Erythrocyte Sedimentation Rate as an Alternative to C-Reactive Protein in Rheumatoid Arthritis Patients with Periodontitis

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Abstract

Rheumatoid arthritis (RA) shows similar etiologic factors and pathogenic mechanisms as periodontitis (PD); however, the two diseases differ from one another. Both diseases have been associated with some common inflammatory markers. Thus, the objective of this study was to evaluate the periodontal status and reliability of erythrocyte sedimentation rate (ESR) and C Reactive Protein (CRP) as systemic inflammatory markers in RA patients with PD.

Sixty subjects were divided into four groups of 15 each on the basis of clinical and laboratory parameters for RA and PD as systemically healthy subjects with a healthy periodontium(H), systemically healthy subjects with periodontitis (PD), RA with a healthy periodontium(RA), RA and PD(RAPD). Blood samples were obtained from all groups. Levels of CRP were estimated by using rapid slide agglutination and levels of ESR were estimated by using Westergren method.

ESR and periodontal parameters showed statistically significant differences between the groups except for CRP. ESR seems to be a better and economical alternative to evaluate the systemic inflammatory burden in rheumatoid arthritis patients with periodontitis.

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Introduction

Periodontitis [PD] is a common disease worldwide, that has a primarily bacterial etiology and is characterized by dysregulation of the host inflammatory response, and eventually resulting in soft and hard tissue destruction.[1] Periodontal medicine is an emerging branch of periodontology that has been establishing a strong relationship between periodontal and systemic health and disease.[2]

Rheumatoid arthritis [RA] is a systemic inflammatory disorder primarily of the joints that, if left untreated, results in functional disability concordant with radiographic progression.[3] RA shows similar etiologic factors as PD; however, the two diseases differ from one another. Moreover, their underlying pathogenic mechanisms are strikingly similar. PD and RA are characterized by similar humoral and cellular immune responses and a common immunogenetic profile. Both diseases represent destructive inflammatory diseases characterized by accumulation and persistence of inflammatory infiltrates in the local lesions.[4] An association between PD and RA also has been shown in animal studies.[5] A bidirectional relationship of RA and PD may involve RA affecting the pathogenesis of PD and vice-versa. Serum markers of inflammation provide possible insights into the pathophysiology of RA and its complications.[6]

The commonly used serum markers of inflammation include White Blood Cells [WBCs], Erythrocyte Sedimentation Rate [ESR] and C-reactive Protein [CRP], amongst others, which have been frequently evaluated, especially in establishing the periodontal-systemic link. Periodontal disease secondarily causes increases in the serum levels of ESR, CRP and

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other markers of systemic inflammation. The elevation of biologic markers has also been associated with an increased risk for developing general diseases, such as ischemic cardiovascular disease, stroke, peripheral arterial disease and RA.[7]

ESR, one of the oldest laboratory tests still in use, is the rate at which red blood cells settle in a vertical tube, used to detect the presence of disease, i.e., it is the measurement of the sedimentation of red cells in diluted blood after standing for 1 hour in an open ended glass tube mounted vertically on a stand. ESR is considered a non-specific disease activity index which may be useful in chronic disease follow-up and is increased in RA.[8,9]

CRP is a pattern recognition molecule, binding to specific molecular configurations that are typically exposed during cell death or are found on the surfaces of pathogens. Its rapid increase in synthesis within hours after tissue injury or infection suggests that it contributes to host defence, and that it is part of the innate immune response.[10] It is a general marker of systemic inflammation.

The literature does not provide conclusive evidence of CRP and ESR to be reliable inflammatory markers of pulmonary disease, [11] or of RA. [12,13] CRP and ESR were reported to be comparably elevated in RA patients with PD.[13,14] CRP may be elevated in periodontitis, and is also considered to be more reliable than ESR in terms of response to infections, but may also not be elevated in hepatic failure or systemic lupus erythematosus.[15] A considerable percentage of RA patients test negative for both ESR and CRP or may be normal.[16] A recent meta-analysis reported that non-surgical periodontal therapy had no association with CRP levels but reduced ESR in RA patients.[17] These data do not conclusively state the reliability of ESR or CRP as systemic biomarkers in RA or PD.

Hence, the aim of this study was to evaluate the periodontal status and reliability of ESR and CRP as systemic inflammatory markers in RA patients with PD.

Materials and methods

This study was conducted in the Department of Periodontics and the Department of Orthopedics, of the concerned institutions. A total of 60 participants were recruited in this study. An ethical clearance was obtained from the institutional ethical committee and an informed written consent was obtained from all the subjects before their participation in the study. All the participants were above the age of 30 years and gender matched with at least 8 natural teeth present having moderate to severe periodontal disease {probing pocket depth [PPD] ≥ 5mm, attachment loss [CAL] ≥ 3mm and radiographic evidence of bone loss}. The study population also included RA patients [as diagnosed by the rheumatologist, corroborated by laboratory parameters]. Exclusion criteria included individuals with any systemic disorder other than those with RA or presence of any disease that may alter the immune system, tobacco smokers/chewers and pregnant women. In addition, participants who were on antibiotics or/and anti-inflammatory drug regimen were excluded.

Periodontal Parameters: All the study participants underwent an oral examination and the clinical periodontal parameters, i.e., Plaque Index [PII],[18] Gingival Index [GI],[19] PPD and CAL were recorded by a single examiner. PPD and CAL assessments were conducted with a William's periodontal probe [Hu Friedy, Chicago, IL, USA]. Measurements were made at six different sites of each tooth present: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, disto-lingual, and mid-lingual/palatal.[20] The CAL was not measured for teeth with calculus or cervical caries or without a clinical tooth crown. The mean value was taken into consideration for each patient.

Biochemical Parameters: Four milliliters[ml] of peripheral venous blood was obtained in blood collection tubes from individuals of all the groups to determine ESR and CRP. Levels of CRP were estimated by using rapid slide agglutination [Span Diagnostics Ltd, Surat, India]. Levels of ESR were estimated by using the Westergren method.

On the basis of the clinical and laboratory parameters for RA, and clinical parameters for PD, participants were divided into four groups of 15 each, which includedsystemically and periodontally healthy participants[H], systemically healthy individuals with periodontitis[PD], periodontally healthy participants with rheumatoid arthritis [RA] and patients diagnosed with RA and PD [RAPD].

Statistical analysis

Normality of distributions of the parameters [GI, PII, PPD, CAL, ESR, CRP] were done using the Kolmogorov-Smirnov test. The comparisons of the groups was analysed by the Mann-Whitney U-test and the Kruskal Wallis ANOVA. Correlations were tested using Spearman's Rank test. The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), Version 20 software computed the analysis. The probability value was set at $p < 0.05$.

Results

The data was analyzed statistically by first using the Kolmogorov-Smirnov test of normality. These tests revealed that the data was not normally distributed among any of the parameters. Hence the non-parametric Mann-Whitney test and Kruskal Wallis ANOVA were used.

	Gender				Age		
Groups	Male	%	Female	%	Male	Female	Total
					Mean ± SD	Mean ± SD	Mean ± SD
H	7	46.67	8	53.33	36.14 ± 4.49	36.38 ± 5.48	36.27 ± 4.86
PD	7	46.67	8	53.33	46.71 ± 11.07	46.63 ± 10.31	46.67 ± 10.28
RA	7	46.67	8	53.33	44.57 ± 9.07	38.38 ± 8.98	41.27 ± 9.26
RAPD	8	53.33	7	46.67	57.50 ± 5.07	59.00 ± 5.83	58.20 ± 5.29
Total	29	48.33	31	51.67	46.62 ± 10.81	44.65 ± 11.63	45.60 ± 11.19

Table 1. Distribution of male and females in the four groups.

Distribution of the participants in this study by age and gender is depicted in Table 1. The mean values of the clinical and biochemical parameters and comparison of the four groups using the Kruskal-Wallis test are depicted in Table 2. All the variables showed a statistically significant difference ($p<0.05$) except for CRP.

Statistically significant differences in ESR with respect to all groups were observed. CRP was significantly higher in RAPD compared with RA. The healthy and PD groups were 0 for CRP. ESR was significantly higher in RAPD as compared with the RA group, and when compared with PD and H. ESR in RA was significantly higher than PD and H [Table 2].

Multiple pair wise comparison for the periodontal variables was done using the Mann-Whitney test.

	PII		GI		PPD		CAL		CRP		ESR	
Groups	Mean ± SD	Mean rank	Mean ± SD	Mean rank	Mean ± SD	Mean rank	Mean ± SD	Mean rank	Mean ± SD	Mean rank	Mean ± SD	Mean rank
H	0.96 ± 0.33	10.47	0.66 ± 0.30	8	0.00	8	0.00	11.5	0.00	0.00	7.60± 3.38	9.40
PD	1.89 ± 0.52	37.20	2.09 ± 0.43	42.97	6.23 ± 0.85	43.67	4.68 ± 0.87	42.20	0.00	0.00	16.00± 6.56	22.90
RA	1.66 ± 0.35	30.80	1.52 ± 0.37	27.17	3.15 ± 0.57	23.07	0.33 ± 0.40	19.50	8.00 ± 6.371	14.50	41.00± 14.59	39.43
RAPD	2.07 ± 0.41	43.53	2.11 ± 0.37	43.87	6.70 ± 1.34	47.27	5.82 ± 1.65	48.8	8.96± 5.911	16.50	62.47 ± 17.83	50.27
p- value	0.0001*		0.0001*		0.0001*		0.0001*		0.5338		0.0001*	

Table 2. Comparison of the four groups with respect to clinical and biochemical parameters by Kruskal-Wallis ANOVA. *$p<0.05$.

	PII	GI	PPD	CAL
H vs PD	0.0001*	0.0001*	0.0001*	0.0001*
H vs RA	0.0001*	0.0001*	0.0001*	0.0001*
H vs RAPD	0.0001*	0.0001*	0.0001*	0.0001*
PD vs RA	0.2134	0.0011*	0.0001*	0.0001*
PD vs RAPD	0.2717	0.8519	0.2540	0.0401*
RA vs RAPD	0.0095*	0.0005*	0.0001*	0.0001*

Table 3. Pair wise group comparison of clinical variables by Mann-Whitney U test. *p<0.05.

Lab variables	Clinical variables	N	Spearman R	t-value	*p*-value
CRP	PII	60	0.3299	2.6611	0.0101*
	PI	60	-0.2026	-1.5753	0.1206
	GI	60	0.2569	2.0242	0.0476*
	PPD	60	0.2677	2.1157	0.0387*
	CAL	60	0.2400	1.8828	0.0647
ESR	PII	60	0.5020	4.4203	0.0001*
	PI	60	0.0793	0.6055	0.5472
	GI	60	0.4822	4.1922	0.0001*
	PPD	60	0.5068	4.4774	0.0001*
	CAL	60	0.4522	3.8611	0.0003*

Table 4. Correlation of CRP and ESR with the clinical variables in all groups by Spearman's rank correlation. *p<0.05.

PII, GI, PPD and CAL were significantly higher in the PD and RAPD groups as compared with H and RA. Although PII, PPD and GI were higher in RAPD group as compared to PD it was not statistically significant. But, CAL showed

statistically significant difference between PD and RAPD [Table 3]. ESR correlated positively with PII, GI, PPD and CAL. CRP correlated positively with PII, GI and PPD but not with CAL [Table 4].

Discussion

The results of this study seem to provide further evidence that the mean values of CRP and ESR are higher in RA patients having PD. This may be attributed to the fact that PII, GI, PPD and CAL values were higher in RAPD group when compared with RA patients without PD.

The relationship between RA and progression of inflammatory conditions elsewhere in the body, such as PD, has been discussed in the literature.[3,21-24] Substantial evidence indicates the significant association between these two common chronic inflammatory conditions.[25,26]

While it is not suggested that there is a causal relationship, the data indicates that individuals with RA are more likely to experience more significant PD, similar to the association between diabetes mellitus and the heightened severity of PD as indicated by recorded periodontal parameters,[27] compared to non-RA patients and vice versa in accordance with Mercado et al.[22]

The mean age in the RAPD group [58.2 years] was higher compared to the other three groups. This is consistent with the report,[22] that this age group has higher incidence of RA and PD. The association remained after adjusting for potential confounders such as gender.

In this study patients having RA with and without periodontitis had high levels of CRP compared to the health and PD groups, which is similar to previous studies.[6,7,28,29] Although there was no significant difference seen in CRP with the RA patients with and without periodontitis, there was a clinical difference between these two groups which could be attributed to the fact that RAPD had a higher inflammatory burden compared to RA. The CRP value was found to be higher in RAPD, and was in accordance with a study done by Mercado et al.[22] The fact that there was a tendency toward higher CRP levels in RAPD patients compared with the other groups only can be explained by two possibilities. First, PD may aggravate RA because PD is accompanied by higher CRP levels which are evidenced in the present study as reported in the literature.[30-34] The elevation of inflammatory biomarkers [such as IL-1,IL-6, TNF-α, MMP-8] that are locally induced by PD[35], or when associated diabetes mellitus or obesity,[36,37] is thought to induce systemic inflammation by increasing serum CRP levels and thus contribute to an increased systemic inflammation in RA.[38] Second, RA may aggravate periodontitis because more severe RA is also accompanied by higher CRP levels,[38,39] higher CRP levels may be a reflection of active RA, which may contribute to an increased inflammatory state in periodontitis. Interestingly, CRP level reduces in patients with RA after periodontal therapy,[40] lending support to the hypothesis that periodontal disease may contribute to an increased systemic inflammation in RA. Another explanation of higher CRP levels in patients with RA and PD compared with patients with RA and no/mild periodontitis may be confounded by impaired maintenance of oral hygiene and low education level. Regarding oral hygiene, RA affects the wrist joint and the small joints of the hand. The joint afflictions may impair motor function of the hand and as a result may impair proper oral hygiene maintenance, resulting in periodontitis.[41] Another study also found higher levels of CRP in patients with RA and periodontal disease.[22]

Acute phase proteins have been implicated in the pathogenesis of periodontitis and CRP has been detected in the GCF.[42,43] Recently, it has been reported that periodontal disease can be associated with an increased inflammatory response manifested as elevated CRP levels.[44] The findings in the present study suggestive of severity of inflammatory burden correlated with CRP level confirm those of previous studies.[45,46]

ESR also correlates with the degree of synovial inflammation, but varies greatly from patient to patient and from time to time.[47] In this study, ESR values showed a statistical significant difference between the four groups. RAPD was the highest followed by Groups RA, PD and the healthy groups, respectively. This suggested that ESR values were normal in healthy patients, slightly increased in periodontitis patients, relatively higher in RA patients and highest in RAPD patients. Hence, a relationship between ESR and inflammatory severity was noted.

A relationship between CRP and ESR to radiographic changes in joints (progressive erosions) has been shown. In a study of 774 RA

patients where the comparative usefulness of CRP and ESR was examined, it was concluded that CRP appears to be the better measure of the acute phase, while ESR could better measure general severity than CRP, despite being a poorer measure of inflammation.[48]

The present study showed higher values of CRP in RAPD and RA groups, but ESR was observed to be higher in the PD group in addition to RAPD and RA. However, CRP did not show a statistically significant difference, whereas, ESR did.

A statistically significant difference was observed in the PII and GI between all the four groups. Bozkurt also reported similar findings.[49] The PPD and CAL was significantly higher (p<0.001) in RAPD as compared to the other groups. This is also in accordance with the studies of Bozkurt,[49] and Mercado and coworkers.[21] However, Mercado and coworkers have used only radiographic bone loss to correlate PD to RA. The present study does not involve the use of radiographs due to lack of standardized techniques for the same; instead CAL was chosen to judge PD activity for all the groups.

In contrast to the present study, Sjostrom,[50] reported better periodontal status among RA patients than controls and attributed this difference to the long term administration of non-steroidal anti-inflammatory drugs.

In the present study, clinical and laboratory parameters were evaluated before the subjects were on medication, hence removing the confounding factor.

CRP has gained an increasing popularity as a marker of systemic inflammation either in the general population or in selected categories of patients, such as those with coronary artery disease, congestive heart failure or different rheumatic diseases.[51] Several assays are currently available to measure CRP, and they greatly differ in sensitivity.[52] This, and the cost of the measurement, which is not common in low-income countries, raises the question of whether a more economic and reproducible alternative is available. Indeed, ESR increases in response to rising serum levels of acute phase proteins.[53] Thus, at variance from CRP, it is not a pure indirect inflammatory index. This might be an advantage rather than a limitation in the assessment of RA patients because RA, is frequently associated with increased acute phase proteins. Accordingly, ESR seems worthy of exploitation as potential index of RA severity if we consider RA a systemic condition. The very easy, well standardized and reproducible procedure of measurement further strengths this perspective.[54] In addition, this is an almost costless procedure, well suited then for low-income countries.[11]

In the healthy, PD and RA groups there was no statistically significant correlation between individual laboratory parameters in relation to individual periodontal clinical parameters. Absence of a significant difference in terms of PII to ESR and CRP in these groups indicates that manual disability may not have interfered with the oral hygiene measures.

The use of mean CAL or mean PPD to describe the prevalence and severity of periodontal disease is based on the concept that all individuals and all sites within an individual are equally susceptible to periodontal breakdown.[55] Further studies with large sample size and long-term follow-up periods are suggested.

Conclusions

Thus, within the limitations of this study it can be concluded that a relationship between disease experience of RA and PD can be demonstrated by assessing a defined group of individuals diagnosed with RA using standard clinical and laboratory parameters. It was seen that the levels of CRP and ESR were higher in RAPD followed by RA, PD and health. ESR seems to be a better and economical alternative to evaluate the systemic inflammatory burden in rheumatoid arthritis patients with periodontitis.

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Declaration of Interest

The authors report no conflict of interest.

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