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Salivary Levels of IgA and IgG in Rheumatoid Arthritis Patients with Hypo Salivation and Normal Salivation (Comparative Study)

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint inflammation, involvement of exocrine salivary and lacrimal glands may occur as extra-articular manifestations in this disease. Salivary gland dysfunction in rheumatoid arthritis is supposed to be closely related to the infiltration of lymphocytes that occur in affected glands and demonstrated as changes in immunological parameters. **Aims of study:** This study was established to shed light on the changes in salivary levels of IgA and IgG in RA patients and controls, and to investigate and compare the levels of IgA and IgG between with hypo salivation and normal salivation patients. **Materials and Methods:** Fifty five patients with RA (7 male and 48 female) were enrolled in this study with age range (20-69) years. The patients were separated into two groups according to their salivation: normal salivation group (37) and hypo salivation group (18). Thirty five (9 male and 26 female) apparently healthy volunteers their ages and sexes were matched with the patients were also participated in the study. Three ml of unstimulated saliva was collected from all patients and control to determine IgA and IgG by ELISA method. **Results:** the current results revealed that there was highly significant increase ($p< 0.001$) in salivary level of IgA among patients as compared to control. Meanwhile the comparison among three study groups (two patients groups and controls group), revealed that there are highly significant increase ($p<0.001$) in the level of IgA among two patients groups as compared to control group. However, there are no significant differences in salivary levels of IgA between hypo salivation and normal salivation groups ($p>0.05$). On the other hand, salivary level of IgG in patient was significantly less than that in controls ($p<0.05$), in addition to that IgG level was significantly low ($p<0.05$) in two patients groups than that in control group. Interestingly, there is no significant difference ($p>0.05$) in level of IgG between two groups of patients. Moreover, there is significant decrease ($p< 0.001$) in salivary flow rate among patients when compared to control. Also, there is significant reduction ($P< 0.01$) in hypo salivation patients as compared to normal salivation. **Conclusion:** The current results suggest that the changes in salivary IgA and IgG might represent involvement of salivary glands in patients with rheumatoid arthritis.

Keywords: *Rheumatoid arthritis, salivary gland, IgA, IgG.*

Introduction

Rheumatoid arthritis is a common, disabling, autoimmune disease that is characterized by joint inflammation and subsequent destruction of cartilage and bone, significant pain and functional disability. Its prevalence is estimated at 0.5 - 1.0 percent of adults worldwide [(1)]. It has been known for a long time that salivary gland involvement occur in RA patients; however it does not take attraction. In 1978 Sullivan

and colleagues stated that 58 of 100 unselected RA out-patients had decreased salivary and/or lacrymal secretion. The diagnosis of salivary gland involvement is based on the detection of functional impairment or anatomical changes resulting from an autoimmune inflammatory process in which the salivary glands are the main target [2]. Salivary glands of patients with RA were heavily invaded with B lymphocytes, which are more predominant than T lymphocytes, and also the helper T cells are higher than suppressor T cells, and that the changes also involved atrophy of acinar cells with fibrosis and also sialadenitis [3,4]. Immunological studies of RA patients revealed abnormal titers of circulating immune complexes in about 71% of cases; it was found that 32% of patients have SSA antibodies and SSB antibodies, and in 27% of patient's antinuclear antibodies was present [4]. It worthy to mention that in RA patients antibodies against salivary ducts which may or may not accompanying secondary Sjogren syndrome but not in primary Sjogren syndrome [5]. This study was established to shed light on the changes in salivary levels of IgA and IgG in RA patients and controls, and to investigate and compare the levels of IgA and IgG between with hypo salivation and normal salivation patients.

Materials and Methods

Fifty five patients with RA (7 male and 48 female) were enrolled in this study with age range (20-69) years. The patients were diagnosed clinically by rheumatology specialists and assessment of disease activity depending on DAS 28; they were from attendance to the Baghdad Teaching Hospital seeking for treatment. The patients group was divided into two groups according to their salivation: normal salivation group (37 patients) and hypo salivation group (18 patients). Data were collected from patients including name, age, gender, whether smoker or alcoholic or not, onset of disease and duration, family history, other systemic diseases, and medications. The control group consist of 35 participants (9 male and 26 female) and they were in healthy conditions (not suffering from systemic diseases and not taking any medication), their ages and genders was matched to the patients group, with age range from (20- 69) years. Three ml of unstimulated (resting) whole saliva samples were collected under resting conditions between 9.0-12.0 A.M. patients were asked to rinse their mouth with water and to generate saliva in their mouth and to spit into a wide test tube. After that the saliva was centrifuged at (3000 rpm) for 10 minutes. The resulting supernatant was stored at – 20 °C in polyethylene tubes until assayed Salivary IgA and IgG were measured by Enzyme Linked Immunosorbent Assay method, and performed as recommended in leaflet with ELISA kits (CusaBio/ China).

Statistical analysis was assessed using P (Bonferroni-test), P (Mann-Whitney-test) and (Kruskal-Wallis-test). Correlation between the different parameters was calculated by the spearman test. P-value less than the 0.05 was considered statistically significant.

Results

The present study showed that there was significant increase ($p<0.001$) in salivary level of IgA in patients (260.7 ng/ml) as compared to controls (4.9 ng/ml), table (1). Meanwhile the comparison among three study groups revealed that there are highly significant increase ($p<0.001$) in IgA among two patients groups (260.7 ng/ml in normal group; 263 ng/ml in hypo group) as compared to in control group (4.9). However, there are no significant differences in salivary levels of IgA between hypo salivation and normal salivation groups ($p>0.05$), as observed in table (2). On the other hand, there was significant reduce ($p<0.05$) in salivary level of IgG among RA patient group (21.2µg\ml) as compared to control group (71.1µg\ml) as clearly shown in table (3). Furthermore, the differences in median of salivary level of IgG among three groups were found in table (4), there was significant decrease ($p<0.05$) in IgG in normal salivation group (14.4µg\ml) and in hypo salivation group (21.2µg\ml) than that in control group (71.1µg\ml), while there is no significant differences ($p>0.05$) in salivary IgG between two patient groups (normal and hypo), table (4). Another important result is that there is significant decrease ($P<0.01$) in median salivary flow rate among patients (0.35 ml\min) when compared to control group (0.6 ml\min), table (5). In regard to the differences in flow rate between two groups of patients (hypo and normal) and controls, the current result showed that there are highly significant differences ($P<0.001$). Salivary flow rate among control group was (0.6 ml/min) whereas in normal salivation group was (0.56 ml/min) and in hypo salivation group was (0.17 ml/min). On the other hand, salivary flow rate was significantly decreasing ($P<0.001$) in patients with hypo salivation as compared to that in patients with normal salivation, table (6).

Table (1): Difference in salivary IgA in patient group and control group.

Salivary IgA	Control group n= 35	Patients group n= 55	P (Mann-Whitney)
Range	(2.3- 164.3)	(35.4- 1021.3)	0.00 **
Median	4.9	260.7	
Mean	27.94	319.92	
SD	40.13	232.07	
SE	6.78	31.29	

Table (2): Differences in salivary IgA between two patient groups and control group.

Salivary IgA	Healthy control n= 35	Normal salivation n= 37	Hypo salivation n= 18	P (Kruskall-Wallis)
Range	(2.3-164.3)	(35.4-978.1)	(46.03-1021.3)	0.000 **
Median	4.9	260.7	263	
Mean	27.94	316.35	327.26	
SD	40.13	222.95	256.37	
SE	6.78	36.65	60.43	
P (Mann-Whitney)				
Normal X Hypo = p>0.05				

Table (3): Difference in salivary IgG in patient group and control group.

Salivary IgG	Control group n= 35	Patients group n= 55	P (Mann-Whitney)
Range	(1.08- 238)	(0.076- 173.5)	0.012 *
Median	71.1	21.2	
Mean	73.89	33.42	
SD	69.02	39.55	
SE	11.67	5.33	

Table (4): Differences in salivary IgG between two patient groups and control group.

Salivary Ig G	Healthy control n= 35	Normal salivation n= 37	Hypo salivation n= 18	P (Kruskall-Wallis)
Range	(1.08-1.08)	(0.076-173.5)	(1.9-114.3)	0.041*
Median	71.1	14.4	21.2	
Mean	73.89	35.75	28.63	
SD	69.02	44.24	28.07	
SE	11.67	7.27	6.62	
P (Mann-Whitney)				
Normal X Hypo = p>0.05				

Table-5: Difference in salivary flow rate in patient group and control group.

Salivary flow rate	Control group n= 35	Patients group n= 55	P (Mann-Whitney)
Range	(0.31- 1.9)	(0.08- 2.5)	0.004**
Median	0.6	0.35	
Mean	0.64	0.52	
SD	0.32	0.44	
SE	0.05	0.06	

Table-6: Differences in salivary flow rate between two patient groups and control group.

Salivary flow rate	Healthy control n= 35	Normal salivation n= 18	Hypo salivation n= 37	P (Kruskall-Wallis)
Range	(0.31-1.9)	(0.3- 2.5)	(0.08- 0.26)	0.001**
Median	0.6	0.56	0.17	
Mean	0.64	0.68	0.17	
SD	0.32	0.45	0.06	
SE	0.05	0.07	0.01	
P (Mann-Whitney)				
Normal X Hypo = P<0.001				

Discussion

The main immunoglobulin isotype of saliva is secretory IgA. The main function of secretory IgA is inhibition of microbial colonization which is done by both aggregating bacteria and then preventing their adhesion [(6)]. The present study demonstrated significant elevation in salivary level of IgA among RA patient group as compared to control group. Meanwhile, the comparison between two patient groups showed no differences in median salivary IgA between hypo salivation RA and normal salivation RA. In agreement with this study Matthews *et al.*, reported that RA patients have increased IgA in parotid and also in submandibular saliva, besides, they revealed that salivary IgA content and flow have an inverse relationship, that is, as salivary flow rises the salivary IgA decrease and these result confirm the present results. Nevertheless, it does not follow that an elevated IgA would be anticipated in saliva from patients with decrease salivary flow. It could be that in immunologically damaged glands of RA patients the secretion and transport mechanism of IgA is perfect [(7)]. Elkon and colleagues also found that salivary IgA concentrations were higher in RA patients with dry eyes than in control subjects [(8)]. However, increased salivary levels of IgA but not salivary levels of amylase have been reported in RA patients with secondary SS [(9)].

On the contrary Zalewska *et al*., (2011) stated that the level of IgA was lower in RA patients group than in control, this may be indicative of disablement of the salivary immune system of the mouth in patients with RA, this result is disagreed with the results of the current study [(10)]. In consistent with present study, the comparison between two patient groups Zalewska *et al*., (2011) reported that the comparison with normal salivation RA and healthy control groups, hypo salivation RA patients had a significant decrease in specific content of sIgA and peroxidase [(10)]. In other study carried out to determine by ELISA the salivary sIgA in 48 RA patients and 102 healthy person case controls found that there were no statistically significant differences between RA patients and healthy subjects with regard to caries extention and salivary sIgA, and concluded that rheumatologists must learn the patients on dental care [(11).]

Interestingly, the present study showed that the salivary IgG level was significantly lower in RA patient group than in control group, similarly Zalewska and colleagues reported that RA patients had a significantly lower specific content of salivary sIgA and IgG [(10)]. Correspondingly Elkon *et al*., (1983) found that salivary IgG concentrations were higher in RA patients than in control subjects [(8)]. Nevertheless, concentrations of salivary IgG, IgA and IgM were high significant increase in rheumatic disease patients

as compared to controls. Elevation in concentrations of salivary IgG and IgA have been detected in primary SS and secondary cases of SS complicated with RA could due to leakage of B cell from serum into the damaged glands or massive infiltration of salivary glands by this cells [(12)]. High numbers of plasma cells which are produce IgG have been noticed in biopsy specimens of minor salivary gland infiltrated with lymphocyte in rheumatic disease patients [(13)]. Whereas Yavuzyilmaz and colleagues found highly significant increase in salivary IgG level among RA group than healthy group, because of elevation of humoral immunity in patient with RA [(14)]. The discrepancies observed between various studies could be caused, in part, by the differences in methodology and sample size.

In this salivary flow rate are significantly decrease in patients as compared to control group, this result is consistent with other studies [(15, 16)].When comparing between two patients group this study notice that highly significant reduce in salivary flow rate was observed in RA hypo salivation group than those in RA normal salivation group and control group, also the salivary flow rate have tendency to decrease in normal salivation group in comparison to control group, this finding coinciding with previous reports [(16, 17 and 18)].

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