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RESEARCH ARTICLE

IS THERE ANY ASSOCIATION OF PERIODONTITIS AND RHEUMATOID ARTHRITIS IN RELATION TO BIOMARKERS TUMOR NECROSIS FACTOR ALPHA AND RHEUMATOID ARTHRITIS FACTOR ?

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ABSTRACT

Background: Although the etiologies of periodontitis and rheumatoid arthritis are different, the similar underlying pathological processes are sufficient to permit consideration of hypothesis that individuals at risk of developing rheumatoid arthritis can also be at risk of developing periodontitis and vice versa. TNF-a and RA factor are amongst the important biomarkers that could be measured to launch a link between periodontitis and rheumatoid arthritis.

Aim: The aim of this study is to evaluate the periodontal condition of the patients with rheumatoid arthritis and to correlate the status of periodontitis to clinical laboratory parameters like TNF-a and RA factor.

Methods: A total of 120 individuals was recruited for this study according to inclusion and exclusion criteria and were divided into four groups. Patients having rheumatoid arthritis "RA" (30), patients having periodontitis "P" (30), patients having rheumatoid arthritis with periodontitis "RAP" (30) and healthy controls "C" (30). Written informed consent was taken from each individual participating in this study prior to performing any examination or sample collection. Oral examination was done for all patients prior to the sampling. Patient's serum sample was collected, labeled, stored and analyzed for the selected biomarkers (serum TNF-a and RA factor) by using Human Bone Magnetic Bead Panel (Millipore) and ELISA.

Results: Multiple comparisons were made to know the possible variation in concentrations of TNF-a and RAF between all four groups (RA, P, RAP and C). Serum levels of TNF-a and RA factor in all four groups were also assessed and intergroup analysis was done. The levels of TNF-a and RA factor has not shown significant variation among all groups.

Conclusion: A better understanding of the intracellular proteins and signaling pathways that regulate TNF-a biosynthesis is crucial for the development of novel anti-TNF-based therapies for rheumatoid arthritis patients.

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INTRODUCTION

It has been proven that patients suffering from advanced rheumatoid arthritis have greater periodontal problems as compared to patients not suffering from rheumatoid arthritis (Bartold *et al*., 2005). They have resemblances in their pathogenesis, immune response, diagnosis and treatment (Detert *et al*., 2010). Both periodontitis and rheumatoid arthritis result from dysregulation of the host inflammatory response and are potentiated by an overstated inflammatory response containing an increase in local and maybe circulating proinflammatory mediators, resulting in demolition of the soft and hard tissues surrounding the teeth (the periodontium) and the synovial joint (Culshaw *et al*., 2011). The resemblances between rheumatoid arthritis and periodontitis have driven numerous studies on periodontal status of patients with rheumatoid arthritis though the relationship between rheumatoid arthritis and periodontitis that developed from

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these studies are controversial (Mercado *et al*., 2001). Thus the major aim of this study is the analysis of systemically and clinically, the inter-relationship between periodontitis and rheumatoid arthritis. Tumor Necrosis Factor alpha is now recognized as mediating a wide variety of effector functions relevant to the pathogenesis of rheumatoid arthiritis, including endothelial cell activation & chemokine amplification, leading to leukocyte accumulation, osteoclast and chondrocyte activation promoting articular destruction, nociceptor sensitization, impaired cognitive function and metabolic syndrome. These are all recognized components of the RA spectrum & explain the broad effects of Tumor Necrosis Factor alpha blockade in patients (Brennan and McInnes, 2008). Patients receiving anti-TNF-a have shown to have lower periodontal indices (Mayer *et al*., 2009) Different rheumatoid factor isotypes alone or in combination can be very useful when managing rheumatoid arthritis patients, from the point of diagnosis till the therapeutic strategy (Ingegnoli *et al*., 2013).

MATERIALS AND METHODS

It was a prospective cross-sectional study. This study was partly carried out at Ghurki Trust hospital, Lahore and partly at the Centre for Research in Molecular Medicine, The University of Lahore. Prior approval from the ethics committee of the hospital was taken before the study. A group of 30 RA patients, 30 periodontitis patients, 30 RA with periodontitis patients and 30 age and gender matched healthy controls were targeted for participation. Written, informed consent was taken from each individual participating in this study prior to performing any examination and sample collection. Oral examinations were done for all patients prior to the sampling.

Patients' serum samples were collected, labeled, stored and analyzed for the selected biomarkers (serum TNF-a and RA Factor) by using Human Bone Magnetic Bead Panel (Millipore) and ELISA. All the participants were explained about the purpose of the study and ensured of confidentiality. The confounding factors were ruled out by detailed history and examination. Blood samples for the analysis of serum biomarkers including TNF-a and Rheumatoid arthritis Factor were drawn from an ante-cubital vein from the patients of each group. Every time after taking samples, they were placed immediately in anti-coagulant EDTA tubes between ice packs and transported to Biochemistry and Molecular Biology Laboratory of CRIMM, The University of Lahore. Approximately 5 mL volume of blood was collected from each subject. Data entry and analysis was done on SPSS 21.

RESULTS

Descriptive statistics

In the present study serum level of bio markers TNF-a and RA factor were studied in three groups of patients and compared with fourth group i.e. healthy controls. The Group 'P' includes patients with "Periodontal disease", group 'RA' contains patients with "Rheumatoid Arthritis", group 'RAP' contains patients with "Rheumatoid Arthritis with periodontitis" and group 'C' had healthy "Controls". Thirty individuals of each of the groups were compared with 30 healthy controls.

The healthy control group "C" included 56% healthy males and 44% healthy females with mean age ± SD of 31.33 ± 6.52 and BMI ± SD of individuals of control group was 22.53 ± 4.22.

The group "P" included 45% males and 55% females with mean age ± SD of 40.03 ± 8.86 and BMI ± SD of individuals of this group was 26.27 ± 1.81.

The group "RA" included 40% males and 60% females with mean age ± SD of 45.83 ± 16.06 and BMI ± SD of individuals of this group was 24.86 ± 3.61.

The group "RAP" included 40% males and 60% females with mean age ± SD of 41.43 ± 11.96 and BMI ± SD of individuals of this group was 24.69 ± 2.32 Table 1.

Serum Bio markers metabolism mediating proteins

The primary objective of this study was to assess the serum concentrations of various bio metabolism mediating proteins in patients with P (Periodontal disease), RA (Rheumatoid arthritis) and RAP (Rheumatoid arthritis-periodontal disease) groups and compare these values with those of C (Healthy control) group. Among bone metabolism mediating proteins TNF-a and RA factor were chosen because of their important effect in bone metabolism. TNF-a and RA factor were chosen wfor serum levels quantification in all P, RA and RAP groups and compared with those of C group.

TNF-alpha

Serum levels of TNF-a were assessed in group 'C' 'P' 'RA' 'RAP' with mean ± SE was found as 14.7878 ± 3.09069, 34.2613 ± 7.01016, 32.1653 ± 5.22773and 31.8343 ± 5.61346 respectively.

Table 1. Descriptive statistics

	Groups			
	C (30)	P (30)	RA (30)	RAP (30)
	MEAN ± SD	MEAN ± SD	MEAN ± SD	MEAN ± SD
Males (%)	56	45	40	40
Females (%)	44	55	60	60
AGE	31.33 ± 6.52	40.03 ± 8.86	45.83 ± 16.06	41.43 ± 11.96
BMI	22.53 ± 4.22	26.27 ± 1.81	24.86 ± 3.61	24.69 ± 2.32

Table 2. Concentrations of TNF-a in groups C, P, RA and RAP

TNF-alpha (pg/mL)				
Group (N)				Total
C (27)	P (30)	RA (30)	RAP (30)	117
MEAN ± SE	MEAN ± SE	MEAN ± SE	MEAN ± SE	
14.7878 ± 3.09069	34.2613 ± 7.01016	32.1653 ± 5.22773	31.8343 ± 5.61346	
Range (Minimum : ; Maximum)				
1.31: 45.37	1.11: 138.44	1.90: 86.16	2.10: 89.54	1.11: 138.44

Table 3. Concentrations of RA factor in groups C, P, RA and RAP

RA factor (pg/mL)				
Group (n)				Total
C (30)	P (29)	RA (30)	RAP (30)	114
MEAN ± SE	MEAN ± SE	MEAN ± SE	MEAN ± SE	
2.7439 ± .73841	4.5176 ± 1.19030	3.7791 ± 1.30785	3.7332 ± 1.18204	
Range (Minimum : Maximum)				
0.00 : 15.23	0.00: 30.09	0.00 : 24.24	0.00 : 26.79	0.00 : 30.09

The minimum: maximum ranges of concentrations of TNF-alpha in group C, P, RA and RAP were found as 1.31: 45.37, 1.11: 138.44, 1.90: 86.16 and 2.10: 89.54pg/mL respectively. Total minimum: maximum concentration in all four groups (N=117) was found in range 1.11: 138.44 Table 2.

RAF

Serum levels of RA factor were assessed in group 'C', 'P', 'RA' and 'RAP' was found as 2.7439± .73841, 4.5176±1.19030, 3.7791± 1.30785and 3.7332± 1.18204 respectively.

Table 4. Comparative analysis of TNF-alpha and RA factor in studied groups (Groups C, P, RA and RAP)

	Sig.
TNF- alpha	.059
RAF	0.742

Table 5. Analysis of variance of TNF-a and RA factor concentrations in C, P, RA and RAP Groups. * The mean difference is significant at the 0.05 level

		TNF- alpha	RA Factor
Groups		Sig.	Sig.
	P	0.015	0.269
C	RA	0.030*	0.515
	RAP	0.033	0.534
	C	0.015	0.269
P	RA	0.786	0.645
	RAP	0.753	0.624
	C	0.030	0.515
RA	P	0.786	0.645
	RAP	0.966	0.977
	C	0.033	0.534
	P	0.753	0.624
	RA	0.966	0.977

The minimum: maximum ranges of concentrations of RA factor in group C, P, RA and s RAP were found as 0.00: 15.23, 0.00: 30.09, 0.00: 24.24.36 and 0.00: 26.79pg/mL respectively. Total minimum: maximum concentration in all four groups (N=119) was found in range 0.00: 30.09 Table 3. Serum levels of TNF-a and RA factor in all four groups were also assessed and inter-group analysis was done. The levels of RA factor and TNF-a had not shown significant variation among all groups Table 4,5.

DISCUSSION

In this report mean TNF-a and RA factor did not show any significant difference in C, P, RA and RAP group. However in C group mean TNF-a level and RA factor level was quite less as compared to that of P, RA and RAP group. However this difference was not statistically significant. In human monocytes/macrophages pre-incubated with TNF-R1-expressing human endothelial cells, reverse signaling via transmembrane TNF-a mediated LPS resistance as indicated by the down-regulation of LPS induced soluble TNF- a and IL-6 as well as IL-1 and -10.Pre-treatment with soluble TNF-R1 for inducing reverse signaling through transmembrane TNF-a sensitized human-monocyte cell line U937 cells to soluble TNF-a-induced activation, while stimulation of transmembrane TNF-a after soluble TNF-a-induced activation of U937 cells abridged mRNA stability of IL-1b and IL- 8 (Wang *et al*., 2002). RF-positive patients with Rheumatoid Arthrits can face extra violent and erosive joint disease and extra articular manifestations than those who are Rheumatoid Factor-negative. Similar findings had been observed in juvenile rheumatoid arthritis. Those common observations, though, are of partial utility in an individual patient due to broad inter patient inconsistency. In this setting, accurate prediction of the disease course is not possible from the rheumatoid factor alone. Although some studies have suggested that erosive disease can be accurately predicted by examining the grouping

of HLA-DRB1 and RF status among patients with rheumatoid arthrits. Those examinations are of partial worth in an individual patient as almost one-half of "high risk" patients had no erosions at one year (Hurd, 1979, Cojocaru *et al*., 2010, Huizinga *et al*., 2005).

Conclusions

According to results of this study no significant correlation was observed for TNF-a and RA factor for each other in C, P, RA and RAP groups. However mean level of TNF-a and RA factors was high in P, RA and in RAP group as that of Controls.

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