

Drugs or disease: evaluating salivary function in RA patients

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Abstract: Oral complications of RA may include temporomandibular joint disorders, mucosa alterations and symptoms of dry mouth. The aim of this study was to evaluate the salivary gland function of subjects with rheumatoid arthritis (RA) comparing it to healthy controls. Subjects with other systemic conditions known to affect salivary functions were excluded. A questionnaire was applied for the evaluation of xerostomia. Resting and chewing-stimulated salivary flow rates (SFR) were obtained under standard conditions. There were 145 subjects included of the study (104 RA and 38 controls). About 66.7% of the RA subjects and 2.4% in control group presented xerostomia. The median resting SFR were 0.24 ml/min for RA subjects and 0.40 mL/min for controls ($p = 0.04$). The median stimulated SFR were 1.31 mL/min for RA subjects and 1.52 ml/min for controls ($p = 0.33$). No significant differences were found between resting and stimulated SFR of RA subjects not using xerogenic medications and controls. There was significantly higher number of subjects presenting hyposalivation in the RA group than among controls, even when subjects using xerogenic medications were eliminated from the analysis. In conclusion, hyposalivation and xerostomia were more frequent among RA subjects not using xerogenic medication than among controls, although there were no significant differences in the median SFR between groups.

Keywords: Saliva; Salivary Glands; Xerostomia; Arthritis, Rheumatoid.

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Introduction

Rheumatoid Arthritis (RA) is the most common rheumatic disease. It is a chronic inflammatory autoimmune disease characterized by joint swelling and tenderness and destruction of synovial joints, leading to severe disability and premature mortality¹. Oral complications of RA may include temporomandibular joint disorders^{2,3}, mucosa alterations⁴ and complaints of dry mouth⁵. Some studies have evaluated the salivary flow rates (SFR) in RA subjects, not associated with secondary Sjögren's syndrome, but most of them do not distinguish patients with secondary autoimmune diseases^{2,6,7,8,9,10,11}.

Extra-articular involvement may be observed in RA patients, including organs like the skin, eye, heart, lung, kidney, and the nervous and gastrointestinal systems¹². Salivary function may be affected in clinically diagnosed RA patients^{2,6,8,13}. Extra-articular manifestations of RA are a result of vessel vasculitis, sometimes followed by necrosis of the vessel wall and artery occlusion, in most of the affected organs¹². Minor salivary gland

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histology taken from lip biopsy of RA patients, varies from small lymphocytic infiltrates without lobular destruction to extensive round-cell infiltration with partial destruction of acinar tissue with or without fibrosis¹⁴. Sjögren's patients present focal lymphocytic sialoadenitis, sometimes with extensive sclerosis destroying the lobular architecture^{14,15}. In patients with secondary Sjögren's syndrome, the autoimmune changes which affect salivary gland function appear due to progressing lymphocytic infiltration in salivary acini, which in turn leads to acinar atrophy and proliferation of connective tissue⁵. The mechanism by which the salivary glands are affected in patients with RA has not been described.

The prevalence of hyposalivation varies from 14.4% to 25.5% in the general population, and it has been reported as 17.4% in the patients with RA^{11,16,17}. However, the reduced SFR in RA patients may be a consequence of the large amount of medications taken by these patients. The influence of xerogenic medications on the SFR of these subjects has rarely been studied⁷.

When salivary functions are reduced there may be severe oral health consequences like xerostomia, changes in salivary composition, difficulty in mastication, dysphagia, dysphasia, dysgeusia/hypogeusia, oral microbiota alterations, and increased decay and periodontal disease susceptibility^{17,18}. Not every individual who presents reduced SFR reports xerostomia, and *vice-versa*^{19,20}. Sialometry is a non-invasive, low-costing, quick and easy test for quantifying SFR. If sialometry is performed routinely in clinical practice, it may be used as a marker for systemic disease diagnosis and for special care in oral health.

The aim of this study was to evaluate the salivary gland function and the role of xerogenic drugs on the salivary function in subjects with RA. Our null hypothesis was that SFR of subjects with RA are similar to the SFR of healthy controls.

Methodology

Study population

This is a cross-sectional study in which the salivary function of RA subjects was compared to healthy controls. Patients with immunomediated/colagenous diseases were referred for oral evaluation at the

Stomatology Clinic of the Universidade Federal do Rio de Janeiro (UFRJ) School of Dentistry, from physicians of the Rheumatology and Collagenose Clinic of the Hospital Universitário Clementino Fraga Filho (HUCFF) of the same university, from March 2002 to June 2005.

A convenience sample with all subjects over 18 years of age with seropositive RA were selected for the study. Rheumatoid arthritis was diagnosed according to the American College of Rheumatology criteria²¹. The RA subjects presenting other underlying conditions that potentially affect salivary flow rates (other immunomediated/colagenous disease, diabetes, human immunodeficiency virus infection, hepatitis C, and with history of radiotherapy or chemotherapy) were excluded from the study.

Control group was composed by healthy subjects over 18 years of age, who attended the clinics at the UFRJ School of Dentistry. Controls in the same age range of RA subjects were invited to participate in the study. Subjects were excluded of control group if reported any health issue or if using medications.

The research was ethically conducted according to the Helsinki Declaration (World Medical Association). The study was approved by the institutional ethics committee, protocol number 015/03-CEP. Fully informed voluntary consent was obtained from each individual that participated in the study.

Data collection

The RA subjects' history and medications were taken from medical records. The medications included as disease-modifying antirheumatic drugs (DMARDs) were azathioprine, biologics, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, and tofacitinib²². Subjects were further analyzed in subgroups using or not xerogenic medications. The following drugs were considered xerogenic medications: anti-acid, anti-hypertensive, beta-blocker, diuretic, and psychotropic drugs. The medical history of controls was obtained through the interview of subjects.

Oral examination and sialometry were performed at the Stomatology Clinic, for every subject. A questionnaire was applied for the evaluation of xerostomia and associated symptoms¹⁵.

Samples of resting and chewing-stimulated whole saliva were obtained under standard conditions.²³ Saliva specimens were collected between 9 am and 11 am and no food, liquids, smoking, or hygienic habits were allowed for 120 min before the test section. For the resting SFR measurement, participants were asked to sit in a relaxed and upright position, and all produced saliva was periodically disposed into a disposable recipient, for a period of five minutes. For the stimulated sialometry, the participants were asked to chew preweighed (1 g) unflavored gum for 6 minutes. During the first minute they were instructed to swallow saliva as they chewed the gum, and then, they were asked to dispose the accumulated saliva, periodically, into a disposable container, for a period of five minutes. Saliva was then aspirated from the disposable cup with a graduated syringe and measured. Only the liquid component (not the foam) of saliva was measured. The SFR was determined as milliliters per minute.

The degree of salivary function was classified as normal (resting ≥ 0.3 ; stimulated ≥ 1 mL/min); intermediate (resting > 0.1 to < 0.3 ; stimulated > 0.7 to < 1.0 mL/min); and hyposalivation (resting ≤ 0.1 ; stimulated ≤ 0.7 mL/min).^{11,13}

Statistical analysis

Chi-square or Fisher's exact test were used to analyze differences in categorical data, and Mann-Whitney test for non-parametrical measured data. The p-value was set at 0.05. The SPSS© program, version 13.0 (SPSS Inc., IBM Company Headquarters, Chicago, Illinois, US), was used for storing and analyzing data.

Results

Two hundred and ten patients with immunomediated/ collagenous disease were referred to the Stomatology Clinic during the study period. From these patients, 131 presented seropositive RA, but only 104 fulfilled the study criteria. Twenty seven RA patients were excluded for having one or more than these conditions: secondary Sjögren's syndrome (n = 11), lupus erythematosus (n = 9), diabetes (n = 7), hypothyroidism (n = 3), radioactive iodine therapy (n = 3), radiotherapy of head and neck (n = 3), stem cell transplant (n = 3), or other conditions like scleroderma, lipoproteinemia, hemochromatosis, cystic fibrosis, Parkinson's disease, or dehydration.

Forty one subjects were included in the control group, after 63 exclusions for having underlying systemic conditions, or for taking drugs that might interfere in salivary function. The clinical and demographic data of the 145 studied subjects are summarized in Table 1.

Regarding the habits that could result in xerostomia, coffee drinking was the most prevalent habit in subjects from both groups of the study, and more RA subjects consumed coffee than subjects in control group ($p < 0.01$). But there were no differences in xerostomia and SFR of RA subjects who consumed coffee when compared with those who did not report the habit (data not shown). Forty six percent of the RA subjects and 68% of control subjects drank more than one liter of water a day. There were more subjects drinking less than half a liter of water in the RA group ($p = 0.04$) (Table 1).

More than half (55.3%) of the subjects with RA reported at least one positive answer in the xerostomia related symptoms questionnaire, while none of the subjects in the control group had a positive answer to these questions. The majority of RA subjects reported intermittently xerostomia (66.7%), and 44.1% of them reported symptoms of dry mouth for more than 6 months. The symptoms related to salivary function are shown in Table 2.

None of the subjects had a history of enlarged parotid gland, and one RA subject had a history of submandibular gland enlargement, which resolved with antibiotic. All controls presented normal saliva drainage of major salivary glands, but more than 10% of the RA subjects presented lack of saliva drainage in at least one of the major salivary glands (Table 3).

The median resting SFR were lower in RA subjects, but there were no differences in the median values of stimulated SFR between RA and controls (Table 3). Regarding the degree of salivary function, there were significantly more subjects with hyposalivation among RA subjects, than among controls, when defined by the results of resting sialometry (Table 3).

No significant differences were found when the resting and stimulated SFR of the 21 (20.2%) RA subjects that presented no saliva drainage from at least one of the major salivary gland were compared with the SFR of the other RA subjects who presented normal saliva drainage from all major glands. The median resting SFR of these

Table 1. Clinical and demographic characteristic of the 145 studied subjects.

Demographic and clinical data	Rheumatoid arthritis	Control group	p-value
	n = 104 (%)	n = 41 (%)	
Age			
Median	53.0	47.0	0.13
Range	19 -81	21 - 80	
Gender			
Male	12 (11.5)	12 (29.3)	0.01
Female	92 (88.5)	29 (70.7)	
Drugs*			
DMARDs	73 (70.2)	-	NA
Corticosteroid	71 (68.3)	-	NA
NSAID	35 (33.7)	-	NA
Anti-acid	16 (15.4)	-	NA
Analgesic	11 (10.6)	-	NA
Psychotropic	10 (9.6)	-	NA
Anti-hypertensive	23 (22.1)	-	NA
Anti-histaminic	2 (1.9)	-	NA
Antiplatelet	5 (4.8)	-	NA
Antibiotic	2 (1.9)	-	NA
Beta-blocker	3 (2.9)	-	NA
Diuretic	11 (10.6)	-	NA
Daily habits**			
Cigarette	18 (17.5)	7 (19.4)	0.80
Alcohol	10 (10.0)	2 (2.8)	1.00
Coffee	69 (69.0)	12 (33.3)	< 0.01
Marijuana	0	1 (2.8)	0.26
Amount of liquid ingested per day**			
< 1/2 L	15 (15.0)	0	0.04
> 1/2 and < 1 L	38 (38.0)	7 (28.0)	0.48
> 1 and < 2 L	30 (30.0)	14 (56.0)	0.20
> 2 L	16 (16.0)	3 (12.0)	0.76

NA = not applicable; DMARDs = disease-modifying antirheumatic drugs; *Individuals could take more than one type of drug. **Information not available for every subject in study.

Table 2. Symptoms related to salivary function of the 145 studied subjects.

Characteristics	Rheumatoid arthritis	Control group	p-value
	n = 104 (%)	n = 41 (%)	
Answers to questionnaire*			
Have you had a daily feeling of dry mouth for more than three months?	57 (55.3)	0	< 0.01
Have you had recurrently or persistent swollen salivary glands as an adult?	20 (19.4)	0	< 0.01
Do you frequently drink liquids to aid swallowing dry food?	33 (32.0)	0	< 0.01
Xerostomia**			
Do not present xerostomia	33 (33.3)	39 (97.5)	< 0.01
Xerostomia occasionally	9 (9.1)	1 (2.5)	0.28
Xerostomia ≤ 6 months	11 (12.2)	0	0.03
Xerostomia > 6 months and ≤ 1 year	10 (9.8)	0	0.06
Xerostomia > 1 and ≤ 2 years	10 (9.8)	0	0.06
Xerostomia > 2 years	23 (22.5)	0	< 0.01

*American-European consensus group proposed criteria¹⁵; ** Information not available for every subject in study.

Table 3. Salivary gland characteristics of the 145 studied subjects.

Salivary gland characteristics	Rheumatoid arthritis	Control group	p-value
	n = 104 (%)	n = 41 (%)	
Salivary gland enlargement (on exam)			
Parotid glands	0	0	-
Submandibular gland	1 (0.9)	0	1.00
Positive drainage from major salivary glands			
Parotid glands	90 (86.5)	41 (100.0)	0.01
Submandibular gland	93 (89.4)	41 (100.0)	0.03
Minor labial glands	93 (89.4)	41 (100.0)	0.03
Salivary flow rates (mL/min)			
Resting			
Median	0.24	0.40	0.04
Range	0–1.20	0.10–1.40	
Stimulated			
Median	1.31	1.52	0.33
Range	0–4.5	0.68–3.80	
Degree of salivary function			
Resting SFRs			
Hyposalivation	20 (19.2)	1 (2.4)	< 0.01
Intermediate	36 (34.6)	7 (17.1)	
Normal	48 (46.2)	33 (80.5)	
Stimulated SFRs			
Hyposalivation	25 (24.0)	2 (4.9)	0.03
Intermediate	7 (6.7)	3 (7.3)	
Normal	72 (69.2)	36 (87.8)	

SFR= salivary flow rates.

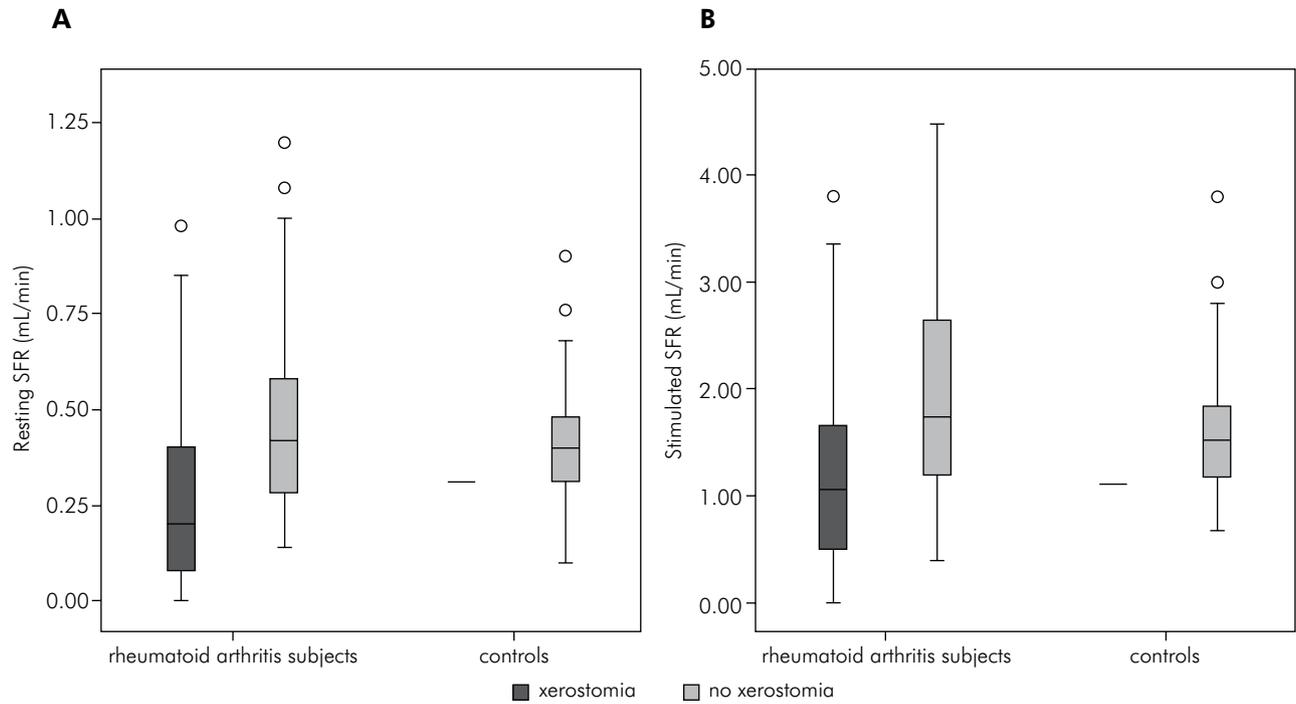
RA subjects (0.12 mL/min; range 0–1.08 mL/min) was lower than controls, but no differences were observed in the stimulated SFR between these subjects with no drainage and controls.

When the SFR of the subjects with RA who reported xerostomia were compared to the ones not presenting xerostomia, the median resting SFR were 0.20 mL/min and 0.42 mL/min, respectively ($p < 0.01$); and the median stimulated SFR were 1.1 mL/min for those who reported xerostomia and 1.6 mL/min for those not presenting any feeling of dry mouth ($p < 0.01$) (Figure 1).

Xerogenic drugs may be responsible for reduced SFR, and there were 45.2% of the RA subjects using xerogenic medications. When these RA subjects using xerogenic medications were analyzed, the median resting SFR was 0.24 mL/min (range 0–1.08 mL/min), and they presented lower median SFR than controls ($p = 0.005$). The median stimulated SFR of RA subjects taking xerogenic medications was 1.22 mL/min

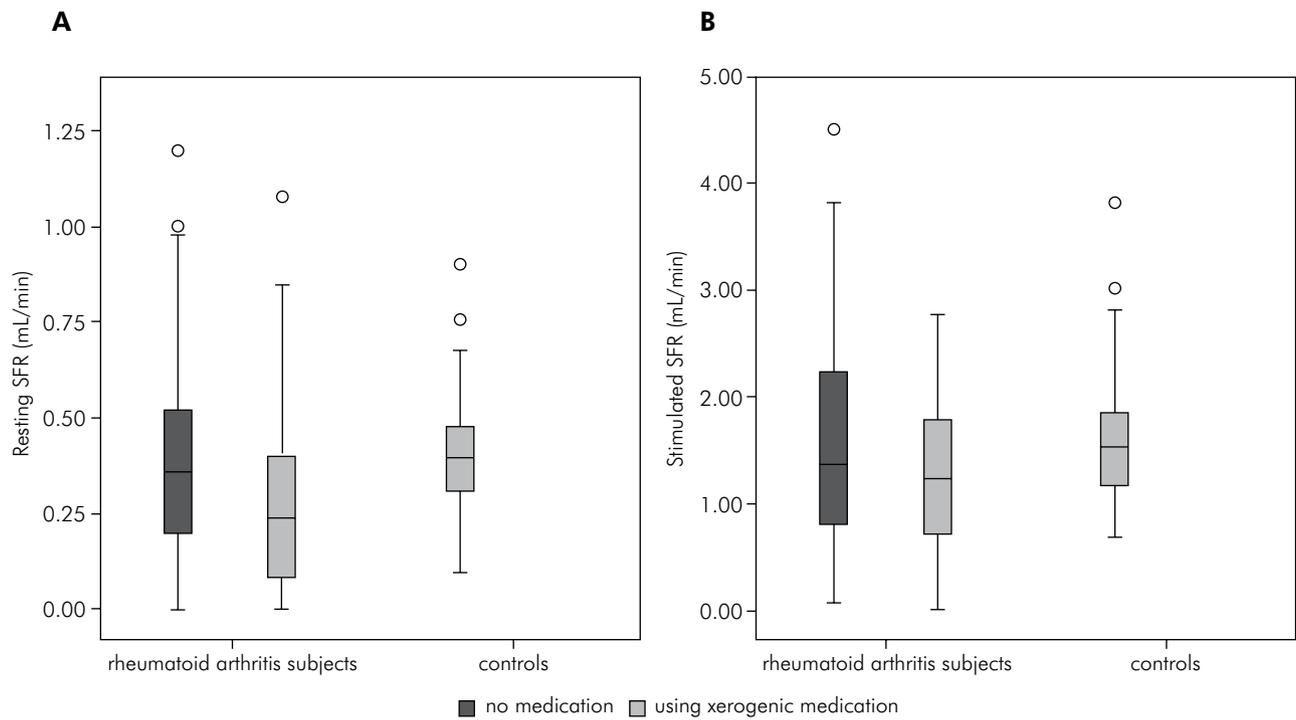
(range 0–2.76 mL/min), and there was no significant difference between this group and controls ($p = 0.13$) (Figure 2). There were no significant differences, when the resting and stimulated SFR were compared between RA subjects using or not xerogenic drugs.

The resting SFR of RA subjects using xerogenic medication were lower than controls. But, when the 47 subjects using xerogenic medications were eliminated from the analysis, no differences between groups were found in the median resting (RA group: median 0.36 mL/min; $p = 0.83$) or stimulated SFR (RA group: median 1.36 mL/min; $p = 0.30$). However, the number of subjects with hyposalivation was still higher in the RA group (Table 4). Xerostomia was observed in 53.8% of subjects not using xerogenic medications, and 15.4% of them did not present saliva drainage from at least one of the major glands. The amount of ingested liquids were not different than controls.



SFR: salivary flow rates.

Figure 1. Box-plot graph with the resting (A) and stimulated (B) salivary flow rates of the 145 rheumatoid arthritis subjects separated by the feeling of dry mouth.



SFR: salivary flow rates.

Figure 2. Box plot graph of the resting (A) and stimulated (B) salivary flow rates of the 145 studied subjects separated by group and the use of xerogenic drugs.

Sixty five percent of the RA subjects presenting hyposalivation (defined by resting SFR) were using xerogenic drugs. No difference was observed in the number of subjects presenting hyposalivation when the two subgroups of RA subjects (using or not xerogenic drugs) were compared. The number of subjects with hyposalivation (defined by resting SFR) was higher in the RA group than in the control group, even subjects using xerogenic medications were eliminated from the analysis (Table 4).

Regarding the protection factor given from corticosteroids or DMARDs on the SFR, no statistical significant differences were found in the median resting and stimulated SFR when subjects taking or not these drugs were compared with each other and with controls.

As there might be gender variations of the SFR, an evaluation of separate male and female genders were performed in subjects not using xerogenic medications, and no differences were observed in the median resting and stimulated SFR between groups.

Discussion

In the present study subjects with RA presented reduced resting SFR when compared to healthy controls. However, when a subset of RA subjects not using xerogenic medications was evaluated, there were no differences between the SFR of RA subjects and controls. These results suggest that medication is the cause of reduced salivary function of these subjects, not the disease itself.

Published studies show controversial results about the salivary function of the RA population^{2,6,8,9,11}, mainly because of differences in methodology. Most of these studies evaluate RA subjects with secondary autoimmune diseases, like Sjögren's syndrome. In the present study, subjects with Sjögren's syndrome and other immunomediated/colagenous disease were eliminated from the analysis, so there would be no confounding factors.

Secondary Sjögren's syndrome is commonly related to other autoimmune diseases and should be often

Table 4. Salivary flow rates characteristics of the of the 145 studied subjects subjects according to the use of xerogenic medication.

Salivary gland characteristics	RA not using xerogenic medications	RA using xerogenic medications	Control group	p1-value	p2 value
	n = 57 (%)	n = 47 (%)	n = 41 (%)		
Salivary Flow Rates (mL/min)					
Resting					
Median	0.36	0.24	0.40	0.83	< 0.001
Range	0–1.20	0–1.08	0.10–1.40		
Stimulated					
Median	1.36	1.22	1.52	0.30	0.03
Range	0–4.5	0–2.76	0.68–3.80		
Degree of salivary function					
Resting SFRs					
Hyposalivation	7 (12.3)	13 (27.7)	1 (2.4)	0.02	< 0.001
Intermediate	19 (33.3)	17 (36.2)	7 (17.1)		
Normal	31 (54.4)	17 (36.2)	33 (80.5)		
Stimulated SFRs					
Hyposalivation	12 (21.1)	13 (27.7)	2 (4.9)	0.07	0.01
Intermediate	4 (7.0)	3 (6.4)	3 (7.3)		
Normal	41 (71.9)	31 (66.0)	36 (87.8)		

SFR: salivary flow rates; RA: Rheumatoid arthritis; p1: differences between RA not using xerogenic medications and controls; p2: differences between RA using xerogenic medications and controls; p1 and p2 were adjusted for two comparisons ($p < 0.025$).

investigated in subjects with RA¹⁵. This syndrome is a major cause for hyposalivation and it has represented a concern when evaluating the salivary function from subjects with RA. Secondary Sjögren's syndrome has been reported as affecting 22.2% of the subjects with RA²⁴. A similar frequency has been observed in this population, as there were 19.6% subjects with Sjögren's syndrome secondary to other autoimmune diseases, before study criteria was applied (data not shown). But Sjögren's syndrome secondary to RA was observed in 8.9% of cases. It is possible that secondary Sjögren's syndrome would still develop in some of these subjects on later stages of the disease. Longitudinal studies are needed to investigate the early onset of secondary Sjögren's syndrome in the population of RA patients.

There were no differences in the median SFR of groups, when subjects using xerogenic medications were isolated from the analysis. It has been suggested that resting SFR may be more influenced from disease than the stimulated SFR^{9,25,26} and medication mainly affect the stimulated SFR²⁷. Data on Figure 2 suggest that xerogenic drugs have influenced both resting and stimulated SFR, although differences are not statistically significant for stimulated SFR.

Interestingly, the frequency of hyposalivation (defined by resting SFR) was higher in subjects with RA, than among controls, even when subjects using xerogenic drugs were eliminated from the analysis. There may be a variety of reasons for finding a higher number of subjects with hyposalivation but not finding a reduction in the median SFR of these subjects. The wide variation in the SFR and also the extremes and outlier cases may be one of the reasons. Other reasons for this finding need to be explored.

Xerostomia may be a symptom neglected from individuals and health care professionals²⁸. The complaint of dry mouth in RA subjects has varied from 21% to 41.3%, according to different studies^{6,11}, but was higher in the present study (66.7%)^{11,19}. Maybe, medications, neurologic conditions, alterations in sialochemistry or other unknown reason may be responsible for this symptom. Interestingly, xerostomia was very frequent (53.8%) even in the RA subjects not using xerogenic medication.

Reduced SFR is the most common cause of xerostomia¹⁹. In fact, RA subjects who presented xerostomia showed lower median SFR than those who did not have the symptom of dry mouth. This aspect should not be generalized for every individual, because some subjects who did not present xerostomia had low SFR and some others presenting xerostomia had normal SFR. This fact is in agreement with other authors⁸, and may be verified in the present study by observing extremes and outliers in Figure 1.

Salivary gland enlargement may be one of the signs of Sjögren's syndrome, but it may also be a sign of infection or other metabolic disease. The submandibular gland enlargement that was reported by of one RA subject might have probably represented an infection, as it resolved with antibiotics.

Clinical drainage of major salivary glands is a non-invasive easy and relatively quick procedure, which represents actual status of isolated glands. It does not expose patients to radiation, like the scintigraphy. In the studied population, more than 10% of RA subjects were lacking saliva drainage from at least one of the major salivary glands. Future studies need to explore the importance of the clinical saliva drainage from major glands for the disease staging and its correlation to Sjögren's syndrome.

Subjects with hyposalivation are usually instructed to avoid the use of some substances like tobacco, cannabis, alcohol and caffeine, as they might interfere in salivary function²⁹. In the studied population, the only difference in habits between the two groups was the consumption of coffee, but no differences were found in the SFR of subjects who did or not have the habit of consuming coffee (data not shown).

Gender variations of the SFR have been reported¹⁹, and it might have represented a flaw in this study, as there was a significant difference in gender between groups. Thus, we have evaluated the SFR of separate genders between groups and found no significant differences in SFR. This finding eliminates the problem of gender variation.

Future longitudinal studies should be developed, in order to determine if early detection of reduced SFR in RA subjects may predict secondary Sjögren's syndrome. Health care professionals should be able to diagnose and manage early salivary dysfunction appropriately.

Conclusion

In the studied population of rheumatoid arthritis individuals, the salivary flow rates of the subjects not using xerogenic medications were not different from the healthy controls. However, cases of hyposalivation and xerostomia were more frequent in the rheumatoid arthritis group. Xerogenic medications may be partially responsible for the reduction of salivary function, but other factors that lead to the decrease of salivary flow rates and the increase of xerostomia need to be further investigated, in populations with rheumatoid arthritis.

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