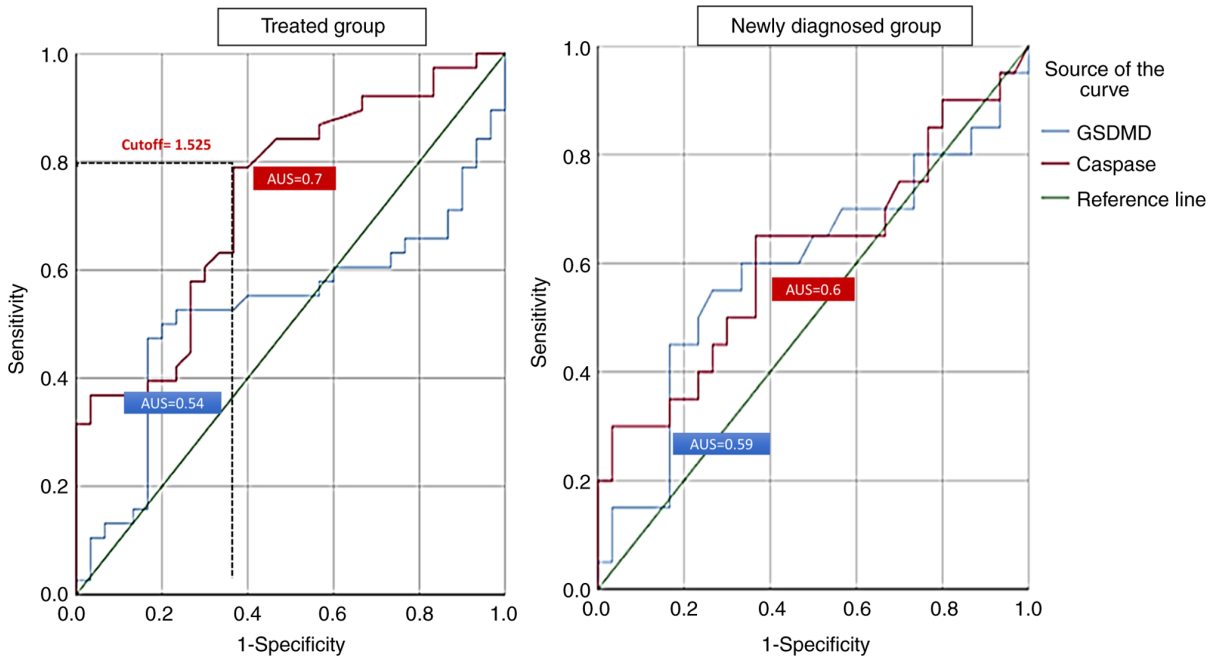

Figure 1. ROC curve analysis of CASP1 and GSDMD in patients with RA. For the treated group (left panel), the AUC for CASP1 was 0.7 (P=0.001) with optimal stratification achieved at a 1.525 cut-off value; for GSDMD, the AUC was 0.54. For the newly diagnosed patients (right panel), both tests were not efficient at predicting disease activity. ROC, receiver operating characteristic; AUC, area under the curve; CASP1, caspase-1; GSDMD, gasdermin D.

study by Fadhil and Ahmed (26), which discovered a substantial decrease in salivary pH levels between the treated RA and control groups, is in conflict with this conclusion. The findings of that study demonstrated that an increase in the physiological salivary pH range corresponds to an increase in saliva flow rate and vice versa (26). The results of the present study revealed that patients with RA exhibited increased levels of salivary CASP1 compared with the control group, and these results were comparable with those obtained in the study by Kim *et al* (27). However, Karabulut *et al* (28) observed the opposite result.

Kim *et al* (27) investigated the reason behind the increase in CASP1 levels in the serum of patients receiving treatment for RA. They found that CASP1 activation is a sign of inflammasome activation, which is crucial for inducing an inflammatory response in macrophages. suggests that the RA drug may have an effect on CASP1 expression. The therapeutic strategy may affect CASP1 expression and activity (29). In the present study, the median value of salivary CASP1 in the newly diagnosed group was higher than that in the control group, which suggests the involvement of CASP1in the early stages of RA development. There were no significant differences in the median value of salivary CASP1 between the treated and newly diagnosed groups. This result is in accordance with the result presented in the study by Cascão *et al* (30).

The results of the present study demonstrated that there were no notable differences in the mean salivary GSDMD levels between the three groups. To the best of our knowledge, the present study is the first to investigate the levels of GSDMD in the saliva of patients with RA. Notably, Zhang *et al* (31) investigated the synovial expression of cleaved GSDMD using immunohistochemistry and multiplex immunohistochemistry. The results of the study by Zhang *et al* (31) demonstrated that patients with RA exhibited increased inflammasomes and GSDMD-N-terminal in the synovium, compared with patients with osteoarthritis. This result is in disagreement with that of the study conducted by Al Obaidi and Al Ghurabi (32), which discovered elevated levels of NLRP3, which caused the release of GASDMD in the patient group (periodontitis).

Of note, a limitation of the present study was that the concentrations of CASP1 (inactive form) and GSDMD (inactive form) were quantified in saliva. Nevertheless, the active forms were not quantified. Thus, further studies are required to further investigate these parameters.

In conclusion, the findings of the present study provide valuable insight into the role of GSDMD and CASP1 in the context of RA. The significance of these differences in the means of CASP1 indicate that it could be a critical factor in the severity and progression of RA. This aligns with existing literature that highlights the importance of inflammatory mediators in the pathogenesis of RA, suggesting that CASP1 may be a potential target for therapeutic intervention.

Acknowledgements

The authors would like to thank Dr Ali Hussein and Dr Adnan Sadkhan, Rheumatologists at the Rheumatology Unit of the Baghdad Teaching Hospital for their great contribution in the assessment of the severity of rheumatoid arthritis in patients depending on the clinical disease activity score.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WLA was involved in the conception and design of the study, in the literature search, in clinical analysis, data analysis, statistical analysis, and in the preparation and reviewing of the manuscript. AFAH was involved in the conception and design of the study, in data analysis, and in the preparation and reviewing of the manuscript. BHAG was involved in the conception and design of the study and was also involved in the preparation and reviewing of the manuscript. WLA and BHAG confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board Ethics Committee at the College of Medicine, Al-Nahrain University, Baghdad, Iraq (ethics approval no. 20221029). The examination and collection of samples from patients with RA was approved by The Ministry of Health, Iraq. Written informed consent was obtained from all patients, and the Declaration of Helsinki was followed.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Scott DL, Wolfe F and Huizinga TWJ: Rheumatoid arthritis. Lancet 376: 1094-1108, 2010.
2. Rudan I, Sidhu S, Papana A, Meng SJ, Xin-Wei Y, Wang W, Campbell-Page RM, Demaio AR, Nair H, Sridhar D, *et al*: Prevalence of rheumatoid arthritis in low- and middle-income countries: A systematic review and analysis. J Glob Health 5: 010409, 2015.
3. Alippe Y and Mbalaviele G: Omnipresence of inflammasome activities in inflammatory bone diseases. Semin Immunopathol 41: 607-618, 2019.
4. Aldhaher Z, Al-Ghurabi B and Alwan BH: Serum levels of IL-22 and ACPA in patients with rheumatoid arthritis. J Pure Appl Microbiol 12: 687-691, 2018.
5. Broz P and Dixit VM: Inflammasomes: Mechanism of assembly, regulation and signalling. Nat Rev Immunol 16: 407-420, 2016.
6. Boucher D, Monteleone M, Coll RC, Chen KW, Ross CM, Teo JL, Gomez GA, Holley CL, Bierschenk D, Stacey KJ, *et al*: Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity. J Exp Med 215: 827-840, 2018.
7. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F and Shao F: Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature 526: 660-665, 2015.
8. Abdullah WL, Al-Hashimy AF, Al-Ghurabi BH and Ramakrishnan M: Focus on the Function and mechanism of pyroptosis in rheumatoid arthritis. Al-Salam J Med Sci 3: 28-36, 2024.
9. Wang J, Deobald K and Re F: Gasdermin D protects from melioidosis through pyroptosis and direct killing of bacteria. J Immunol 202: 3468-3473, 2019.
10. Wang J, Yao J, Liu Y and Huang L: Targeting the gasdermin D as a strategy for ischemic stroke therapy. Biochem Pharmacol 188: 114585, 2021.
11. Garib BT and Qaradaxi SS: Temporomandibular joint problems and periodontal condition in rheumatoid arthritis patients in relation to their rheumatologic status. J Oral Maxillofac Surg 69: 2971-2978, 2011.
12. Guobis Z, Baseviciene N, Paipaliene P, Niedzelskiene I and Januseviciūte G: Aspects of xerostomia prevalence and treatment among rheumatic inpatients. Medicina (Kaunas) 44: 960-968, 2008.
13. Abdulla WL, A-Ghurabi BH and Gathwan KH: An Impairment of salivary gland function in rheumatoid arthritis: Association with change in salivary biomarkers and disease activity. J Bagh Coll Dent 28: 165-170, 2016.
14. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD and Tanasescu R: Extra-articular manifestations in rheumatoid arthritis. Maedica (Bucur) 5: 286-291, 2010.
15. Torres SR, Pedrazas CH, Correia MP, de Azevedo MNL, Zamprogno T, Silva A Jr, Gonçalves LS and Papi JA: Drugs or disease: Evaluating salivary function in RA patients. Bra Oral Res 30: e106, 2016.
16. Van der Heijde DM, Van't Hof M, Van Riel PL and Van de Putte LB: Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 20: 579-581, 1993.
17. Tenovuo J and Lagerlof F: Saliva. In: Thylstrup A and Fejerskov O (eds). Textbook of clinical cariology. 2nd edition. Copenhagen: Munksgaard, pp17-43, 1994.
18. Navazesh M and Kumar SKS; University of Southern California School of Dentistry: Measuring salivary flow: Challenges and opportunities. J Am Dent Assoc 139 (Suppl): 35S-40S, 2008.
19. Baliga S, Muglikar S and Kale R: Salivary pH: A diagnostic biomarker. J Indian Soc Periodontol 17: 461-465, 2013.
20. Ranade SB and Doiphode S: Is there a relationship between periodontitis and rheumatoid arthritis? J Indian Soc Periodontol 16: 22-27, 2012.
21. Al Ghuraibawi ZAG, Sharquie IK and Gorial FI: A novel link of serum IL-39 levels in patients with rheumatoid arthritis. Iraqi J Sci 64: 1651-1661, 2023.
22. Alkazzaz AMH: Incidence of rheumatoid arthritis [2001 to 2011]. Iraqi Postgrad Med J 12: 568-572, 2013.
23. Valencia M: Sex and gender in rheumatoid arthritis: considering a risk factor hierarchy. Cornell Undergrad Res J 1: 23-29, 2022.
24. Majid AY, Talal S and Abdulla WL: Estimation of some salivary elements in rheumatoid arthritis patients. Int J Adv Res 3: 13-17, 2016.
25. Nagler RM, Salameh F, Reznick AZ, Livshits V and Nahir AM: Salivary gland involvement in rheumatoid arthritis and its relationship to induced oxidative stress. Rheumatology (Oxford) 42: 1234-1241, 2003.
26. Fadhil HNM and Ahmed KM: Evaluation of salivary anti-CCP in relation to some oral manifestations in rheumatoid arthritis patients, Sulaimaniyah, Iraq. Res Sq: 1-18, 2023.
27. Kim SH, Lee JH, Jeong HJ, Kim JM, Baek WK, Kim TH, Jun JB and Son CN: Clinical significance of elevated serum caspase-1 levels in patients with ankylosing spondylitis. Ann Lab Med 42: 293-295, 2022.
28. Karabulut G, Kitapçıoğlu G, Özçaka Ö, Alpöz E, Nalbantsoy A, Koçanaoğulları H, Gücenmez S, Keser G and Kabasakal Y: Saliva levels of caspase-1, TNF-α, and IFN-γ in primary Sjögren's syndrome: Oral mucosal abnormalities revisited. Turk J Med Sci 48: 554-559, 2018.
29. Manna SK, Mukhopadhyay A and Aggarwal BB: Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: Potential role of reactive oxygen intermediates and lipid peroxidation. J Immunol 164: 6509-6519, 2000.
30. Cascão R, Polido-Pereira J, Canhão H, Rodrigues AM, Navalho M, Raquel H, Neves-Costa A, Mourão AF, Resende C, da Silva JA, *et al*: Caspase-1 is active since the early phase of rheumatoid arthritis. Clin Exp Rheumatol 30: 144, 2012.
31. Zhang X, Wang Q, Cao G, Luo M, Hou H and Yue C: Pyroptosis by NLRP3/caspase-1/gasdermin-D pathway in synovial tissues of rheumatoid arthritis patients. J Cell Mol Med 27: 2448-2456, 2023.
32. Al Obaidi MJ and Al Ghurabi BH: Potential role of NLRP3 inflammasome activation in the pathogenesis of periodontitis patients with type 2 diabetes mellitus. J Med Chem Sci 6: 522-531, 2023.

Copyright © 2024 Abdullah et al. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) License.