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Dental and Oral Manifestations of Rheumatoid Arthritis: Is It Related to General Disease Activity?

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ORIGINAL STUDY

Dental and oral manifestations of rheumatoid arthritis: is it related to general disease activity?

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Abstract

Background: **RA is a chronic immune-mediated systemic disorder; its pathogenesis is complex. Genetic, environmental, hormonal, and lifestyle are the main risk factors. The correlation between oral health and RA is rising. Oral manifestations in RA include temporomandibular joint disorder, secondary Sjögren's syndrome, xerostomia, and periodontal disease. Previous studies suggest a bidirectional relationship between RA and periodontal diseases. This study aims to detect oral mucosal and dental disease in RA patients and its relation to demographic features, disease activity, and extra-articular manifestation.**

Patients and methods: **This cross-sectional study included 150 patients with RA allocated into two groups, 75 patients in each group, according to RA disease control with Anti-rheumatic medications: Group A included patients who had controlled RA and receiving Anti-rheumatic medications, and Group B included uncontrolled RA patients not receiving Anti-rheumatic medications. The assessment included DAS-28, ESR, CRP, RF, and ACCPA measurements. The oral and dental examination included: probing pocket depth, clinical attachment level, gingival recession height measurement, gingival Index, mobility Index, the Plaque Index System, dry mouth, the DMF index, and bleeding on probing.**

Result: **The dental and oral findings were statistically significantly higher in group B compared to group A, except for gingival recession height. There was a positive correlation between probing pocket depth, clinical attachment level, gingival Index, mobility Index, the Plaque Index System, dry mouth, the DMF index, bleeding on probing and age, extra-articular manifestations, TMJ disorder, DAS-28, ESR, CRP, RF and ACCPA levels. No correlation was found between gingival recession height and age, extra-articular manifestations, TMJ disorder, and RF.**

Conclusion: **Our study revealed higher dental and oral manifestations in patients not receiving anti-rheumatic medications. Dental manifestations correlated positively with age, extra-articular manifestations, tempromandibular joint disorder, rheumatoid arthritis disease activity score, acute phase reactant, and autoantibodies levels.**

Keywords: Dental, Oral, Periodontitis, Rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated systemic disorder that mainly affects the joints causing synovial membrane inflammation, joints, and bone destruction resulting in functional disturbance and impaired quality of life. The extra-articular manifestations of RA include affection of the skin, eyes, lungs, cardiovascular system, nerves, and blood [1]. RA also may increase the risk of certain cancers like lymphoma and lung cancer [2].

RA prevalence ranges from 0.5 to 1% worldwide. Although it can occur at any age its incidence is higher during middle age, with female to male ratio of 3:1 [3]. The pathogenesis of RA is complex in which genetic, environmental, hormonal, and lifestyle are the main risk factors [4].

The correlation between oral health and autoimmune inflammatory disease is rising. Different oral

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manifestations have been described in patients with RA; temporal-mandibular joint disorder, xerostomia, secondary Sjögren's syndrome, and periodontal disease [5]. Xerostomia is one the most clinical finding in patients with RA as it affects up to 50% of patients, while about 30% of patients with RA have a reduced function of salivary glands, in particular the parotid gland [6]. Common symptoms of reduced salivary production are oral dryness, oral burning, difficulty swallowing, and decreased or loss of taste sensation [7]. Xerostomia increases the susceptibility to other oral conditions like dental caries in particular cervical caries, periodontal disease, candidiasis, and halitosis. Furthermore, patients using dentures experience loss of retention and denture discomfort [8].

Periodontal disease includes gingivitis and periodontitis. In gingivitis, there is inflammation of the gingival epithelium and the connective tissue, while in periodontitis the inflammation affects the tooth-supportive tissue leading to attachment loss and destruction of the bone. Periodontal disease is triggered by infection caused by polymicrobial synergy and dysbiosis where there is a microbial shift from gram-positive microbiota to gram-negative microbiota. This dysbiosis disrupts both the innate and the adaptive immune systems with an imbalance between the pro-inflammatory and anti-inflammatory mediators, with the release of many inflammatory cytokines and metalloproteinases expression leading to the destruction of the tooth-supportive tissue and the bone [9].

RA and Periodontal disease share several risk factors including genetic factors, as both are associated with HLA DRB104 and PTPN22, infection; studies suggest that porphyromonas gingivalis and aggregatibacter and actinomycetemcomitans, a common periodontal bacteria, play a crucial role in the link between periodontitis and RA. Smoking can worsen periodontitis, stimulates the citrullination of peptides by peptiylarginine deiminases, and triggers anticitrullinated peptide antibody response in RA [10]. A specific bacteria species, *P. gingivalis*, has been recognized in patients with RA, and it increases the progression from gingivitis to aggressive periodontitis (***Snyderman R*** et al., *1982*).

Several studies suggest a bidirectional relationship between RA and Periodontal disease. Both conditions are characterized by chronic inflammation where there is a discrepancy of the pro-inflammatory and anti-inflammatory mediators that leads to tissue and bone destruction, which is mediated by the increased production of TNF, IL-1, IL-6, prostaglandin-E2, and other inflammatory mediators. Several pathways have been proposed on how periodontitis interferes with the pathogenesis of RA, like the presence of bacteremia and the release of inflammatory cytokines, bacterial antigens, and immunoglobulin into the serum [11]. Peptide citrullination plays an important role in the pathogenesis of RA. *P. gingivalis* is capable of citrullination by increasing the expression and function of peptidylarginin enzyme translational modification, neoepitope generation, and formation of anticitrullinated peptide antibodies [12]. On the other hand, RA can impact periodontitis as patients with RA often suffer from reduced motor activity and the involvement of the temporomandibular joint which makes it harder for them to carry out or maintain oral hygiene. Reduced salivary flow which could be a side effect of anti-rheumatic medication or due to secondary Sjögren syndrome increases the supragingival plaque formation which in turn increases the risk of periodontal diseases [11].

Most previous studies focused on one or more aspects of oral and dental manifestations in RA. In this study, we aimed to detect oral mucosal and dental disease in RA patients and its relation to demographic features, disease activity, and extra-articular manifestation.

2. Patient and method

This cross-sectional study included 150 patients with RA diagnosed according to the American College of Rheumatology/EULAR 2010 RA Classification Criteria [13]. Patients were recruited from the outpatients' clinics of the Department of Oral Medicine and Periodontology and the Department of Rheumatology, Banha Teaching Hospital, Banha, Egypt. Patients were allocated into two groups according to RA disease control through anti-rheumatic medications: group A included patients with controlled disease activity, patients were either in remission or had low disease activity, and receiving anti-rheumatic drugs and group B which included patients with uncontrolled disease activity and were not receiving any Anti-rheumatic medications, each group included 75 patients. Inclusion criteria were: age >18 years, diagnosed with RA for at least one year, ability to tolerate oral and dental examination procedures, and the ability and willingness to give written informed consent. The following patients were excluded from the study; the presence of other co-morbidities (sepsis, diabetes, cardiac, hepatic, renal diseases), pregnant or nursing females, patients diagnosed with overlap syndrome, presence of congenital dental abnormalities, poor oral hygiene, and heavy smoking. The study was explained

to the participants and written Informed consent was given by each participant. The study was approved by the Ethics Committee of Scientific Research, Banha Teaching Hospital.

2.1. Methods

The patients were subjected to the following assessment:

(1) Full history taking including drug history
(2) General and musculoskeletal examination (including temporomandibular joint line tenderness, click, reduced jaw opening)
(3) Assessment of disease activity using disease activity score 28- ESR (DAS-28-ESR) [14]. ***The score was interpreted as following***
   (a) <2.6 Disease remission.
   (b) 2.6−3.2 Low disease activity
   (c) >3.2−5.1 Moderate disease activity
   (d) >5.1 High disease activity
(4) Measurement of acute phase reactants: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
(5) Measurement of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACCPA)
(6) An oral and dental examination included the following parameters:

2.1.1. Probing pocket depth (PPD)

For each tooth in the arch, the probing pocket depth was measured from the free gingival margin till the end of the pocket on the mesial, buccal, distal, and lingual surfaces. The standard William's graduated periodontal probe was used with the long axis parallel to the examined tooth with a force of nearly 25 g [15].

2.1.2. Clinical attachment level (CAL)

The attachment level was measured from the cementoenamel junction to the base of the sulcus using the standard William's graduated periodontal probe with the same principles of detecting probing probe.

2.1.3. Gingival recession height measurement (RH)

By measuring the distance in millimeters between the cementoenamel junction (CEJ) and the gingival margin. The gingival recession defect was graded using *Miller's classification system 1985* as following:

(1) Class I: Marginal tissue recession does not extend to the mucogingival junction (MGJ) with no periodontal loss (bone or soft tissue) in the interdental area, and 100% root coverage can be anticipated
(2) Class II: Marginal tissue recession extends to or beyond the MGJ with no periodontal loss in the interdental area, and 100% root coverage can be anticipated
(3) Class III: Marginal tissue recession extends to or beyond the MGJ. Bone or soft tissue loss in the interdental area is present or there is a mal-positioning of the teeth, which prevents the attempting of 100% of root coverage. Partial root coverage can be anticipated. The amount of root coverage can be determined presurgically using a periodontal probe
(4) Class IV: Marginal tissue recession extends to or beyond the MGJ. The bone or soft tissue loss in the interdental area and/or mal-positioning of teeth is so severe that root coverage cannot be anticipated.

2.1.4. Gingival index (GI)

The gingival index of [16] is used to assess the degree of gingival inflammation on a scale of 0−3.

0: Normal gingival
1: Mild inflammation: a slight change in color and slight edema. No bleeding on probing.
2: Moderate inflammation: redness, edema, glazing, and bleeding on probing.
3: Severe inflammation: marked redness, edema, and laceration with a tendency toward spontaneous bleeding.

2.1.5. Mobility Index [17]

Grade 0: No apparent mobility.
Grade 1: Perceptible mobility <1 mm in buccolingual direction.
Grade 2: >1 mm but <2 mm.
Grade 3: >2 mm or depressibility in the socket.

2.1.6. The plaque index [18]

0: No plaque
1: A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after the application of disclosing solution or by using the probe on the tooth surface.
2: Moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin, can be seen with the naked eye.

3: Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

2.1.7. Dry mouth

Dry mouth was assessed based on physical observation [19].

2.1.8. The DMF index

DMF is expressed as the total number of teeth or surfaces that are Decayed (D), Missing (M), and Filled (F) for an individual [20].

2.1.9. Bleeding on probing [21]

0: No bleeding.
1: Only one bleeding point appears.
2: Several isolated bleeding points or small blood areas appear.
3: Interdental triangle filled with blood soon after probing.
4: Profuse bleeding when probing, blood spreads towards the marginal gingiva.

Statistical analysis was performed using the full detailed form: SPSS 24, IBM, Armonk, NY, United States of America. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-sample t-test of significance was used when comparing the two means. A Chi-square (X^2) test of significance was used to compare proportions between two qualitative parameters. Pearson's correlation coefficient (r) test was used for correlating data. A statistically significant difference was regarded when the probability value is < 0.05.

3. Result

A total of 150 patients with RA were included in this study; patients were allocated into two groups according to the RA disease activity control and usage of Anti-rheumatic medications. Patients in group A had controlled disease and were receiving anti-rheumatic medications while patients in group B had uncontrolled disease and were not receiving anti-rheumatic medications. Each group included 75 patients.

3.1. Demographic and disease characteristics

There were 71 female and 4 males in group A, while in group B there was 67 females and 8 males. In Group A, the age ranged from 50 to 57, while in Group B it was 43−56. There was no significant difference between the two groups regarding gender and age. All disease characteristics were significantly higher in Group B compared to Group A that includes: extra-articular manifestations, temporomandibular joint affection, DAS-28, Acute phase reactant (ESR, CRP), and serology (RF and ACCPA) (Table 1).

3.2. Dental and oral findings

The dental and oral findings were statistically significantly higher in group B compared to group A, except for gingival recession height, there was no statistically significant difference between the two groups (Table 2), Figs. 1−4.

3.3. The relation between the dental and oral findings and various demographic, extra-articular manifestations and RA disease activity

A correlation study between the different parameter of dental findings and various demographic, extra-articular manifestations, and RA disease activity showed a positive correlation between different dental findings and each of age, extra-articular manifestations including dry mouth, tempromandibular joint disorder, disease activity score, ESR, CRP, RF, and ACCPA levels, while there was no correlation between dental findings and gender. Also, there was no correlation between gingival recession height and each of age, extra-articular manifestations, tempromandibular joint disorder, and RF (Table 3).

4. Discussion

Different oral and dental manifestations such as tempromandibular joint disorders, secondary Sjogren syndrome, xerostomia and periodonatal disease have been associated with RA. RA and periodontitis are chronic inflammatory conditions that share many risk factors and pathological similarities [22].

In this study, we aimed to detect oral mucosal and dental disease in RA patients and its relation to demographic features, disease activity, and extra-articular manifestation. In our study there was a positive correlation between age and different dental parameters (except for gingival recession height) while there was no correlation between all the dental findings and gender. As a more aggressive RA with increased disease activity and disability were reported in females, it was expected that females have more severe periodontal disease. Our finding agrees with a study by [23] which showed a correlation between age and CAL, while there was no correlation with gender. Multivariate

Table 1. Demographic and disease characteristics.

	Group A	Group B No. (%)	t/X^2	*P*
Gender (No, %)				
Female	71 (94.7%)	67 (89.3%)	1.449	0.229
Male	4 (5.3%)	8 (10.7%)		
Age (Years)				
Mean ± SD	52.99 ± 1.56	53.29 ± 1.93	1.069	0.287
Range	50–57	43–56		
Extra-articular manifestations (No, %)				
Rheumatoid nodule	6 (8%)	15 (20%)	4.46	0.01
Amyloidosis	1 (1.33%)	7 (9.33%)	4.73	0.03
ILD	1 (1.33%)	8 (10.67%)	5.76	0.02
anemia	29 (38.67%)	62 (82.67%)	30.22	0.001
TMJ tenderness				
(No,%)	12 (16%)	39 (52%)	21.513	0.001
DAS-28 (No, %)				
Remission	7 (9.3%)	0 (0%)	130.909	0.001
Low	68 (90.7%)	0 (0%)		
Moderate	0 (0%)	15 (20%)		
High	0 (0%)	60 (80%)		
ESR (1st hour, mm/hr)				
Range	20–40	49–80	26.827	0.001
Mean ± SD	31.99 ± 4.78	64.34 ± 9.29		
CRP				
Range	20–70	60–500	19.169	0.001
Mean ± SD	31.04 ± 12.55	273.12 ± 108.65		
RF				
Range	23–39	45–78	34.148	0.001
Mean ± SD	31.23 ± 4.12	61.29 ± 6.42		
ACCPA				
Range	23–35	34–70	26.082	0.001
Mean ± SD	26.39 ± 4.39	56.71 ± 9.06		

ACCPA, anti-cyclic citrullinated antibody; CRP, C-reactive protein; DAS-28, disease activity score; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; TMJ, temporomandibular joint.
$P < 0.05$ statistically significant.

analysis in a study by [24] showed an association between age and female gender and periodontitis severity. This was supported by the findings of Tadjoedin et al. [25], which showed that the prevalence and the severity of periodontal disease tend to relate to age. The reduction in mitotic activity and metabolic rate associated with age leads to deterioration in tissue integrity and impairment of the immune system. As a result, elderly patients are more susceptible to bacterial infection and periodontal diseases. On the other hand, another study by Marotte et al. [26] showed no correlation between age and periodontitis severity, and Ioannidou [27] reported a higher prevalence of periodontitis in males which was explained by their smoking habits, association with other chronic diseases like diabetes and oral hygiene.

We also found a positive correlation between dental findings except for the gingival recession height and different extra-articular manifestations including the dry mouth. Dry mouth was found to be linked to gingival disease through accumulation of dental plaque [28]. This finding disagrees with a study by [29] in which there was no association between periodontal disease and secondary Sjögren's syndrome. The discrepancy between findings could be a result of the way the dry mouth was evaluated in our study it was assessed by physical observation with no objective assessment of the salivary flow rate. Another study by [24] showed an association between severe periodontitis and rheumatoid nodules which agrees with our study. The association between periodontal disease and extra-articular manifestations could be explained by the higher frequency of these manifestations in patients with uncontrolled higher disease activity of RA [24].

We also found a positive correlation between tempromandibular joint disorder and dental manifestation (except for gingival recession height). Involvement of the temporomandibular joint makes it harder for patients to carry out or maintain oral hygiene [11]. This finding agrees with [30] study but disagrees with [29] study as they found no association between periodontal disease and tempromandibular joint involvement.

Table 2. Dental and oral findings.

Variable (No,%)	Group A	Group B	X^2	*P*
Mobility				
Normal	18 (24%)	0 (0%)	105.356	0.001
Low	44 (58.7%)	1 (1.3%)		
Moderate	13 (17.3%)	47 (62.7%)		
High	0 (0%)	27 (36%)		
Propping depth				
Normal	9 (12%)	0 (0%)	128.001	0.001
Low	66 (88%)	6 (8%)		
Moderate	0 (0%)	19 (25.3%)		
High	0 (0%)	50 (66.7%)		
CAL				
Low	5 (6.7%)	0 (0%)	121.282	0.001
Moderate	70 (93.3%)	8 (10.7%)		
High	0 (0%)	67 (89.3%)		
Gingival recession				
Low	43 (57.3%)	26 (34.7%)	1.449	0.229
Moderate	32 (42.7%)	49 (65.3%)		
High	0 (0%)	0 (0%)		
Gingival index				
0	2 (2.7%)	0 (0%)	104.330	0.001
1	57 (76.0%)	1 (1.3%)		
2	16 (21.3%)	30 (40%)		
3	0 (0%)	44 (58.7%)		
Plaque index				
Normal	2 (2.7%)	0 (0%)	105.883	0.001
Low	57 (76%)	1 (1.3%)		
Moderate	16 (21.3%)	27 (36%)		
High	0 (0%)	47 (62.7%)		
DMF index				
Low	21 (28%)	0 (0%)	108.090	0.001
Moderate	54 (72%)	17 (22.7%)		
High	0 (0%)	58 (77.3%)		
Bleeding on probing				
Low	55 (73.3%)	0 (0%)	113.243	0.001
Moderate	20 (26.7%)	17 (22.7%)		
High	0 (0%)	58 (77.3%)		
Dry mouth	23 (30.67%)	45 (60%)	12.849	0.001

CAL, Clinical attachment level; DMF, decay missing filled index. $P < 0.05$ statistically significant.

In the current work there was a correlation between different dental manifestations and RA disease activity score which agrees with a study by [29,31]. The authors suggested that the severity of RA and joint destruction activity and reduced functional activity affects the periodontal status. This finding disagrees with a study by [32], which showed no association between RA activity and the severity of periodontal disease. There was also a positive correlation between acute phase reactant, ESR and CRP, with different dental findings. Both RA and periodontitis are chronic inflammatory conditions that are associated with increased markers of inflammation [33].

A positive correlation between autoantibodies, ACCPA and RF levels, and dental manifestations was found, with the exception of the correlation between RF the gingival recession height, where there was no correlation between them. This agrees with a study by [34] which also showed that the stages of periodontitis in ACCPA's positive patients were more severe than ACCPA's negative patients,

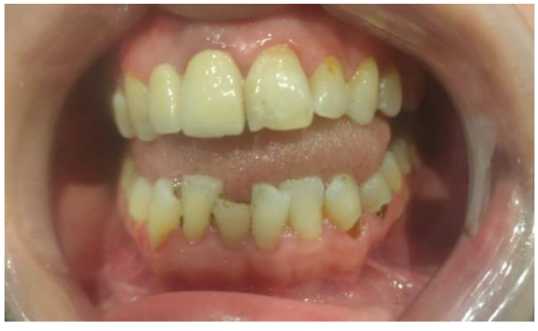

Fig. 1. Chronic periodontitis and caries on labial surface of teeth.

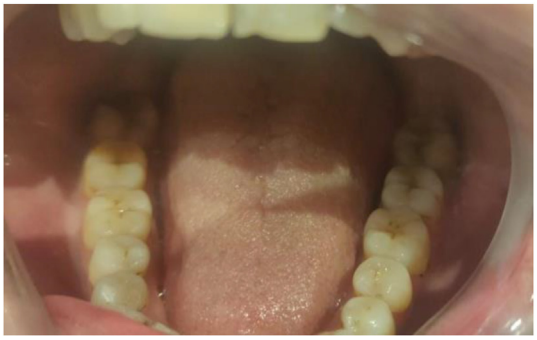

Fig. 2. Caries on the tooth.

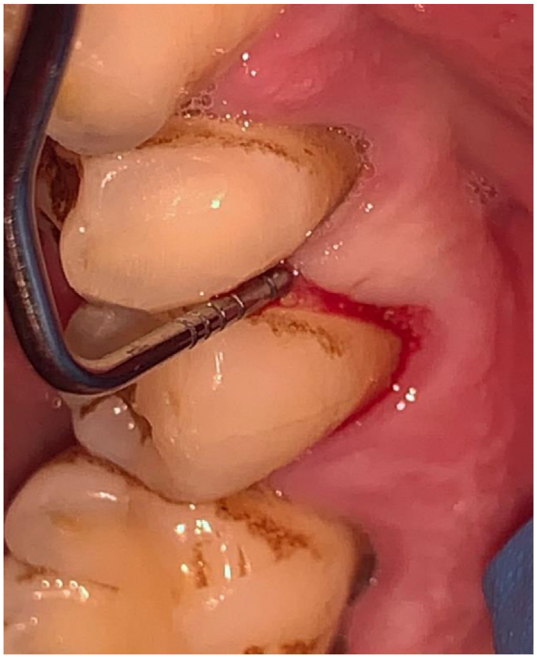

Fig. 3. Periodontal pocket.

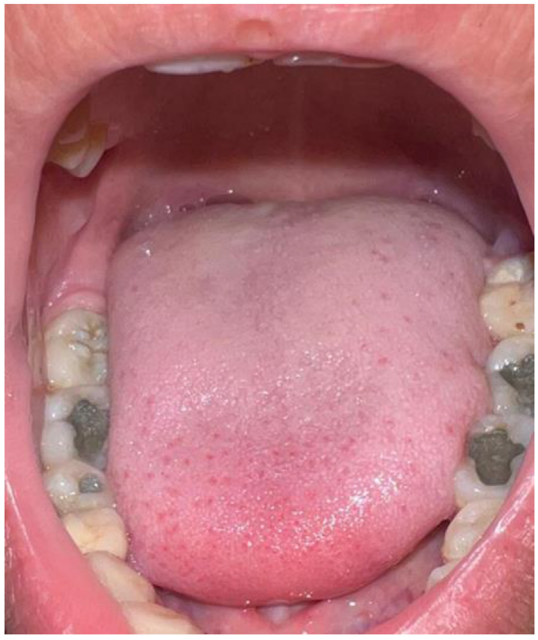

Fig. 4. Caries and filling molars.

which supports the biological mechanism which links the two diseases. *P. gingivalis* peptidylarginine deiminase enzyme triggers an antibody response against citrullinated peptides which may trigger RA. The same study showed that patients with positive RF have higher periodontal disease. Currently, there is no proposed mechanism that links periodontitis and rheumatoid factor. A study by [35] showed significant association between periodontal disease parameters and levels of ACCP antibody. The authors suggested that periodontal disease is associated with the production of anticylic-citrullinated peptide antibody which, may trigger the development of RA. This also could explain the lack of association between rheumatoid factor and periodontitis severity in the same study.

In the current study, there was no statistically significant difference between the two groups as regard gingival recession height. Also, there was no correlation between each age, extra-articular manifestations, tempromandibular joint disorders, rheumatoid factor, and gingival recession height. We do not have an exact explanation of these findings.

Table 3. Correlation between dental parameters and demographic and disease characteristics.

	Probing depth	CAL	Gingival recession	Gingival index	Mobility	Plaque index	DMF	Bleeding on probing
Age								
r	0.218**	0.227**	0.042	0.268**	0.250**	0.294**	0.318**	0.276**
P	0.007	0.005	0.614	0.001	0.002	0.000	0.000	0.001
Sex								
r	−0.129-	−0.090-	0.024	−0.042-	−0.116-	−0.091-	−0.026-	−0.106-
P	0.116	0.273	0.774	0.612	0.156	0.267	0.756	0.195
EAM								
r	0.801**	0.791**	0.184*	0.762**	0.723**	0.757**	0.736**	0.826**
P	0.000	0.000	0.024	0.000	0.000	0.000	0.000	0.000
TMJ								
r	0.278**	0.327**	0.126	0.301**	0.330**	0.295**	0.327**	0.389**
P	0.001	0.000	0.125	0.000	0.000	0.000	0.000	0.000
DAS								
r	0.831**	0.823**	0.208*	0.759**	0.699**	0.781**	0.786**	0.859**
P	0.000	0.000	0.011	0.000	0.000	0.000	0.000	0.000
ACCPA								
r	0.857**	0.866**	0.235**	0.796**	0.752**	0.811**	0.772**	0.841**
P	0.000	0.000	0.004	0.000	0.000	0.000	0.000	0.000
ESR								
r	0.711**	0.707**	0.274**	0.551**	0.592**	0.565**	0.680**	0.664**
P	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000
CRP								
r	0.848**	0.863**	0.279**	0.759**	0.704**	0.773**	0.776**	0.815**
P	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000
RF								
r	0.768**	0.776**	0.160	0.763**	0.754**	0.771**	0.772**	0.819**
P	0.000	0.000	0.051	0.000	0.000	0.000	0.000	0.000

ACCPA, anti-cyclic citrullinated peptide antibody; CAL, Clinical attachment level; CRP, C-reactive protein; DAS, disease activity score; DMF, decay missing filled index; EAM, extra-articular manifestations; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; TMJ, tempromandibular joint.
$P < 0.05$ statistically significant.

However, these findings necessitate further investigation.

Furthermore, we compared patients who had controlled RA disease activity and were receiving anti-rheumatic drugs (group A) to patients who had uncontrolled RA disease activity and were not receiving anti-rheumatic drugs (group B). Patients in group A were receiving combination of conventional disease modifying anti-rheumatic medications (DMARDs), biological DMARDs, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

In group A, DAS-28, acute phase reactant, rheumatoid factor, and ACCPA were lower when compared to those in group B, this agrees with a study by [36] showed a reduction of acute phase reactant and autoantibody production in patients receiving conventional DMARDs. Another study by Alessandri et al. [37], showed a decrease in ACCPA and RF following anti-TNFα therapy which was accompanied by improvement in disease activity. This was also supported by the findings of [38] which showed that 3-month treatment with etanercept combined with conventional DMARDs had a marked reduction in disease activity, autoantibody production and acute phase reactant. On the other hand, a study by [39] showed that 30 weeks of infliximab treatment had a differential effect; it lowered RF levels but had no effect on ACCPA level. Chen et al. [40], reported that both ESR and CRP are very sensitive to changes in disease activity and their levels decrease in response to treatment. The anti-inflammatory effect of anti-rheumatic medications can account for the decrease of the acute phase reactant and autoantibody production. While the mechanism by which anti-TNFα medications block the production of autoantibodies is unknown, it has an anti-inflammatory effect, it reduces the number of mononuclear cells secreting IL1β, IFɣ, and IL-6 in the synovial monocytes, and it also induces cell type specific apoptosis and decreases the number of inflammatory cells. This anti-inflammatory effect can account for the decrease of acute phase reactant and autoantibody production.

In our study, the extra-articular manifestations were significantly higher in group B compared to group A, which came in accordance with [41] study. A previous study by [42], concluded that the widespread of DMARDs and the introduction of biological treatment could be the reason of the decrease in extra-articular manifestations in patients with RA.

Our study showed that dental and oral manifestations were higher in group B in comparison to group A except for gingival recession height. Previous studies showed that the effect of anti-rheumatic medications on periodontal disease is varying. A study by [43] showed that infliximab treatment had led to an improvement in periodontal disease which was accompanied by a lowering of the levels of TNF-α in gingival crevicular fluid and they suggested that anti-TNF α drugs through the suppression of the pro-inflammatory cytokines and by the restoration of the cytokine balance can halt periodontal inflammation and bone resorption. Heredia-P et al. [44], showed that patients on DMARDs and corticosteroids had fewer progressive CAL as DMARDs has an anti-inflammatory effect of periodontum. Kobayashi et al. [45], in there study concluded that anti-IL-6 (Tocilizumab) had a beneficial effect on periodontal inflammation in patients with RA which could be due to the decrease in the serum level of inflammatory mediators. On the other side, a study by [46] found that when anti- TNFα medications combined with methotrexate, leuflonamide, and methotrexate combined with rituximab, were associated with a higher gingival inflammation. This finding was supported by another study by [47], which showed that treatment with anti-TNFα accompanied by an increase in periodontal and gingival inflammation. A study by [48] showed that patients receiving anti-TNFα drugs had a slightly higher periodontal disease than those receiving conventional DMARDs (93.22%, 88.7%, respectively) and suggested that treatment with more than one DMARDs is associated with an increase in subgingival microbiota that leads to more periodontal inflammation. Our findings also disagree with a study by [49] which showed that patients receiving DMARDs have higher periodontal disease activity than newly diagnosed patients with RA which could be as a result of the cumulative periodontal destruction in long-standing RA.

We are aware of some limitations in our study, like the small sample size, we didn't evaluate the effect of different types of anti-rheumatic medication on dental manifestation, and we didn't include oral hygiene and health habit in our study.

We recommend further studies with larger sample size and detailed evaluation of the effect of different types of anti-rheumatic medication on dental manifestations. Regular dental check-up is also recommended for early detection and management of dental and oral manifestations in patients with RA.

4.1. Conclusion

Our study revealed higher dental and oral manifestations in patients not receiving anti-rheumatic medications. Dental manifestations correlated positively with age, extra-articular manifestations,

tempromandibular joint disorder, RA disease activity score, acute phase reactant, RF and ACCPA levels.

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Conflicts of interest

The authors declared no conflicts of interest concerning the authorship and/or publication of this article.

References

[1] Kobayashi T, Ito S, Kuroda T, Yamamoto K, Sugita N, Narita I, et al. The interleukin-1 and Fcgamma receptor gene polymorphisms in Japanese patients with rheumatoid arthritis and periodontitis. J Periodontol 2007;78:2311−8. https://doi.org/10.1902/jop.2007.070136.

[2] Choi HG, Kang HS, Lim H, Kim JH, Kim JH, Cho SJ, et al. Potential cancer risk in patients with rheumatoid arthritis: a longitudinal Korean population-based analysis. J Personalized Med 2022;12:965. https://doi.org/10.3390/jpm12060965. PMID: 35743750; PMCID: PMC9224951.

[3] Treister N, Glick M. Rheumatoid arthritis: a review and suggested dental care considerations. J Am Dent Assoc 1999; 130:689−98.

[4] Galita G, Sarnik J, Brzezinska O, Budlewski T, Dragan G, Poplawska M, et al. Polymorphisms in DNA repair genes and association with rheumatoid arthritis in a pilot study on a central European population. Int J Mol Sci 2023;24:3804. https://doi.org/10.3390/ijms24043804. PMID: 36835215; PMCID: PMC9964492.

[5] Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol 2021 Jul;21(7):426−40.

[6] Nagler RM, Salameh F, Reznick AZ, Livshits V, Nahir AM. Salivary gland involvement in rheumatoid arthritis and its relationship to induced oxidative stress. Rheumatology 2003; 42:1234−41. https://doi.org/10.1093/rheumatology/keg362. Epub 2003 Jul 30. PMID: 12890858.

[7] Tanasiewicz M, Hildebrandt T, Obersztyn I. Xerostomia of various etiologies: a review of the literature. Adv Clin Exp Med 2016;25:199−206 [PubMed].

[8] Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. Therapeut Clin Risk Manag 2015;11:45−51 [PMC free article] [PubMed].

[9] Krutyhołowa A, Strzelec K, Dziedzic A, Bereta GP, Łazarz-Bartyzel K, Potempa J, et al. Host and bacterial factors linking periodontitis and rheumatoid arthritis. Front Immunol 2022; 13:980805. https://doi.org/10.3389/fimmu.2022.980805. PMID: 36091038; PMCID: PMC9453162.

[10] Chang Y, Chung MK, Park JH, Song TJ. Association of oral health with risk of rheumatoid arthritis: a nationwide cohort study. J Personalized Med 2023;13:340. https://doi.org/10.3390/jpm13020340. PMID: 36836574; PMCID: PMC9960411.

[11] Varshney S, Sharma M, Kapoor S, Siddharth M. Association between rheumatoid arthritis and periodontitis in an adult population - a cross sectional study. J Clin Exp Dent 2021;13: e980−6. https://doi.org/10.4317/jced.57562. PMID: 34667492; PMCID: PMC8501867.

[12] BinghamIII OC, Moni M. Periodontal disease and rheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions. Curr Opin Rheumatol 2013;25:345−53.

[13] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham COIII, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569−81. https://doi.org/10.1002/art.27584.

[14] Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44−8.

[15] Nakashima K, Roehrich N, Cimasoni G. Osteocalcin, prostaglanding E2 and alkaline phosphatase in gingival crevicular fluid. Their relation to periodontal status. J Clin Periodontol 1994;21:327−33.

[16] Löe H, Silness J. Periodontal disease in pregnancy. Acta Odontol Scand 1963;21:533−51. ISSN 0001-6357.

[17] Miller PD Jr. A classification of marginal tissue recession. Int J Periodontics Restor Dent 1985;5:8−13.

[18] Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121−35.

[19] Parvaei P, Dorri-giv A, Sharifzadeh G, Malakimoghadam H, Atabati E. Oral mucosal lesions and DMFT index assessment in rheumatoid arthritis patients in Birjand, Iran, in 2018. Open Rheumatol J 2020;14:34−9.

[20] Broadbent JM, Thomson WM. For debate: problems with the DMF index pertinent to dental caries data analysis. Community Dent Oral Epidemiol 2005;33:400−9.

[21] Löe H, Theilade E, Jensen SB. Experimental gingivitis in men. J Periodontol 1965;36:177−87.

[22] Silvestre-Rangil J, Bagán L, Silvestre FJ, Bagán JV. Oral manifestations of rheumatoid arthritis. A cross-sectional study of 73 patients. Clin Oral Invest 2016;20:2575−80. https://doi.org/10.1007/s00784-016-1745-z. Epub 2016 Feb 18. PMID: 26888220.

[23] Disale PR, Zope SA, Suragimath G, Varma AS, Pisal A. Prevalence and severity of periodontitis in patients with established rheumatoid arthritis and osteoarthritis. J Fam Med Prim Care 2020;9:2919−25. https://doi.org/10.4103/jfmpc.jfmpc_398_20. PMID: 32984149; PMCID: PMC7491801.

[24] Rodríguez-Lozano B, González-Febles J, Garnier-Rodríguez JL, Dadlani S, Bustabad-Reyes S, Sanz M, et al. Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients: a case−control study. Arthritis Res Ther 2019 Dec;21:1−2.

[25] Tadjoedin FM, Fitri AH, Kuswandani S, Sulijaya B, Soeroso Y. The correlation between age and periodontal diseases. J Int Dental Med Res 2017;10:327−32.

[26] Marotte H, Farge P, Gaudin P, Alexandre C, Mougin B, Miossec P. The association between periodontal disease and joint destruction in rheumatoid arthritis extends the link between the HLA-DR shared epitope and severity of bone destruction. Ann Rheum Dis 2006;65:905−9. https://doi.org/10.1136/ard.2005.036913. Epub 2005 Nov 10. PMID: 16284099; PMCID: PMC1798215.

[27] Ioannidou E. The sex and gender intersection in chronic periodontitis. Front Public Health 2017;5:189. https://doi.org/10.3389/fpubh.2017.00189. PMID: 28824898; PMCID: PMC5543279.

[28] Mizutani S, Ekuni D, Tomofuji T, Azuma T, Kataoka K, Yamane M, et al. Relationship between xerostomia and gingival condition in young adults. J Periodontal Res 2015;50: 74−9. https://doi.org/10.1111/jre.12183. Epub 2014 Apr 4. PMID: 24697562.

[29] Fathi HM, Gheita TA, Khairy N, El-Battawy WA, Taha R. Clinical significance of periodontitis in rheumatoid arthritis patients: association with disease activity and functional status. Int J Med 2018;111(suppl 1). https://doi.org/10.1093/qjmed/hcy200.061. hcy200.061.

[30] Kumar V, Yashoda R, Puranik, Manjunath P. Association between periodontal disease temporomandibular disorders and rheumatoid arthritis among patients visiting

Rheumatology centers in Bengaluru city: a cross-sectional study. J Indian Assoc Public Health Dentist 2017;15:312−8. https://doi.org/10.4103/jiaphd.jiaphd_125_17.

[31] Hashimoto H, Hashimoto S, Shimazaki Y. Functional impairment and periodontitis in rheumatoid arthritis. Int Dent J 2022; 72:641−7. https://doi.org/10.1016/j.identj.2022.01.002. ISSN 0020-6539.

[32] Mobini M, Maboudi A, Ali Mohammadpour R. Periodontitis in rheumatoid arthritis patients, abundance and association with disease activity. Med J Islam Repub Iran 2017;31:44.

[33] Joseph R, Rajappan S, Nath SG, Paul BJ. Association between chronic periodontitis and rheumatoid arthritis: a hospital-based case-control study. Rheumatol Int 2013;33:103−9. https://doi.org/10.1007/s00296-011-2284-1. Epub 2012 Jan 7. PMID: 22228465.

[34] Nik-Azis NM, Mohd N, Mohd Fadzilah F, Mohamed Haflah NH, Mohamed Said MS, Baharin B. Rheumatoid arthritis serotype and synthetic disease-modifying anti-rheumatic drugs in patients with periodontitis: a case-control study. PLoS One 2021;16:e0252859. https://doi.org/10.1371/journal.-pone.0252859. PMID: 34153036; PMCID: PMC8216515.

[35] Terao C, Asai K, Hashimoto M, Yamazaki T, Ohmura K, Yamaguchi A, et al., Nagahama Study Group. Significant association of periodontal disease with anti-citrullinated peptide antibody in a Japanese healthy population - the Nagahama study. J Autoimmun 2015;59:85−90. https://doi.org/10.1016/j.jaut.2015.03.002. Epub 2015 Mar 26. PMID: 25819755.

[36] Mikuls TR, O'Dell JR, Stoner JA, Parrish LA, Arend WP, Norris JM, et al. Association of rheumatoid arthritis treatment response and disease duration with declines in serum levels of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibody. Arthritis Rheum 2004;50:3776−82. https://doi.org/10.1002/art.20659. PMID: 15593224.

[37] Alessandri C, Bombardieri M, Papa N, Cinquini M, Magrini L, Tincani A, et al. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. Ann Rheum Dis 2004; 63:1218−21. https://doi.org/10.1136/ard.2003.014647. PMID: 15361374; PMCID: PMC1754775.

[38] Jung GU, Han JY, Hwang KG, Park CJ, Stathopoulou PG, Fiorellini JP. Effects of conventional synthetic disease-modifying antirheumatic drugs on response to periodontal treatment in patients with rheumatoid arthritis. BioMed Res Int 2018;2018:1465402. https://doi.org/10.1155/2018/1465402. PMID: 30211216; PMCID: PMC6120284.

[39] De Rycke L, Verhelst X, Kruithof E, Van den Bosch F, Hoffman IE, Veys EM, et al. Rheumatoid factor, but not anti-cyclic citrullinated peptide antibodies, is modulated by infliximab treatment in rheumatoid arthritis. Ann Rheum Dis 2005;64:299−302. https://doi.org/10.1136/ard.2004.023523. Epub 2004 May 27. PMID: 15166003; PMCID: PMC1755340.

[40] Chen HA, Lin KC, Chen CH, Liao HT, Wang HP, Chang HN, et al. The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:35−9. https://doi.org/10.1136/ard.2005.038851. Epub 2005 Jun 23. PMID: 15975966; PMCID: PMC1797988.

[41] Sayah A, English JCIII. Rheumatoid arthritis: a review of the cutaneous manifestations. J Am Acad Dermatol 2005;53: 191−209. https://doi.org/10.1016/j.jaad.2004.07.023. PMID: 16021111.

[42] Bartels CM, Bell CL, Shinki K, Rosenthal A, Bridges AJ. Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United State veterans over 20 years. Rheumatology 2010;49:1670−5. https://doi.org/10.1093/rheumatology/keq.135. Epub 2010 May 12. PMID: 20463190; PMCID: PMC2919197.

[43] Mayer Y, Balbir-Gurman A, Machtei EE. Anti-tumor necrosis factor-alpha therapy and periodontal parameters in patients with rheumatoid arthritis. J Periodontol 2009;80:1414−20. https://doi.org/10.1902/jop.2009.090015. PMID: 19722791.

[44] Heredia PAM, Lafaurie GI, Bautista-Molano W, Trujillo TG, Chalem-Choueka P, Bello-Gualtero JM, et al. Predictive factors related to the progression of periodontal disease in patients with early rheumatoid arthritis: a cohort study. BMC Oral Health 2019;19:240. https://doi.org/10.1186/s12903-019-0939-6. PMID: 31703715; PMCID: PMC6842164.

[45] Kobayashi T, Ito S, Kobayashi D, Kojima A, Shimada A, Narita I, et al. Interleukin-6 receptor inhibitor tocilizumab ameliorates periodontal inflammation in patients with rheumatoid arthritis and periodontitis as well as tumor necrosis factor inhibitors. Clin Exp Dent Res 2015;1:63−73. https://doi.org/10.1002/cre2.11. PMID: 29744142; PMCID: PMC5839195.

[46] Ziebolz D, Rupprecht A, Schmickler J, Bothmann L, Krämer J, Patschan D, et al. Association of different immunosuppressive medications with periodontal condition in patients with rheumatoid arthritis: results from a cross-sectional study. J Periodontol 2018;89:1310−7.

[47] Pers JO, Saraux A, Pierre R, Youinou P. Anti-TNF-alpha immunotherapy is associated with increased gingival inflammation without clinical attachment loss in subjects with rheumatoid arthritis. J Periodontol 2008;79:1645−51. https://doi.org/10.1902/jop.2008.070616. PMID: 18771364.

[48] Romero-Sanchez C, Rodríguez C, Santos-Moreno P, Mesa AM, Lafaurie GI, Giraldo QS, et al. Is the treatment with biological or non-biological DMARDS a modifier of periodontal condition in patients with rheumatoid arthritis? Curr Rheumatol Rev 2017;13:139−51. https://doi.org/10.2174/1573397113666170407161520. PMID: 28403797.

[49] Wu Z, Yang X, Li N. Effects of different immunosuppressive drugs on the periodontal status and changes in periodontal pathogenic bacterial flora in rheumatoid arthritis patients. Trop J Pharmaceut Res 2021 Nov 21;20(10):2219−26.