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Effect of periodontal therapy on disease activity in patients of rheumatoid arthritis with chronic periodontitis

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ABSTRACT

Background: Evidence have been proposed a positive association between severity of Periodontitis and Rheumatoid arthritis (RA) activity, individuals with advanced RA are more likely to develop periodontal problems compared to their non-RA counterparts, and vice versa. Studies have been suggested that RA manifest as a result of an inflammatory imbalance and autoimmunity. In this perspective, treatment modalities that lead to inhibition of proinflammatory mediators, may prove beneficial for reducing the severity of RA. This study examined the effects of non surgical periodontal therapy (NSPT) on disease activity of RA.

Methods: Diagnosed patients of active rheumatoid arthritis with chronic periodontitis were recruited in this study and divided in to treatment and controls groups, both groups were similar in all demographics assessed. Treatment group (n = 20) and controls group (n = 20) underwent assessment for periodontal clinical parameters (plaque index, gingival index, probing pocket depth, clinical attachment level), Rheumatologic clinical (simplified disease activity index) and biochemical parameters(C-reactive protein, Rheumatoid factor, Anticyclic citrullinated protein) at baseline and 8 weeks. Serum levels of biochemical parameters were measured by enzyme-linked immunosorbent assay (ELISA).

Results: The statistically significant ($p < 0.001$) reduction observed in mean values of PI, GI, PPD, CAL, SDAI in treatment group at 8weeks after NSPT as compare to control group. However serum level of ACCPA, CRP and RF did not show statistically significant ($p > 0.05$) changes from baseline to reassessment (8 weeks) in both groups.

Conclusions: The improvement in RA disease activity may occurs after non surgical periodontal therapy.

1. Introduction

Chronic Periodontitis (CP) is an inflammatory disorder initiated by bacterial infection which destructively affect the integrity of supporting structures of the tooth, eventually leading to tooth loss.[1] It is not restricted to local tissue reaction but may have systemic impact. CP is estimated to affect 10–30% of the world-wide population.[2]Studies have been shown that many systemic conditions such as adverse pregnancy outcomes cardiovascular disease, type 2 diabetes mellitus, osteoporosis, rheumatoid arthritis (RA)[3] are associated with CP.

RA is an autoimmune disease characterized by joint inflammation and destruction leading to chronic disability.[4] It has a prevalence of .5–1% in US population and high socioeconomic burden on society as a whole.[4]

It has been shown that P. gingivalis induce the citrullination of peptides. Genetically predisposed people develop antibody to citrullinated peptides (ACCPA).[5] ACCPA are found in 80% of the patients with RA, with a 99% specificity[5] and can predict the severity of the disease.

CRP is a marker for systemic inflammation and is useful for determining disease activity in RA.[2] RF has been found in patients of both CP and RA.[3] It is produced in CP-affected lesions and increase systemic inflammatory responses, which may contribute to the disease progression of RA.[6]

Studies have shown that periodontal treatment improves endothelial function and reduces biomarkers of arteriosclerotic disease.[7] The pathogenesis of CP and RA is similar in dysregulation of host inflammatory processes. In this point of view it has been proposed that by reducing the systemic load of inflammation through non surgical periodontal therapy may have beneficial effects on the clinical activity of RA.

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2. Materials and methods

This study involved subjects of Active Rheumatoid Arthritis with Chronic Periodontitis. Recruitment of the subjects were undertaken at the, Department of Rheumatology in collaboration with Department of Periodontology, Faculty of Dental Sciences, Informed and voluntary written consent from patients was obtained before the start of the clinical examination according to the ethical principles.

Ethical clearance (No.9811/Ethics/R.Cell-16) was obtained from the Ethical Committee, King George's Medical University, Lucknow.

Assuming 80% power, 5% significance level (95% confidence interval), the sample calculation test revealed that > 11 patients in each of the two groups.

A total of 40 patients involved in this study were both males and females in the age group between 25 and 65 yrs were selected according to the following exclusion and inclusion criteria.

2.1. Inclusion criteria

1. Subjects with two or more tooth sites with pocket depth ≥ 4 mm or clinical attachment loss (CAL) ≥4 mm that bled on probing were categorized as chronic periodontitis **(Armitage GC *et al.*, 1999)**.[8]
2. Patients in the age group of 18–65 years.
3. At least 20 teeth present in the oral cavity.
4. Patients of active rheumatoid arthritis with ≥6 joint involvement.
5. Patients under medication of rheumatoid arthritis since 1 month.
6. Patients continued with medications prescribed to them for rheumatoid arthritis during 8 week duration of study without any change.
7. Patients who gave their written consent.

2.2. Exclusion criteria

1. History of any systemic disease or condition other than RA that could affect the progression or treatment of periodontitis.
2. Having antibiotic treatment within previous 3 months.
3. Any periodontal therapy within the previous 3 months.
4. Smokers.

2.3. Study design

The present study was longitudinal interventional study consisted of 40 patients of rheumatoid arthritis with chronic periodontitis and divided in to Treatment group (n = 20) and Control group (n = 20).

Treatment group - Participants in this group received periodontal treatment (oral hygiene instruction along with full-mouth scaling and root planning) immediately after the base line RA and periodontal assessment.

Control group- Participants in this group did not received periodontal treatment during study, they scheduled an appointment for periodontal treatment after the completion of the study.

All the clinical and biochemical parameters were recorded at baseline and 8 weeks by the same clinician in both groups.

2.4. RA clinical measurements

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recommended assessment of disease activity in RA patients using Simplified Disease Activity Index.

The SDAI is a valid and sensitive assessment of disease activity and treatment response that is comparable with the Disease Activity Score 28(DAS 28) and ACR response criteria; it is easy to calculate and therefore a viable tool for day-to-day clinical assessment of RA treatment.[9]

The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28 joint assessment), patient and physician global assessment of disease activity (visual analogue scale (VAS) 0–10 cm) and level of C-reactive protein (mg/dl).

2.5. Tender joint count (TJC)

The joint count was done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination.

2.6. Swollen joint count (SJC)

Joints were classified as either swollen or not swollen.

2.7. Patient's global assessment of disease activity (PGA)

The patient's overall assessment of how the arthritis is doing. One acceptable method for determining this is the question: "*Considering all the ways your arthritis affects you, mark 'X' on the scale for how well you are doing.*": An anchored, horizontal, visual analog scale (usually 10 cm) was provided.

2.8. Evaluator's global assessment of disease activity (EGA)

A horizontal visual analog scale (10 cm) measure of the physician's assessment of current disease activity in the patient.

SDAI = SJC + TJC + PGA (visual-analogue scale (VAS; in cm)) + EGA (VAS (in cm)) + CRP (in mg/dl).

2.9. SDAI score interpretation

0–3.3 Remission
3.4–11.0 Low Activity
11.1–26.0 Moderate Activity
26.1–86.0 High Activity

2.10. Biochemical measurements-

Venous blood samples were obtained at baseline and at 8weeks after periodontal therapy. Serum was isolated from the blood by centrifugation at 1500*g* for 20 min, and it was stored at −80 °C until use.

To assess CRP, RF, ACCPA 5 ml of blood was drawn at baseline and at 8 weeks. Enzyme linked immunosorbent assay (ELISA) was used to measure ACCPA, CRP, RF, using Sun Red ELISA Kit.

2.11. Periodontal parameters

To assess periodontal status, the following data were recorded at baseline and at 8 weeks by a calibrated examiner: probing depth (PD) and clinical attachment level (CAL) at 6 sites per tooth, plaque index (PI) and gingival index (GI) of Loe.[10]

2.12. Nonsurgical periodontal treatment

Oral hygiene instructions and full mouth scaling and root planing were performed using periodontal hand instruments (Graceycuretts, scaler) and ultrasonic devices in one session in both group. Periodontal treatment was performed immediately after base line assessment in treatment group and after study completion (8 weeks) in control group.

2.12.1. Statistical analyses

The data were subjected to statistical analysis after tabulating the clinical and biochemical data for the patients of both groups included in this study. Changes in clinical and biochemical data are presented as mean ± S. E. Demographic data of the study participants (age, gender) at baseline were compared between two groups using Chi-square tests.

Table 1
Demographic characteristics of treatment and control group.

Demographic characteristics	Treatment group (n = 20)	Control group (n = 20)	P value
Age (yrs):			
Mean ± SD	42.83 ± 10.678	39.65 ± 11.848	0.409
Sex:			
Female	15 (77.8%)	16 (82.4%)	
Male	5 (22.2%)	4 (17.6%)	0.735

Parametric tests (Student's t-test) were used for normally distributed data. Reduction in RA severity (SDAI) in the two groups was statistically tested for significance. Differences in changes from baseline to reassessment in parameter values between the groups were assessed by Mann- Whitney U tests.

3. Results

3.1. Periodontal clinical parameters

All periodontal parameter values proved comparable between treatment and control group ($P > 0.05$) at baseline. On intragroup analysis the treatment group showed a significant ($P < 0.0001$)decrease in PI, GI, PPD and CAL at 8 weeks after periodontal therapy, whereas in control group no significant changes ($p > 0.05$) was observed in PI, GI, PPD and CAL from baseline to reassessment(at 8 weeks) (Table .2).

As shown in Table 3, with an intergroup comparison, the treatment group displayed a significantly greater decrease in PI ($P < 0.0001$), GI ($P > 0.0001$), PPD ($P > 0.0001$) and CAL ($P < 0.0001$), CAL ($P < 0.0001$) from baseline to reassessment than the control group.

3.2. Rheumatologic clinical parameters

SDAI values proved comparable between treatment and control group ($P > 0.05$) at baseline. The treatment group showed a significant ($P < 0.0001$) decrease in SDAI at 8 weeks after periodontal therapy(Table s 4 and 6) In control group no significant changes ($p > 0.05$) was observed in SDAI from baseline to reassessment(at 8 weeks) (Table s 4 and 6).

The intergroup analyses revealed that decrease in SDAI (11.48 ± 4.21) was statistically significant ($p < 0.001$) in treatment group when compared to control group from baseline to 8 weeks (4.24 ± 3.3) (Table.5).

3.3. Biochemical parameters

In our study, the intragroup analyses revealed that decrease in CRP was statistically significant ($p < 0.001$) in treatment group from baseline to 8 weeks (0.31 ± .16 to 0.24 ± .12) (Table 4). However in control group, it did not decrease significantly ($p = 0.291$) between this period (0.35 ± .16 to 0.30 ± .15) (Table 4).

Table 3
Intergroup Analyses of Changes in Periodontal Parameters between Treatment and Control group at Baseline and Reassessment.

Parameters	Treatment group	Control group	p-value
	Mean ± SD	Mean ± SD	
PI	25.11 ± 10.24	0.46 ± 0.56	< **0.001**
GI	0.35 ± 0.20	0.04 ± 0.05	< **0.001**
PPD(mm)	1.15 ± 0.32	0.08 ± 0.09	< **0.001**
CAL(mm)	1.15 ± 0.49	0.07 ± 0.11	< **0.001**

$P < 0.05$, significantly different between the two groups, as assessed by Unaired student's *t*-test.

The intergroup analyses revealed that no significant difference ($P > 0.05$) was found in changes in serum CRP levels (Table 5) between treatment group (0.04 ± 0.02) and control group (0.15 ± 0.13) from baseline to reassessment(at 8 weeks). Serum level of ACCPA, RF did not change significantly from baseline to 8 weeks in both the groups (Table .4). On an intergroup comparison, no significant change was found in ACCPA ($P = 0.091$) and RF (0.287) at reassessment in treatment group when compared with control group (Table .5).

4. Discussion

The treatment and control groups did not differ statistically in the demographic (Table .1), periodontal conditions, rheumatologic conditions and serum marker scores at baseline. No significant difference ($p = 0.409$) was observed in mean age between treatment group (42.83 ± 10.68 years) and control group (39.65 ± 11.85 years). The high proportion of female patients (80%) were involved in this study and also this is in accordance with the fact that prevalence of RA is more common in females (84.2%) than males.[11] All patients were taking corticosteroids, disease modifying antirheumatic drugs (DMARDs), or non-steroidal anti-inflammatory drugs (NSAIDs) and there were no prescription changes during the study.The two groups were comparable and had not influenced the study outcome measures.

The treatment group exhibited a **significantly** greater decrease in PI, GI, PPD and CAL than control group at 8 weeks after NSPT. This showed that periodontal inflammation decreases after NSPT. Our results are in accordance with studies of**Knowles *et al.*, (1979)**[12]**, Badersten *et al.*, (1981)**[13], and **Haffajee *et al.*, (1997)**[14].**Ribeiro *et al.*, (2005)**[15]**; Al-Katma *et al.*, (2007)**[16]**; Ortiz *et al.*, (2009)**[17] which demonstrated the clinical effects of NSPT. The SDAI is a well-founded index for the measurement of RA disease activity and response after RA treatment. SDAI is comparable with the DAS 28 and ACR response criteria.[9]

In our study, after intragroup analysis of the RA disease activity according to SDAI, **significant** reduction was found in SDAI on reassessment in treatment group, but in control group no significant

Table 2
Intragroup analysis of Periodontal Parameters in Treatment group and Control group at Baseline and Reassessment.

Para meters	Treatment Group				Control Group			
	Baseline (mean ± SD)	Reassess ment(mean ± SD)	Change (mean ± SD)	P value	Baseline (mean ± SD)	Reassess ment(mean ± SD)	Change (mean ± SD)	P value
PI	58.07 ± 9.13	32.95 ± 5.19	25.11 ± 10.24	< **0.001**	56.44 ± 8.97	56.46 ± 8.83	0.46 ± 0.56	0.868
GI	1.32 ± 0.13	0.96 ± 0.14	0.35 ± 0.20	< **0.001**	1.31 ± 0.13	1.32 ± 0.12	0.04 ± 0.05	0.460
PPD	3.44 ± 0.30	2.29 ± 0.19	1.15 ± 0.32	< **0.001**	3.59 ± 0.42	3.59 ± 0.35	0.08 ± 0.09	0.796
CAL	3.66 ± 0.41	2.51 ± 0.31	1.15 ± 0.49	< **0.001**	3.85 ± 0.45	3.89 ± 0.41	0.07 ± 0.11	0.216

PI = Plaque Index, GI = Gingival Index, PPD = Probing Pocket Depth.
CAL = Clinical Attachment Level.
$P < 0.05$, significantly different between the baseline and reassessment, as assessed by Paired student's *t*-test.

Table 4
Intragroup Analysis of Rheumatologic and Serum Parameters in Treatment group and Control group at Baseline and Reassessment.

Para meters	Treatment Group(n = 20)			Control Group(n = 20)		
	Baseline (mean ± SD)	Reassess ment (mean ± SD)	P value	Baseline (mean ± SD)	Reassess ment (mean ± SD)	P value
ACCPA (ng/L)	161.78 ± 12.71	161.89 ± 12.73	0.140	153.18 ± 16.05	153.39 ± 16.09	0.346
CRP (mg/dl)	.31 ± 0.16	.24 ± 0.12	< **0.001**	.35 ± 0.16	.30 ± 0.15	.291
RF (ng/ml)	20.36 ± 3.89	20.28 ± 3.89	0.664	21.75 ± 4.21	21.78 ± 4.23	0.918
SDAI	30.53 ± 10.32	19.02 ± 7.18	< **0.001**	28.94 ± 10.10	26.48 ± 8.36	0.053

P < 0.05, significantly different between the baseline and reassessment, as assessed by Paired student's *t*-test.

Table 5
Intergroup Analysis of Changes in Rheumatological Parameters in Patients of both groups at Baseline and Reassessment.

Parameter	Treatment group	Control group	p-value
	Mean ± SD	Mean ± SD	
ACCP (ng/L)	0.13 ± 0.32	0.18 ± 0.36	0.091
CRP (mg/dl)	0.04 ± 0.02	0.11 ± 0.13	0.055
RF (ng/ml)	0.52 ± 0.51	0.66 ± 0.50	0.287
SDAI	11.48 ± 4.21	4.24 ± 3.30	< 0.001

P < 0.05, significantly different between the two groups, as assessed by Mann-Whitney *U* test.

reduction was observed in SDAI. It was found that, at baseline 61.1% of the patients in treatment group had high disease activity, which was **significantly** reduced to 27.8% at 8 weeks **on reassessment**, whereas control group did not show significant improvement in disease activity.These results are consistent with the findings of other studies,[18–21] showing the beneficial effects of supragingival scaling after 8 weeks on the condition of RA.

On an intergroup comparison, **significantly** greater decrease was found in SDAI at reassessment in treatment group than control group which might be as a result of total change in the SDAI component, including TJC, SJC, PGA, EGA and CRP. These findings are in agreement with earlier studies, **Al-Katma *et al.*, (2007)**[18], **Pinho *et al.*, (2009)**[15], **Ortiz P *et al.*, (2009)**[19], **Okada *et al.*, (2013)**[20],**Erciyas *et al.*, (2013)**[21] that have shown a favourable effect of NSPT on RA disease activity. Periodontal disease is a systemic inflammatory condition[16], Thus the improvement in RA disease activity after periodontal therapy might be attributed to decrease in systemic inflammatory mediators. Another possible justification is that removal of periodontal pathogens by NSPT might reduced exposure of the joints structures to bacteria and their toxins and lead to improved disease activity.[17]

ACCPA appear early in the pathogenesis of RA[22] and act as marker of RA due to their specificity and sensitivity. The specificity of ACCPA in established RA may be 95% and 40%–55% in early-onset RA.[23] The ACCPA serum levels can vary with disease activity of RA.[24]

Citrullinated proteins have been found within inflamed periodontium.[25] It is important to find out whether a decrease in periodontal inflammation after periodontal therapy could reduce ACCPA levels.

In our study, intragroup analysis displayed no statistical difference in ACCPA titres at reassessment in treatment and control group. Intergroup analysis also did not show any significant changes in ACCPA between both the groups.Our findings are supported by the result of the study of **Okada *et al.* (2013)**[20], where it was demonstrated that there was no statistically significant difference in ACCPA titres in patients with RA treated with nonsurgical periodontal treatment compared with those in the control groups. This could be explained by the small numbers of patients included in this study or due to low severity of periodontitis was observed. Another possible basis is the relatively shorter time for observation (8 weeks), which was based on the studies that showed decrease in disease activity of RA at minimal of 4 weeks after periodontal treatment.[19,26] Our results are in contrast to the study done by **Lappin DF *et al.*, (2013)**[27], in which significant reductions in anti-CCPA was found 6 months after periodontal treatment, however smoking was a confounding factor in their study. According to **S Kaur *et al.*** ACCPA titres do not always reflect disease activity and are less responsive to the effects of RA disease suppression.[28]

Serum level of CRP increase with systemic inflammatory diseases such as RA[29] or with different microbial infections such as periodontitis.[15,30,31]

Serum level of CRPis valuable disease activity marker in RA patients. Decrease in serum CRP level is associated with improvement in RA functional score and constant CRP increase is related with functional worsening in patients with active RA.[32]

In our study, decrease in CRP level was statistically **significant** in treatment group, whereas control group did not show significant decrease at 8 weeks, this is in accordance with study of (**Okada M *et al.*, 2013**).[20]Resolution of periodontal inflammation after non-surgical periodontal treatment may well have a role in the decrease in serum CRP levels. On a intergroup analyses, statistically non significant change was found in CRP at reassessment in treatment group when compared with control group. Our findings are in line with those of studies which reported that there was no significant difference in CRP value between both groups at recall visit **(Okada M *et al.*[20], 2013; Pinho *et al.*,[15] 2009)**. This lack of effect in RA subjects may be due to

Table 6
Intragroup analysis of Disease activity Status according to SDAI at Baseline and Reassessment in treatment group and control group.

			Disease Status		Total	chi sq	p-value
			Moderate Activity	High Activity			
Treatment Group	Baseline	No.	8 (38.9%)	12 (61.1%)	18 (100.0%)	4.05	**0.044**
		%					
	8 weeks	No.	14 (72.2%)	6 (27.8%)	18 (100.0%)		
		%					
Control Group	Baseline	No.	9 (47.1%)	11 (52.9%)	17 (100.0%)	1.07	0.300
		%					
	8 weeks	No.	12 (64.7%)	8 (35.3%)	17 (100.0%)		
		%					

P < 0.05, significantly different between the two groups, as assessed by chi square test.

masking of effect of disease-modifying anti-rheumatic drugs, which decreased the activity of RA.Our results are in contrast to studies done by, **D'Aiuto *et al.*, (2005)**[33], **Erciyas *et al.*, (2013)**[21] in which there were statistically significant decrease was found in CRP levels two months after SRP.

Evidence demonstrated a relationship between the decrease of RF titers and periodontal treatment complemented by tooth extractions.[34]

Thus, It is logical to suggest that treatment of periodontitis could decrease LPS production and subsequently reduce the levels of RF.

In our study, statistically no significant decrease was found in serum RF in treatment group and control group at 8 weeks. Intergroup analysis revealed that no significant change was observed in RF level in treatment group when compared with control group at reassessment, this may be either due to the low severity of periodontitis observed or else to small sample sizes. Our findings are supported by the result of the study of **Ribeiro *et al.*, (2005)**[35]**; Okada *et al.*, (2013)**.[20] Neither of the studies demonstrated a statistically significant change in RF levels following periodontal therapy in RA patients with CP.

In our study, treatment group displayed improvement in disease activity of RA and periodontal clinical conditions whereas no significant changes in serum levels of ACCPA, CRP and RF at 8 weeks. Thus, within the limitations of this study, there was significant improvement in disease activity of RA after NSPT. However, these results are based on a small set of subjects. Further studies on larger group of patients for longer period of observation are required to validate our findings.

5. Conclusions

Within the limitations of this study, there was significant improvement in disease activity of RA after NSPT. Thus, patients with rheumatoid arthritis should be screened and treated for the periodontal involvement as adjunct to antirheumatoid therapy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jobcr.2019.02.002.

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