Salivary C- reactive protein in relation to periodontal health among a group of patients with rheumatoid arthritis in Iraq

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ABSTRACT

Background: Rheumatoid arthritis is a chronic destructive inflammatory disease associated with destruction of joint connective tissues and bones, affecting 0.5%–1% of the population worldwide reporting higher prevalence of periodontitis among rheumatoid arthritis patients. The purpose of this study is to estimate level of salivary C-reactive protein in relation to the occurrence and severity of the periodontal disease and other oral parameters among group of patients with rheumatoid arthritis

Material and methods: Fifty women patients with rheumatoid arthritis; twenty five on Methotrexate treatment and twenty five on combination treatment of Methotrexate and Etanercept selected as study groups with an age range (30-40) years old and twenty five gender, age and Body Mass Index matched healthy looking persons were selected as control. The diagnosis and recording of periodontal condition recorded through the application of community periodontal index according to WHO1997.Collection of unstimulated salivary samples was carried out under standard conditions, in addition to estimation of salivary C-reactive protein.

Results: Regarding count of sextants with community periodontal index, median count of sextant with CPI-score 0 was highest among controls (2) and lowest among both rheumatoid arthritis cases (0).The median count of sextant with CPI-score 3 was lowest among controls (0) and highest among both RA cases (2) and the difference observed in median count of sextant with CPI-score 3 between three groups was statistically significant ($p< 0.01$).The mean rank of salivary C-reactive protein was highest among controls 39.7mg/L However, the difference was not significant between three groups ($P>0.05$).

Conclusion: The results of the current research revealed that periodontal diseases were higher among rheumatoid arthritis patients without impact of both treatments on periodontal health without significant role of salivary C-reactive protein clinically in assessment of disease activity.

Key words: rheumatoid arthritis, salivary C-reactive protein, community periodontal index. (J Bagh Coll Dentistry 2014; 26(3):138-143).

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects all ethnic groups throughout the world. Females are 2.5 times more likely to be affected than males because men may be protected by hormonal factors and require a stronger genetic component to develop disease [(1,2)].

A prevalence survey for rheumatoid arthritis in Iraq was carried out during the summer of 1975 and definite rheumatoid arthritis was observed in 1 % of the 6999 individuals studied [(3)].

Periodontal diseases (PD) are the second most common oral diseases next to dental caries, they are considered to be inflammatory disorder that damages tissue through the complex interaction between perio-pathogens and the host defense systems [(4,5)]. Periodontitis is one of common oral manifestation of RA, evidence that individuals suffering from RA are more likely to experience periodontitis was found by several studies [(6-8)]. Periodontitis and RA are both chronic destructive inflammatory disorders and result from deregulation of the host inflammatory response [(9)].

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Corgel et al. [(10)] reported thatInflammatory periodontal diseases exhibit an association with RA andthe effective treatment of periodontal infections is important to achieve oral health goals, as well as to reduce the systemic risks of chronic local inflammation and bacteremias. C - reactive protein (CRP) is a liver-produced, acute-phase reactant; that serves as a systemic marker of inflammation; the name is derived due to the ability of the CRP to react with C-polysaccharide isolated from pneumococcal cell walls [(11)]; its levels can be used to monitor patients with overwhelming infections, and elevated CRP levels have been demonstrated in persons with ischemia and myocardial infarction [(12)]. Alsopersistent elevations in CRP are seen in chronic inflammatory states such as active RA, pulmonary tuberculosis, or extensive malignant disease [(13)].

Periodontal disease, being a low grade inflammatory disease of the tooth supporting structures, may increase blood levels of inflammatory markers including IL-6 and CRP [(14)]. Al-Ghurabei found a significant elevation of mean serum level of high sensitive CRP (hsCRP) with periodontitis and hs-CRP was showed significant positive correlation with each of probing pocket depth (PPD), clinical attachment

loss (CAL) and bleeding on probing (BOP) among group of Iraqi patients [15].

Slade et al. found an association between extensive periodontal disease and BMI with increased CRP levels in otherwise healthy, middle-aged adults, suggesting the need for medical and dental diagnoses when evaluating sources of acute-phase response in some patients [12].

Saliva is a body fluid, its role as a diagnostic tool has advanced exponentially over the past decade assaliva sampling is safe for both operator and patient, making saliva possible to monitor several biomarkers when blood sampling is not available [16,17]. Components within saliva may provide additional clues on systemic health conditions. Besides, the development of new technologies may promote a wider use of salivary assays in the near future [18]. Yet, no previous Iraqi study could be found that investigates the salivary levels C-reactive protein and its relation to periodontal health among rheumatoid arthritis patients, for this research designed.

MATERIALS AND METHODS

Approval was achieved from the Ministry of Health in Iraq for examining the patients with rheumatoid arthritis and collecting samples, in addition to that, the objectives of the study was explained for each participant. The study group composed of fifty RA women patients, with an age range (30-40) years. They were diagnosed clinically, by rheumatology specialist as rheumatoid arthritis depending on the seven criteria of the American Rheumatism Association with assessment of disease activity depending on Disease Activity Score 28 (DAS28), they were divided in to two subdivisions groups: the first group (twenty five) under conventional treatment disease-modifying anti-rheumatic drugs DMARD (Methotrexate MTX) and the second group (twenty five) under combination treatment with anti-TNF-α (Etanercept) and DMARDs (MTX). They were attending Baghdad Teaching Hospital for their treatment. The control group composed of twenty five subjects and they wereapparently healthy according to their medical history matching with age, gender and body mass index BMI of the study group.The disease activity score 28 was calculated with the following equation using ESR:

DAS 28 = (0.56 × √TJC) + (0.28 × √SJC) + (0.70 × logn ESR) + (0.014 × PGA).ESR = erythrocyte sedimentation rate.GAS = Global Arthritis Score, logn = log-normal, SJC = swollen joint count of 28 joints, TJC = tender joint count of 28 jointsPGA= patient global assessment. Height and weight were determined with the subjects wearing light clothing without shoes using height and weight measurement mechanical scale. The body mass index (BMI) was calculated as (body weight/height ^{2}) (kg/m^2). The periodontal status was assessed by using specially designed light weight community periodontal index probe. The community periodontal indexdivide mouth into sextants defined by tooth numbers: (18-14), (13-23), (24-28), (38-34), (33-43) and (44-48)with 10 index teeth(17,16,11,26,27,47,46,31,36,37),
examination of four surfaces ofthe index teeth, and/or all remaining teeth in a sextant where there are no index teeth, was probed and the highest score was recordedfollowing the criteria of Community Periodontal Index 1997.Aspecific measure for periodontitis; plaque index was assessed (Silness and Loe 1964).The whole unstimulated salivary samples was collected for five minutes from the study and control groups and was performed under standardized conditions according to the instructions cited by Tenovuo and Lagerlöf [19].The salivary samples were then taken to the laboratory for biochemical analysis and centrifuged at 3000 r.p.m. for 10 minutes. The clear supernatant was separated by micropipette and was stored at (- 20°C) in a deep freeze and further detection of the CRP presence in saliva was done by (Huma Tex CRP). CRP determination is based on the immunological reaction between human C-reactive protein of a patient specimen and the corresponding anti-human CRP antibodies bound to latex particles, the positive reaction is indicated by a distinctly visible agglutination of the latex particles; positive reaction meaning that a content of CRP in the sample equal to or greater than 6 mg/1. Samples with positive results in the screening test were retested in the titration test. Samples diluted with Glycine-NaCl Buffer (GBS) ((REF 40037)) according to manufacture criteria of the kit, the titer read in the last dilution step with visible agglutination and multiplied the titer with the conversion factor 6 getting the result in mg/l.

Inter and intra examiner calibrations were performed to obtain the most critical consistency of diagnostic criteria.The results were analyzed using paired t-test and there were no significant differences ($P<0.05$) between the first and second observation of inter examiner calibration. Statistical analysis data were translated into a computerized database structure. The database was examined for errors using range and logical data cleaning methods, and inconsistencies were remedied. An expert statistical advice was sought for. Statistical analyses were done using SPSS

version 20 computer software (Statistical Package for Social Sciences). Compliance of quantitative random variables with Gaussian curve (normal distribution) was analyzed using the Kolmogorov-Smirnov test. The correlation coefficient tests between the variables were done by using Spearman's rank linear correlation coefficient.P value less than 0.05 and 0.01 was considered statistically significant.

RESULTS

The study and control groups were comparable in age and body structure (Table**1**).The mean values in addition to standard deviation and P values measured by the Least Significant Difference (LSD) in mean of plaque index among study and control groups demonstrated in table (**2**).The mean Plaque Index was highest among RA cases on MTX treatment (1.9) and lowest among controls (1.1). The difference observed in mean Plaque Index between three groups was statistically significant. The mean Plaque Index was significantly lower (1.1) in controls compared to both RA on Etanercept and RA on MTX (1.7 and 1.9 respectively).Table (**3**) illustrates the median, mean rank and P (Mann-Whitney) for difference of sextants with CPI scores (0, 1, 2, 3 and 4) among study and control groups.The median count of sextant with CPI-score 0 was highest among controls (2) and lowest among both RA cases (0).

The difference observed in median count of sextant with CPI-score 0 between three groups was statistically significant. The median count of sextant with CPI-score 0 was significantly higher (2) among controls compared to both RA on Etanercept and RA on MTX (0 and 0 respectively).Mean rank of sextants with CPI-score 1 was obviously highest among RA cases on MTX (40.7) followed by RA cases on Etanercept (37.8) and lowest among controls (35.5). The differences observed however, failed to reach the level of statistical significance.Mean rank of sextants with CPI- score 2 was obviously highest among RA cases on Etanercept (40.6) followed by RA cases on MTX (36.8) and lowest among controls (36.6). The differences observed however, failed to reach the level of statistical significance.The median count of sextant with CPI-score 3 was lowest among controls (0) and highest among both RA cases (2).

The difference observed in median count of sextant with CPI-score 3 between three groups was statistically significant. The median count of sextant with CPI-score 3 was significantly higher among both RA on Etanercept and RA on MTX (2 and 2 respectively) compared to controls (0). Mean rank of sextants with CPI- score 4 was obviously highest among RA cases on Etanercept (39.5) followed by controls (38.0) and lowest RA on MTX (36.5). The differences observed however, failed to reach the level of statistical significance.Table (**4**) illustrates the difference in median and mean rank of salivary CRP and between the two RA cases groups and control.Mean rank of salivary CRP was obviously highest among controls (39.7 mg/1) followed by RA cases on MTX (38.6 mg/1) and lowest RA cases on Etanercept (35.7 mg/1). The differences observed however, failed to reach the level of statistical significance.Table (**5**) clarifies the difference in median and mean rank of salivary CRP between RA cases with high disease activity (DAS=5.1+) and those with low disease activity. There was statistically not significant difference between positive and negative of high disease activity in salivary CRP.Table (6) demonstrates the correlations coefficient between count of sextants with CPI-scores and salivary CRP for RA cases. There was weak and not significant linear correlation among count of sextants with CPI-scores and salivary CRP for RA cases and in all direction of relation.

Table 1: Age and Body Mass Index among Study Groups.

Age in years	Apparently healthy controls n=25	Rheumatoid arthritis treated with Methotrexate n=25	Rheumatoid arthritis treated with Etanercept n=25	P value
Range	(30-40)	(30-40)	(30-40)	(NS)
Mean	33.8	34.1	35.8	
SD	3.2	3.78	3.57	
BMI (Kg/m^2)				(NS)
Range	(18.3-38.6)	(16.9-44.4)	(17.3-45)	
Mean	28.4	30.1	28.5	
SD	5.66	7.7	5.73	

*** d.f (between groups/within groups) = 2/72.**

Table 2: Comparison of mean plaque index among three groups (Control, RA on MTX and RA on Etanercept)

Variable	Control group (mean ±SD) N=25	Methorexate group (mean ±SD) N=25	Etanercept group (mean ±SD) N=25	P1 Control + Methotrxate	P2 Control + Etanercept	P3 Methotrxate + Etanercept	F value	P Value for Difference Between 3 groups
Plaque Index	1.1±0.81	1.9±0.78	1.7±0.73	< 0.001	0.007	0.46(NS)	6.919	0.002

*** d.f (between groups/within groups) = 2/72.**

Table 3: The difference in: median and mean rank of sextants with CPI-scores (0, 1, 2, 3 and 4) between the two RA cases groups and control group.

Count of Sextant With CPI	Control group Median (Mean rank). N=25	Methotrexate group Median (Mean rank). N=25	Etanercept group Median (Mean rank). N=25	P1 (Mann-Wtiney) Control + MTX	P2 (Mann-Wtiney) Control + Etanercept	P3 (Mann-Wtiney) MTX + Etanercept	P Value for Difference Between 3 groups
Score 0	2 (53.4)	0 (31.8)	0(28.8)	**<0.001**	**<0.001**	(NS)	**<0.001**
Score 1	2 (35.5)	2 (40.7)	2(37.8)	**	**	**	(NS)
Score 2	1 (36.6)	1 (36.8)	1(40.6)	**	**	**	(NS)
Score 3	0 (23.6)	2 (43.1)	2(47.2)	**<0.001**	**<0.001**	(NS)	**<0.001**
Score 4	0 (38.0)	0 (36.5)	0(39.5)	**	**	**	(NS)

**** Not calculated, because the overall P values for difference between the three groups not reach the level of statistically significance.**

Table 4: The difference in median and mean rank of salivary CRP between two RA cases groups and control

Salivary CRP (mg/1)	Apparently healthy controls N=25	RA treated with Methotrexate N=25	RA treated Etanercept N=25	P value
Range	(0-48)	(0-192)	(0-48)	(NS)
Median	0	0	0	
Mean Rank	39.7	38.6	35.7	
Inter-quartile range	(0-0)	(0-0)	(0-0)	

Table 5: Correlation coefficient between count of sextants with CPI-scores and salivary CRP for RA cases

Variable	Linear correlation coefficient	Salivary CRP (mg/l)
Count of sextants with CPI-score 0	r	0.083
	p	(NS)
Count of sextants with CPI-score 1	r	0.075
	p	(NS)
Count of sextants with CPI-score 2	r	0.161
	p	(NS)
Count of sextants with CPI-score 3	r	0.06
	p	(NS)
Count of sextants with CPI-score 4	r	0.089
	p	(NS)

Table 6: Correlation coefficient between salivary CRP with disease activity score among RA cases

Variables	Linear correlation coefficient	Salivary Leptin(ng/ml)	Salivary CRP(mg/l)	Disease Activity score
Salivary CRP (mg/l)	r	0.242	-	0.004
	p	(NS)	-	(NS)

DISCUSSION

Rheumatoid arthritis (RA) is a common chronic systemic, inflammatory disease affecting the adult population; affected individuals experience significant morbidity, including loss of function, joint destruction, and permanent deformity, and have higher mortality than the general population [20].

In recent years, studies reported remarkable epidemiological and pathological relationships between periodontal diseases and rheumatic diseases, especially rheumatoid arthritis [7,8]. In present study the mean Plaque Index was significantly lower in controls compared to both RA on Etanercept and RA on MTX. The results of current study come in agreement with findings obtained by recent Iraqi study carried out by Mahmood et al. in 2012, as plaque index differed significantly between RA (higher) patients and control (lower). The stiffness of hands muscles to achieve good oral hygiene among RA patients and changing in the life style of RA patients, as hands muscle function reduces leading to improper oral hygiene mechanism may explain elevation in plaque index among RA cases, also psychological well-being of patients with RA; they are more likely to suffer from anxiety, depression and low self-esteem which may affect their proper oral hygiene. In terms of periodontal diseases among the study and control groups, the community periodontal index used in which the median count for each score count the number of sextants containing that score only and then present the median for the group.

The present study was found that the median count of sextant with CPI-score 0 was significantly higher among controls compared to both RA on Etanercept and RA on MTX. Gingival inflammation was obviously highest among RA cases on MTX (40.7) followed by RA cases on Etanercept (37.8) and lowest among controls (35.5), but statistically not significant. Although the prevalence of dental plaque was higher among study groups, gingival bleeding was not different between study and control groups. These results come in agreement with results obtained from previous studies [22, 23]. The accepted explanation for these results that the chronic use (prolonged and continuous) of anti-inflammatory drugs; Non Steroid Anti-Inflammatory Drugs (NSAIDs) and steroidal anti-inflammatory drugs (SAIDs) which are used by majority of RA patients and cannot be excluded individuals who use these drugs may modulate plaque-associated gingivitis, however, results of present study are contradict findings of other studies regarding gingival bleeding and gingival inflammation which reported elevation among RA patients and explained by higher plaque index as a causative factor for gingival inflammation [24], this variation in the results may related to difference in age, type of treatment and index use for evaluation of gingival condition.

The periodontal pocket is one of the most important clinical features of periodontal disease [25]. Pocket depth (4-5 mm) was evaluated in this study to be statistically significant higher among RA cases (both on MTX and Etanercept) compared with healthy controls, these results come to confirm findings obtained from several studies; where most patients with RA study showed moderate-to-severe periodontitis [26] and also support the concept that patients with long-standing rheumatoid arthritis have substantially increased periodontal disease compared to healthy subjects. In the current study effect of both treatments (Methotrexate and Etanercept) on periodontal health was evaluated revealing no significant difference between two treatments regarding effect on periodontal health, this is consistent with findings of a previous study in RA subjects that anti-TNF-α therapy without periodontal treatment has no significant effect on the periodontal condition [27]. In the same study the Methotrexate effect on periodontal health was evaluated and also has no effect on periodontal condition without periodontal treatment confirming the inter-relationship between RA and PD.

Estimation levels of salivary biomarker CRP among RA patients was one of aims of current study, as quantitative changes of specific salivary biomarkers could have significance in the diagnosis and management of both oral and systemic diseases; levels of salivary CRP in present study reveals no significant difference was observed between the two RA study groups (MTX and Etanercept) and controls (38.6 mg/l, 35.7 mg/l and 39.7 mg/l) respectively. Serum CRP in rheumatoid arthritis patients has been evaluated extensively but unfortunately, there was no study able to be found estimates its level in saliva. This non-significant difference between study and control groups may relate to effect of treatment, since Hochberg et al.in 2011 reported that MTX rapidly decrease serum CRP with the minimum value being noted on day 3 after once-weekly dosing and Su et al. in 2009 demonstrated significant improvements in serum CRP values at the end of the first 3 months treatment with Etanercept and as saliva is mirror of the body reflects its concentration in serum, this may be an acceptable explanation. This study reveals weak correlation of salivary CRP with DAS 28 among

both groups of RA patients, this agree with Keenan et al. [28] who concluded from his study regarding ESRand CRP values in RA andwhether or not they were correlated with outcomes in RAby measures of disease activity;the study revealed that they were weakly correlated with disease activity measures.In conclusion periodontal destruction represented in pocket depth was statistically significant higher among both RA cases (on MTX and combination of MTX and Etanercept) compared with healthy controls concluded severity of periodontal disease and that both treatments have no impact on periodontal destruction without periodontaltreatment among patients with RA, suggesting especial periodontal treatment and preventive programs, alsoanother outcome of current study that salivary CRP using this assay is of low importance and not meaningfulclinically to assess the activity of the disease suggesting more specific and sensitive assays such as salivary high sensitivity CRP assay.

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