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Association between rheumatoid factors and proinflammatory biomarkers with implant health in rheumatoid arthritis patients with dental implants

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Abstract. – OBJECTIVE: To evaluate the levels of crevicular fluid rheumatoid factors (RFs), and other proinflammatory cytokines including interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α) and correlate these biomarkers with the clinical peri-implant parameters among rheumatoid arthritis (RA) patients with or without concomitant connective tissue disorder (CTD).

PATIENTS AND METHODS: Three groups of 14 participants each [Group-I: healthy, Group-II: RA without CTD, and Group-III: RA with CTD] were selected. The clinical parameters observed were bleeding on probing (BOP), plaque scores (PS), pocket depth (PD) and alveolar bone loss (ABL). RFs, IL-6 and TNF-α were Enzyme-linked immunosorbent assay (ELISA) was incorporated to quantify RFs, IL-6 and TNF-α.

RESULTS: BOP was significantly higher in Groups II and III as compared with Group I. Alveolar bone loss was significantly higher in Group III followed by Group II and least in Group I. Patients with RA with CTD presented with statistically higher levels of RF, IL-6 and TNF-α followed by Group II compared with Group I ($p<0.05$). A positive correlation existed between BOP and all the three biomarkers RF ($r=0.0562$; $p=0.0039$), IL-6 and TNF-α for Group-II patients. Similarly, a significant positive correlation existed between BOP and all the three biomarkers RF, IL-6 and TNF-α for Group-III patients. In addition, a positive correlation was also seen between ABL and RF, PD, and IL-6 in Group-III patients.

CONCLUSIONS: RF might influence peri-implant inflammation in RA patients with CTD. Moreover, the increased RF levels are indicative of diagnostic marker for peri-implant complications in RA.

Key Words:
Rheumatoid arthritis, Rheumatoid factors, Dental implants, Gingival crevicular fluid, Inflammation.

Introduction

Dental implant therapy is a unique treatment procedure that is being readily used in dental and hospital-based practices to restore edentulous jaws. Over the course of time, dental implant therapy has had a massive increase in its popularity amongst the clinicians and general population. The basic aim of this treatment is to restore the masticatory function of the jaw and also to improve the aesthetic display of the patient's oral cavity. The systemic diseases have had a notable impact on dental implant therapy[1]. Reports[1,2] have been published in which relative and absolute contraindications have been identified for implant rehabilitation.

Rheumatoid arthritis (RA) can be defined as a chronic systemic disease which is associated with cellular hyperplasia and inflammation at the level of the synovial lining of joints that results in cartilage damage and bone destruction[3,4]. RA is linked with multifactorial etiologies and co-morbidities which include cardiovascular, respiratory, hepatic, vascular, muscular, and skeletal disorders[5-7]. This disease is commonly seen in individuals comprising of the HLA-DR4 genotype[8] and thus patients with RA may or may not manifest with concomitant connective tissue disorder (CTD) that could affect soft and hard tissues. For this reason, these tissues are of major interest for periodontal and peri-implant structures[9].

Although the pathogenesis of RA and its precise mechanism is still unclear, however, the discovery of different molecular factors has been investigated in RA which is responsible for modulating the pathogenicity of the disease. At the molecular level, a cascade of cytokines and cyclooxygenase enzymes are involved which insti-

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gate the inflammatory process. Tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6 play a significant role in the progression of the disease[10,11]. Several clinical manifestations are associated with RA that includes Sjogren Syndrome, scleritis, vasculitis, spindle-shaped joints (metacarpophalangeal and interphalangeal), muscle wasting, and stiffness[12-14].

Like all other systemic diseases, RA also presents with certain manifestations related to the oral cavity such as dry mouth (xerostomia) and periodontal problems[15,16]. Several studies[17-19] have established correlation between periodontitis and RA. According to Rodríguez-Lozano et al[20] a higher incidence of periodontitis was observed in patients suffering from RA in comparison to control group. On the other hand, according to Donos et al[21] a success rate of 97% was observed for dental implants inserted in the bone of RA patients. However, there has been no study in which rheumatoid factors (RFs) along with pro-inflammatory cytokines (IL-6, TNF-α) have been investigated in RA patients having dental implants. Therefore, this case-control study aimed to evaluate the levels of peri-implant crevicular fluid (PICF) RFs, and other proinflammatory cytokines including IL-6, and TNF-α and to compare these biomarkers with the clinical peri-implant parameters among RA patients with or without CTD.

Patients and Methods

Study Design and Ethical Approval

The present case-control research was carried out following the Declaration of the World Medical Association in Helsinki and followed the design as reported by Algohar and Alqerban (2020). The investigation was commenced after the approval provided by Prince Sattam Bin Abdulaziz University [Protocol Number: PSA-000087#34]. Before the study was initiated, all the participating individuals signed the informed consent along with the aims and objectives thoroughly explained. Participants were also given full authority to exit from the study without any consequences.

Sample Power Analysis

A total of 42 patients (14/group) were required in the investigation to attain a difference of 50% in mean crevicular fluid levels of RF, agreeing a power of 85% with alpha level set at 0.05.

Study Population and Groups

The database of the hospital was checked, and registered participants who had received dental implants between 2008 and 2020 were invited and sought informed consent. Eligible patients had received implant-prosthodontic rehabilitation treatment and divided into 4 groups. Group – I (n=14) comprised of systemically healthy individuals having no past or current history of RA with dental implants, Group – II (n=14; isolated RA group) included participants having been diagnosed without CTD and Group – III (n=14) included participants diagnosed with RA with CTD. Patients diagnosed with RA were classified according to the 2010 ACR/EULAR classification criteria[23]. Lactating and pregnant females, patients recently undergoing periodontal therapy in the last 6 months, and patients with long term use of antibiotics were excluded from the study. A thorough history including age, disease duration, anti-rheumatic drug prescription, and other comorbidities was also reported. Serum high-sensitivity C-reactive protein (CRP) levels were estimated by means of an automated immunoanalyzer (Beckman Coulter; Los Angeles, CA, USA) for all the patients by collecting blood samples in the morning and stored at -80°C until further analyses.

Assessment of Peri-Implant Characteristics

Bleeding on probing (BOP), probing depth (PD) and plaque index (PI) were assessed at six sites of the implant fixture. The recordings for the study variables were taken by a skilled examiner [Adel Alenazi (AA)]. A periodontal probe (UNC-15, Henry Schein, USA) was used to evaluate the peri-implant clinical parameters. A dichotomous scoring was reported at four sites of each of the implant, where 0 represented- an absence of plaque and bleeding, and 1 showed – the presence of plaque and bleeding. The alveolar bone levels (ABL) were also evaluated by a calibrated examiner with the help of radiographic imaging. ABL was estimated as the calibrated height from the highest point of the margin of the alveolar bone to the implant abutment junction. For radiographic assessment, all the included individuals were subjected to have periapical radiographs of sites having dental implants. These images were studied on a standardized computer display by using a software (Adobe Bridge, USA).

Peri-Implant Crevicular Fluid Collection

PICF collection was performed at a subsequent visit following the first examination. Before collection, the site for collection was cleaned for any plaque debris, air dried and isolated with cotton rolls. A perio paper (Amityville, NY, USA) was inserted into the gingival crevice for 30 s. The volume of the PICF was determined using a Periotron 800 (Oraflow Inc., NY, USA). Obvious contamination with blood was discarded and not analyzed. Strips were transferred in the PBS and protease inhibitor. The collected PICF in the paper strips were shaken for 15 min and the eluates centrifuged for 5 min at 6000 rpm. The samples were frozen at -80°C.

Quantification of RF

RF from the PICF was estimated using enzyme-linked immunosorbent assay (ELISA; Eagle Biosciences, Catalog number RFM-31-K01). Patients PICF was diluted using sample diluent. All reagents were thawed and brought to room temperature. A total of 100 µL volume of each calibrator, positive control, and diluted PICF samples was dispensed into the respective wells. The plate was covered and incubated for 60 min at 25°C. The plate was then decanted, and each well was washed thrice using 300 µL wash solution. Next, 100 µL of conjugate solution containing anti-human-IgM (sheep) coupled with horseradish peroxidase (HRP) enzyme was added in each well. The well plate was covered and incubated for 30 min at 25°C. The plate was again decanted and washed thrice with 300 µL of wash solution. 100 µL of TMB substrate was added in each well and covered and protected from light at 25°C. Lastly, 100 µL of stop solution was added in each well and mixed gently. The OD of the well plate was read at 450 nm. Data were processed using the standard curves established by plotting the mean OD values of the calibrators versus RF IgM concentrations.

Evaluation of IL-6 and TNF-α

Crevicular fluid aliquots were also quantified for IL-6 (ABCAM ab178013) and TNF-α (ABCAM ab181421) utilizing ELISA (enzyme linked immunosorbent assay) kit. Before starting the procedure, all reagents, samples and working standards were brought to room temperature. Fifty µL of the standard and aliquots were placed inside the well. Antibody cocktail (50 µL) was added into the same wells, sealed, and incubated for 60 min. Washing of the wells was performed using wash buffer (200 µL). Afterwards, TMB solution (200 µL) was incorporated and kept in the dark. Finally, stop solution (100 µL) was incorporated into each well and mixed in the shaker for 60 s. Optical density was noted at 480 nm.

Statistical Analysis

Statistical software (SPSS version 20, IBM, Armonk, NY, USA) was used to compute the statistical tests. The normality distribution of the recorded data was estimated with the help of the Shapiro-Wilk test. The data was also run through inferential statistic Levene's test to establish the homogeneity of variances. Comparisons between groups were established using Kruskal-Wallis test. When p-values were statistically significant, the post hoc comparisons applying Mann-Whitney *U* tests with Bonferroni corrections were used. Correlations between RFs, IL-6, TNF-α and clinical scores were evaluated by Spearman rank correlation test. The observed *p*-values less than 0.05 were considered significant.

Results

A total of 42 patients were selected for the present study comprising of 14 patients in each study group. Females predominated over males in Groups II and III while there was an equal number of males and females in Group I. The mean age for participants in groups I, II and II was 44.9, 43.8 and 47.6 years, respectively. Mean CRP levels were the highest for Group-III patients (5.2 mg/dl) followed by Group-II (3.6 mg/dl). Self-reported mean duration of systemic disease in Groups II and III was 18.7 and 9.2 years, respectively. Associated clinical manifestations among patients in Group-III included 7 patients diagnosed with scleroderma, 4 patients diagnosed with Sjögren's syndrome, and 3 with dermatomyositis. Patients were divided into groups on the basis of RA treatment as; (1) no treatment, (2) patients being treated by non-steroidal anti-inflammatory drugs (NSAIDs), and (3) patients being treated by glucocorticoids with or without NSAIDs. Almost equal distribution was seen for patients in both Groups-II and III. A total of 114 dental implants were studied. In Group I, 39 implants were examined out of which 22 were placed in maxilla and 17 were placed in mandible. Similarly, in Groups II and

Table I. Baseline demographics, systemic, implant-related, and oral hygiene characteristics of the study groups.

Characteristics	Group I (Healthy control)	Group II (RA without CTD)	Group III (RA with CTD)
Number of participants (n)	14	14	14
Gender (Male/Female)	7/7	5/9	4/10
Age (mean ± SD)	44.9 ± 9.6	43.8 ± 11.3	47.6 ± 8.5
CRP (mean ± SD) (mg/dl)	1.2 ± 0.6	3.6 ± 0.9	5.2 ± 1.1
Duration of systemic disease (mean ± SD)	–	18.7 ± 3.7	9.2 ± 1.2
Treatment for RA (n)			
• No treatment	–	4	2
• NSAIDs		5	7
• Glucocorticoids with or without NSAIDs		5	5
No of implants studied	39	32	43
Site of implant placement [maxilla/mandible]	22/17	24/8	31/12
Duration of implants in months (mean ± SD)	39.4 ± 9.1	42.3 ± 12.5	44.6 ± 6.4
Brushing frequency (%)			
Once daily	11	28	35
Twice daily	89	72	65

CRP; c-reactive protein, CTD; concomitant connective tissue diseases, NSAIDs; Non-steroidal anti-inflammatory drugs, SD; standard deviation.

III, 24 and 31 implants were maxillary, while 8 and 12 were mandibular implants, respectively. Mean duration of dental implants ranged from 39 to 44 months. Majority of patients reported brushing twice (Table I).

Clinical peri-implant parameters were described in Table II. It was observed that BOP was significantly higher in Groups II ($p<0.01$) and III ($p<0.05$) as compared with Group I. Plaque scores was similar among all the groups ($p>0.05$). Pocket depth was significantly higher in Group III compared with Group II and I ($p<0.05$). Alveolar bone loss was significantly higher in Group III followed by Group II and least in Group I.

Table III describes laboratory parameters among the study groups. It was observed that Group III indicated the highest PICF flow rate ($p<0.05$). Patients with RA with CTD presented with statistically higher levels of RF, IL-6 and TNF-α followed by Group II compared with Group I ($p<0.05$).

Spearman rank correlation analysis was performed to estimate any correlations between the PICF biomarkers and peri-implant parameters (Table IV). It was noted that a positive correlation existed between BOP and all the three biomarkers RF ($r=0.0562$; $p=0.0039$), IL-6 ($r=0.0342$; $p=0.0197$) and TNF-α ($r=0.1167$; $p=0.0421$) for Group-II patients. Similarly, a significant positive correlation existed between BOP and all the three biomarkers RF ($r=0.0632$; $p=0.0001$), IL-6 ($r=0.1553$; $p=0.0491$) and TNF-α ($r=0.0095$; $p=0.0189$) for Group-III patients. Furthermore, a positive correlation was also seen between ABL and RF ($r=0.1154$; $p=0.0072$), PD and IL-6 ($r=0.1583$; $p=0.0385$) in Group-III patients.

Discussion

The purpose of the current investigation was to estimate the clinical peri-implant character-

Table II. Bleeding on probing, plaque index, probing depth and crestal bone loss among groups. Data are expressed in median and interquartile range. Statistical significance between groups analyzed using Kruskal-Wallis test for each independent variable and after Bonferroni adjustment.

Peri-implant parameters	Group I (Healthy control)	Group II (RA without CTD)	Group III (RA with CTD)
Bleeding on probing (BOP) in % SD	7.4 (3.6)†	19.6 (6.4)¶	27.4 (8.1)¶,§
Plaque index (PI) in %	8.3 (3.9)†	13.4 (5.4)†	12.2 (4.9)†
Probing depth (PD) in mm	2.1 (0.7)†	2.8 (1.6)†	3.5 (0.9)¶
Crestal bone levels in mm	0.6 (0.4)†	1.2 (0.7)¶	2.2 (0.8)§

Dissimilar superscript symbols denote statistical significance at $p < 0.05$.

Table III. Peri-implant crevicular fluid flow rate and levels of RF, IL-6, and TNF-α among groups. Data are expressed in median and interquartile range. Statistical significance between groups analyzed using Kruskal-Wallis test for each independent variable and after Bonferroni adjustment.

Laboratory parameters	Group I (Healthy control)	Group II (RA without CTD)	Group III (RA with CTD)
PICF flow rate (µl/min)	0.74 (0.39)†	1.03 (0.53)†	1.18 (0.44)¶
Rheumatoid factor (RF) (IU/L)	2.49 (1.7)†	39.3 (13.8)¶	52.8 (12.3)¶,§
IL-6 (pg/mL)	57 (22)†	165 (79)¶	228 (112)§
TNF-α (pg/mL)	110 (54)†	246 (141)¶	396 (176)§

Dissimilar superscript symbols denote statistical significance at $p < 0.05$.

Table IV. Spearman rank correlation analysis between peri-implant crevicular fluid biomarkers and peri-implant parameters among all groups. Statistical significance analyzed by Spearman rank correlation coefficient analysis.

Peri-implant parameters	Group I (Healthy control)	Group II (RA without CTD)	Group III (RA with CTD)
RF			
Plaque index			
Correlation coefficient	0.8236	-0.6745	-0.7521
p-value	0.9843	0.1049	0.9746
Bleeding on probing			
Correlation coefficient	0.9238	0.0562*	0.0632*
p-value	1.4843	0.0039	0.0001
Probing depth			
Correlation coefficient	0.6430	0.9341	0.8374
p-value	0.2387	0.5736	0.9342
Crestal bone loss			
Correlation coefficient	-0.8753	0.5222	0.1154*
p-value	0.9364	0.9236	0.0072
IL-6			
Plaque index			
Correlation coefficient	-0.9887	0.8754	0.8947
p-value	0.6544	0.2445	0.7454
Bleeding on probing			
Correlation coefficient	0.4905	0.0342*	0.1553*
p-value	1.4886	0.0197	0.0491
Probing depth			
Correlation coefficient	0.5561	0.7728	0.1583*
p-value	1.0633	0.0532	0.0385
Crestal bone loss			
Correlation coefficient	-0.3326	-0.0732	-0.9432
p-value	0.8236	0.9345	0.4563
TNF-α			
Plaque index			
Correlation coefficient	-0.0964	0.9237	0.4368
p-value	0.5643	0.7437	0.2348
Bleeding on probing			
Correlation coefficient	0.9541	0.1167*	0.0095*
p-value	1.4326	0.0421	0.0189
Probing depth			
Correlation coefficient	0.9368	0.6553	0.9356
p-value	1.0246	0.0755	0.0974
Crestal bone loss			
Correlation coefficient	-0.7346	-0.2442	-0.0732
p-value	0.8453	0.7334	0.3298

*Significant at $p < 0.05$.

istics and inflammatory biomarkers in the PICF among patients with RA with and without CTD and compare these parameters with healthy subjects. Moreover, this study aimed to establish an association between RFs and proinflammatory biomarkers with dental implant health among patients having RA with and without CTD. The results of the study demonstrated higher levels of RFs, pro-inflammatory biomarkers (IL-6, TNF-α) and alveolar bone levels (ABL) along with worse clinical peri-implant parameters in RA patients with CTD in comparison to RA without CTD and healthy subjects.

Rheumatoid arthritis (RA) is a chronic, debilitating, autoimmune disease that targets the synovial lining of the joints. It is more common in middle and old age, and its prevalence is more readily observed in females[23]. The exclusive presence of middle-aged subjects and females in our study verifies the overall incidence of RA with and without CTD among such cohort[24]. This disease is also associated with osteolytic changes (increased bone turnover rate), abnormal immunological activity along with increased production of RF and auto-citrullinated protein antibody (ACPA). Rheumatoid factor is an auto-antibody that is designed to target the Fc region of the immunoglobulin G (Ig-G) antibodies[25]. The marker assessment performed to evaluate the level of RFs may be considered to be an important diagnostic tool in determining the auto-immunity of the diseased individual[26].

Although plaque scores were equally low in all the three groups, it could be observed that bleeding scores were significantly higher in patients with RA with and without CTD. The low level of plaque scores may be attributed to the patients being treated in the same institute and complying with regular recall and maintenance program. According to the results obtained from this study, patients in Groups II and III projected increased levels of bleeding signs in comparison to the healthy counterparts. Research[27] suggests that patients associated with RA have been reported to have greater vascular activity (angiogenesis and vascular permeability) due to the release of vascular endothelial growth factor (VEGF) in the synovial joints. Therefore, it may be hypothesized that due to increased production of VEGF in RA patients, increased bleeding levels were observed at the peri-implant sites, considering the plaque levels were generally low.

While the implant characteristics did not vary between RA with and without CTD, some distinctions were recognized for other implant characteristics such as soft tissue probing depths and alveolar bone levels. It was noted that ABL was more noticeable for rheumatoid arthritis patients with CTD. Differences in the primary disease, that is, RA+CTD or isolated RA indicated a substantially note-worthy effect on peri-implant structures, while medical treatment revealed an insignificant effect on ABL only. Conferring to such outcomes, the peri-implant alveolar bone destruction including marked peri-implant bleeding may be clarified by the pathology of the underlying disease with reduced vascularization of the mucosa and accompanying reduction of bone nutrition also suggesting tissue reduction[28,29]. Susceptibility of the soft tissue due to vascular involvement along with immune pathogenesis of connective tissue may also participate in this pathophysiology[28,29]. Furthermore, no obvious typical failures were noted except for 1 patient each in healthy and RA+CTD groups were observed due to abutment screw loosening and crown chipping, respectively.

Interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are both highly associated with peri-implant health and rheumatoid arthritis, respectively[30,31]. According to the observed results, both the pro-inflammatory cytokines showed a statistically significant increase in the values in Group II individuals in comparison to the control group (Group I). IL-6 is the most abundant cytokine that is expressed in the synovial joint in individuals with RA. IL-6, along with IL-8 play a significant role in the development of RA[32]. The synovial joint cells produce IL-6, whereas the latter induces synovial cell proliferation and osteoclastic differentiation by the receptor activator NF-kappa B ligand (RANKL) expression[33]. The increased level of IL-6 initiates a response that allows the production of autoantibodies by modulating the plasmoblasts. IL-6 and IL-1 act synergistically to modulate the production of matrix-metalloproteinase (MMPs) through synovial cells, destroying joints[34]. Similarly, the increased production of TNF-α, also accounts for greater bone destruction by increasing the activity of macrophages, B-cells, activated T-cells, and endothelial cells[35]. All these molecules allow the formation of a cascade of destruction which includes the activation of different cytokines and receptors such as IL-1, IL-8, ICAM-1, ELAM-1, respectively[36]. All these factors may indicate the surge of IL-6 and TNF-α in RA and implant health.

To strengthen the study design, sophisticated tests should be conducted. These tests should evaluate the therapeutic regimes provided and the underlying disease agents. By doing so, it will aid in demonstrating the type of rheumatic disease that could impact the dental implant conditions such as alveolar bone resorption and bleeding scores significantly. In addition, further longitudinal studies must be conducted to appraise the levels of RFs and other proinflammatory biomarkers in an evolutionary manner.

Conclusions

RF might influence the peri-implant inflammation in RA patients with CTD. Moreover, the increased RF levels are also suggestive of diagnostic biomarker for peri-implant diseases in RA patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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