







Are salivary flow rates associated with histopathologic aspects in patients with rheumatoid arthritis?

Janaina Barbieri dos Santos HELMS^(a) 
Carlos Augusto BARBOSA^(a) 
Aline Corrêa ABRAHÃO^(a) 
Marcia Grillo CABRAL^(a) 
Blanca Elena Rios Gomes BICA^(b) 
Sandra Regina TORRES^(a) 

^(a)Universidade Federal do Rio de Janeiro – UFRJ, School of Dentistry, Department of Oral Pathology and Diagnosis, Rio de Janeiro, RJ, Brazil.

^(b)Universidade Federal do Rio de Janeiro – UFRJ, School of Medicine, Department of Internal Medicine, Rio de Janeiro, RJ, Brazil.

Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

Corresponding Author:

Sandra Regina Torres
E-mail: sandratorres@odonto.ufrj.br

<https://doi.org/10.1590/1807-3107bor-2022.vol36.0120>

Submitted: August 6, 2020
Accepted for publication: March 9, 2022
Last revision: June 2, 2022

Abstract: The aim of this retrospective cross-sectional study was to verify the association between salivary flow rates (SFR) and the histopathologic aspects of labial salivary glands (LSG) in patients with rheumatoid arthritis (RA). Patients presenting rheumatologic diseases referred for oral evaluation were included in the study if they had RA and had SFR measured and LSG biopsy performed. Patients were excluded if they had systemic conditions that affect SFR or if they were being treated for hyposalivation. Cases without enough material for histopathologic analysis were also excluded. Data were collected through questionnaires, oral examination, resting and stimulated SFR, and LSG biopsies. A histopathologic reevaluation was carried out in order to seek for additional histopathologic aspects. Fifty-one patients met the inclusion criteria. The mean age was 53.5 years (25–77), and 94.1% were women. The median resting and stimulated SFRs were 0.24 mL/min and 1.02 mL/min, respectively. The presence of lymphocytic focus and fibrosis were significantly associated with stimulated SFR, but not with resting SFR. The odds ratio of patients who had hyposalivation for presenting a positive lymphocytic focus was 7.33 (confidence interval CI: 1.53–35.23) by the stimulated technique, and 2.56 (CI: 0.57–11.40) in resting SFR. In the medical records, 14 (31.80%) patients had been diagnosed with secondary Sjögren’s syndrome. In conclusion, stimulated SFR represent a good screening test to predict lymphocytic focus in LSG in patients with RA, which represents the most specific test to diagnose Sjögren’s syndrome.

Keywords: Saliva; Salivary Glands; Biopsy; Arthritis; Rheumatology.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mainly affects synovial joints and is often accompanied by different extra-articular manifestations.¹ Oral complications of RA may include temporomandibular joint disorders, mucosal changes, hyposalivation, and xerostomia.²⁻⁵ Only few studies have verified the correlation between salivary flow rates (SFR) and the morphological aspects of the salivary glands in patients with RA.³⁻⁶

It has been suggested that resting SFR may be more influenced by disease than the stimulated SFR.⁷⁻⁹ Medications seem to affect mainly the



stimulated SFR.¹⁰ The SFR and the role of xerogenic drugs in salivary function has been studied in RA patients.¹¹ As a whole, hyposalivation and xerostomia have been more frequent in subjects with RA than in healthy controls. However, when a subset of RA subjects not using xerogenic medications was evaluated, there were no differences between the SFRs of RA subjects and controls. These results suggest that medication, not the disease itself, was the cause of reduced salivary function in the population of patients with RA. Thus, xerogenic medications may be partially responsible for the reduction of salivary function, but other factors that lead to the decrease of SFR and xerostomia need to be further investigated in populations with RA.¹¹

Approximately 20% of individuals with RA present secondary Sjögren's syndrome (sSS), with a significant decrease in SFR.^{2,11-14} Early diagnosis and appropriate monitoring of SS associated with RA are important to improve the quality of life of these patients.^{12,15} SS occurs as a primary form that is not associated with other diseases and as a secondary form that complicates other rheumatic conditions. The most common diseases associated with SS are RA and systemic lupus erythematosus. SS is most common in women in their 50s and 60s, but it can affect adolescents and young adults, as well as men.

Sjögren's syndrome affects almost 1% of the world population, and up to 22.2% of patients with autoimmune diseases, causing a significant decrease in SFR.^{11,16} The glandular features and management of primary SS and secondary SS are generally similar. The SFR alteration presented by patients with SS may be explained by an intense glandular inflammatory infiltration that leads to parenchymal degeneration.^{17,18} The diagnosis of SS is complex because of a wide variety of symptoms, which prompt patients to see several specialists, thus having their diagnosis postponed.^{13,19,20} According to the European League Against Rheumatism (EULAR), the diagnosis of SS is based on exams that evaluate lachrymal gland function, SFR, biopsy of labial salivary glands (LSG), and autoantibodies.²⁰⁻²² Among these exams, LSG biopsy is the most specific one.^{13,17,19,21-23}

A decrease in salivary function may be suspected by symptoms of xerostomia and presence of new dental caries, but physical and complementary exams are necessary to confirm the diagnosis. Sialography, ultrasonography, computed tomography, and magnetic resonance imaging of the salivary glands can detect changes in the structure of salivary glands.²⁴ The salivary gland function can only be assessed by "milking" the major salivary glands, or through sialometry, or scintigraphy.²¹ Decreased salivary function may be an early marker for other autoimmune conditions in rheumatologic patients, highlighting the predictive value of oral findings in sSS development.^{11,16}

The presence of lymphocytic infiltrate in LSG biopsy and reduced SFR play an important role in the diagnosis and management of sSS.²¹ Only few studies have verified the correlation between SFR and the morphological aspects of salivary glands.^{6,13} The histopathologic aspects of LSG have been better correlated to stimulated SFR than to unstimulated sialometry.⁶

In a previous study, we have evaluated the association of SFR with clinical data in RA patients.¹¹ Some of those patients were referred for LSG biopsy to investigate sSS. This study aims to evaluate the association between SFR and the histopathologic aspects of LSG in patients with RA. In addition, the importance of sialometry and LSG biopsy in the diagnosis of SS is also verified.

Methodology

This retrospective cross-sectional study was carried out in patients with RA previously subjected to SFR measurements and LSG biopsies. The collected data were stored in a database for later evaluation.

Patient population

Patients from the Rheumatology Clinic of the Hospital Universitário Clementino Fraga Filho (HUCFF), of the Universidade Federal do Rio de Janeiro (UFRJ), Brazil, were referred to the Stomatology Clinic at the School of Dentistry of the same university, between August 2003 and August 2005, for oral evaluation. At the time, the procedures and the

clinical significance of the study were explained to each individual, and all signed the consent form. The study followed the principles of the Declaration of Helsinki and was approved by the institutional ethics committee under protocol number 133-19, with a waiver of consent.

Participants were included in the study if they presented seropositive RA and underwent oral evaluation with sialometry and LSG biopsy performed at the Stomatology Clinic. Patients were excluded if they had systemic conditions that affect SFR; if they were being treated for hyposalivation; or if material was not sufficient for histopathologic analysis.^{11,25}

Data collection

Researchers had access to the database with the records of patients with rheumatologic diseases referred to the Stomatology Clinic for oral evaluation. Data were obtained through anamnesis, physical and complementary exams, and registered in the patient's protocol. Medical records were accessed for confirmation and retrieval of relevant study data at the HUCFF.

Resting and stimulated sialometry techniques were used for the collection of total saliva. Patients were instructed not to eat, drink, smoke, or sanitize their mouth for one hour prior to collection. For the resting technique, patients were instructed to expectorate saliva periodically into a disposable container for five minutes. The total saliva volume produced was divided by five (duration of collection) and the results were measured as milliliters of saliva per minute (mL/min). For the evaluation of stimulated salivary flow, the patient was instructed to chew flavorless gum for one minute, swallowing the saliva. After this initial period, the patient continued to chew the gum for five minutes and periodically expel all the saliva produced in a disposable container. Reduced SFRs (hyposalivation) were considered when resting SFR were equal to or less than 0.1 mL/min, or when the mechanically stimulated SFR was equal to or less than 0.7 mL/min.^{21,25}

Biopsy of the salivary gland

Rheumatoid arthritis patients were referred for LSG biopsy whenever they needed to be investigated

for sSS, not confirmed by other exams; or when no explanation could be found for the reduced SFR.

If patient's health status allowed a surgical procedure, biopsies were performed on the lower lip, given that accessory LSG are generally abundant and easily accessible in that region.²⁶ After local anesthesia, the anesthetic, an incision was made in the lower labial mucosa, extending to the muscle layer. Ideally, three to four minor salivary glands were surgically removed and placed in a container with 10% formaldehyde. The surgical wound was sutured with 4.0-gauge silk suture. The sutures were removed after one week.

Histopathologic aspects

The histopathologic slides and records were catalogued in the Oral Pathology Laboratory archives of the School of Dentistry/UFRJ. The histopathologic aspects were previously classified according to the Chisolm & Mason classification system of 1968.²⁷ This classification is based on the presence of lymphocytic foci per four square millimeters (focus/mm²) of salivary tissue, where 0 - absence of any lymphocyte; I - slight lymphocytic infiltrate; II - moderate lymphocytic infiltrate or less than one outbreak; III - one lymphocytic focus; and, IV- more than one lymphocytic focus. A lymphocytic focus was defined as a cluster of 50 or more lymphocytes and histiocytes was observed.

The slides were reevaluated according to the classification proposed by Daniels et al. in 2011, as suggested by the 2016 EULAR criteria.^{17,21,22,26} Under this classification, cases with at least one lymphocytic focus per four square millimeters (focus/mm²) of glandular tissue are suggestive of SS. Thus, these are the cases corresponding to Chisolm & Mason's score III or IV.²⁷ In addition to the inflammatory infiltrate, the slides were evaluated for the appropriate number of lobes; ; preservation of glandular acini; presence of periductal and perivascular inflammation; germinal centers; liposubstitution; fibrosis; or hyalinization of the LSG parenchyma.^{13,17,20,21,28,29}

Statistical analysis

Data were stored in a database of SPSS 10.0® (IBM, Chicago, USA) and were subjected to descriptive

analysis of frequencies and means. The chi-square and Mann-Whitney tests were used to verify the association between dichotomous and measurable variables, respectively. The SFRs were dichotomized into hyposalivation and moderate/normal SFR in order to establish the odds ratio (OR). The significance level was established at 0.05.

Table 1. Clinical characteristics of the 51 subjects with rheumatoid arthritis in the study.

Clinical characteristics	n = 51	%
Comorbidities		
Hypertension	10	19.6
Depression	7	13.7
Medications		
Corticosteroids	37	74.0
Immunomodulators	32	64.0
Non-steroidal anti-inflammatory drugs	18	36.0
Modulator of acid gastric secretion	13	26.0
Antihypertensive	9	18.0
Psychotropic	5	10.0
Analgesic	5	10.0
Antiplatelet aggregation drug	2	4.0
Antihistamine	2	4.0
Other immunosuppressant	1	2.0

Results

Two hundred and ten patients with immunomediated/collagen diseases were referred to the Stomatology Clinic for oral evaluation. Data from the 129 patients with RA were selected. Among these, 56 patients had been submitted to LSG biopsy. Five patients were excluded: three for presenting comorbidities that affect SFR (diabetes, hypothyroidism, or lipoproteinemia (n = 1 each), and two for insufficient material for histopathologic analysis (n = 2).

The clinical data of the 51 studied subjects with RA included in the study are summarized in Table 1. There were 48 (94.1%) females and 3 (5.9%) males. The median age was 53.5 years, with minimum of 25 years and maximum of 77 years.

The median resting and stimulated SFR were 0.24 mL/min (minimum 0 – maximum 0.84 mL/min) and 1.02 mL/min (minimum 0 – maximum 3.36 mL/min), respectively. Hyposalivation evaluated by resting sialometry was observed in 14 (27.5%) patients, and stimulated hyposalivation was observed in 15 (29.4%) patients. SFR variations according to the presence of lymphocytic foci in the histopathologic analysis are shown in Figure A and B. There were 9 (17.65%) patients with inflammatory foci in the histopathologic analysis.

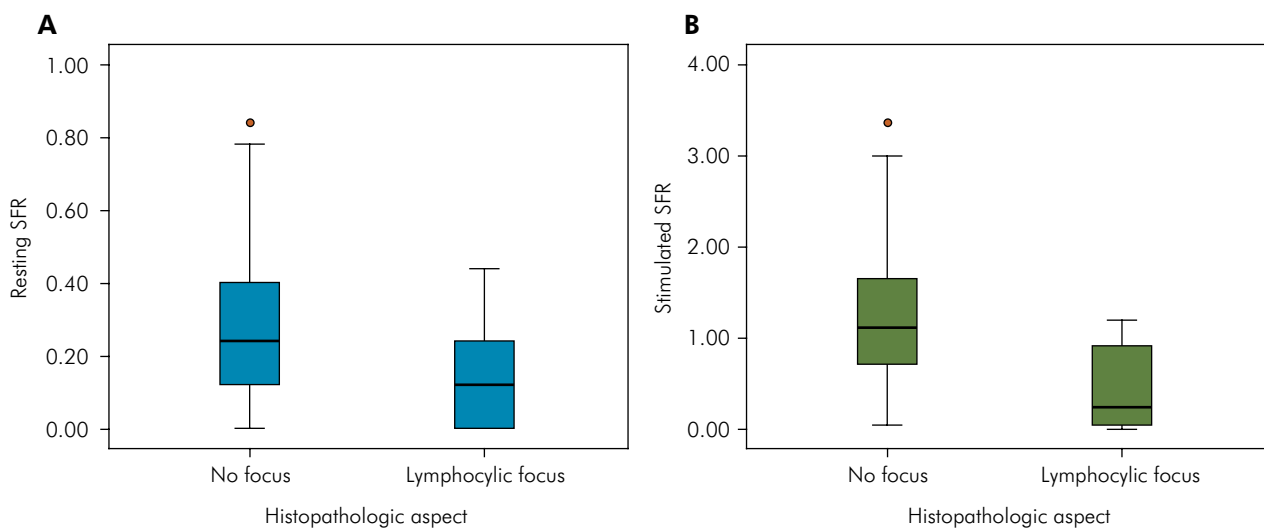


Figure. (A) Variation in resting salivary flow rates (RFR) (A) according to the presence of lymphocytic foci in histopathologic analysis; (B) Variation in stimulated salivary flow rates (SFR) (B), according to the presence of lymphocytic foci in histopathologic analysis.

Regarding other histopathologic aspects, preserved acini were observed in 84.37% of the patients; diffuse inflammation in 84.37%; periductal inflammation in 59.57%; perivascular inflammation in 37.50%; moderate liposubstitution in 37.50%; severe liposubstitution in 13.89%; fibrosis in 15.62%; and hyalinization in 3.12%. Table 2 shows the main histopathologic aspects of LSG according to SFRs. The presence of lymphocytic foci and fibrosis was significantly associated with stimulated SFR, but no statistically significant association was observed between these parameters and resting SFR.

In the studied RA population, the OR was 2.56 (confidence interval (CI): 0.57–11.40) for patients with hyposalivation indicated by the resting technique, showing positive lymphocytic foci. While the OR was 7.33 (CI:1.53–35.23) for patients with hyposalivation measured by stimulated SFR, showing lymphocytic foci in the LSG biopsy.

There were 24 (48.0%) patients on xerogenic drugs. There were no statistically significant differences between the SFRs (resting and stimulated) in the comparison of RA patients on xerogenic medication with those who did not use this medication.

After checking the medical records of 44 patients, the final diagnosis of secondary SS was applied to 14 (31.8%) patients. For technical reasons, the medical records of seven patients were not available at the time of the consultation.

Discussion

The goal of this study was to verify if SFR is associated with histopathologic LSG aspects in patients with RA. The presence of lymphocytic foci and fibrosis was significantly associated with reduced stimulated SFR. But no significant association was observed between these parameters and resting

Table 2. Salivary flow rates according to histopathologic aspects of minor salivary gland of the 51 subjects with rheumatoid arthritis in the study.

Histopathologic aspects	Resting SFR (mL/min)			Stimulated SFR (mL/min)		
	median	(min-max)	p-value	median	(min-max)	p-value
Periductal inflammation			1.560			0.660
Yes	0.16	(0-0.78)		0.76	(0.4-2.26)	
No	0.20	(0-0.56)		1.20	(0.24-3.36)	
Perivascular inflammation			0.128			0.344
Yes	0.13	(0-0.40)		0.74	(0.40-2.8)	
No	0.20	(0-0.78)		1.12	(0.12-3.36)	
Liposubstitution			0.341	0.72		0.282
Severe	0.20	(0.08-0.36)		0.72	(0.32-2.26)	
Light/moderate	0.26	(0.09-0.78)		1.16	(0.40-1.80)	
No	0.12	(0-0.56)		0.78	(0.04-3.36)	
Fibrosis			0.243			0.032
Yes	0.090	(0-0.40)		0.40	(0.06-1.08)	
No	0.20	(0-0.78)		1.12	(0.04-3.36)	
Hyalinization			0.778			0.278
Yes	0.25	-		2.0	-	
No	0.20	(0-0.78)		1.00	(0.4-3.36)	
Lymphocytic foci			0.202			0.032
Yes	0.12	(0 – 0.44)		0.24	(0 – 1.20)	
No	0.24	(0 – 0.84)		1.12	(0.06 – 0.36)	

SFR. The OR was also high for hyposalivation in the stimulated technique, showing lymphocytic foci. Therefore, stimulated SFR may be a helpful tool for screening RA patients who need to be investigated for secondary SS.

In healthy populations, the prevalence of hyposalivation ranges from 14.4% to 25.5%, and it has been reported that, hyposalivation may affect between 17.4% to 35.5% of individuals with RA, depending on the type of sialometry technique used.^{15,20,21,30} In the present study, resting sialometry showed hyposalivation in 27.5% of the patients, while the stimulated technique revealed hyposalivation in 29.4%.

Secondary SS is commonly related to other autoimmune diseases and should be investigated in individuals with RA.^{2,11-14,31} Secondary SS has been reported to affect 22.2% of patients with RA.¹⁶ Secondary SS was diagnosed in 31.8% of the patients in the present study, a rate that is higher than those reported in the literature. If all medical records were available, the results might have been different. This information shows the importance of sialometry and LSG biopsy in the diagnosis of secondary SS.

Other authors have also reported associations between stimulated SFR and fibrosis and the presence of inflammatory foci in patients with primary SS, reinforcing the hypothesis that the glandular involvement observed in RA patients may be associated with their systemic condition.⁶ It has been suggested that resting SFR may be an early marker for other autoimmune diseases, confirming the importance of oral alterations in predicting the development of sSS in this population.^{1,16}

Most of the studied population was composed of women (94.1%), with a median age of 53.5 years. Likewise, RA and SS have been described as autoimmune diseases, which preferably affect women between the fourth and sixth decades of life, despite records for all age groups.³² The present study is in agreement with these findings, as 64.6% of the patients with RA were women aged 40 to 60 years, and 31.3% of them were clinically diagnosed with sSS (data not shown). Otherwise, when female RA patients with sSS were evaluated, 62.5% were aged 40 to 60 years (data not shown). This is in accordance

with the epidemiological data on the disease and with the study carried out in Brazil in 2012, in which 87.8 of the participants were women and 20.5% met the sSS criteria.¹⁴

Medication use has been associated with lower SFR,¹⁰ leading to the assumption that the reduction of SFR in patients with RA can be a consequence of the great amount of medications used by these patients. Nevertheless, the influence of xerogenic medications on the SFR of these patients has been rarely studied.¹¹ In the present study, there were no statistically significant differences between the SFR (resting and stimulated) in the comparison of RA patients on xerogenic medication with those who did not use such medication. This suggests that, in the studied group, salivary involvement should be associated with glandular parenchymal conditions.

Factors such as comorbidities, medications, and menopause may reduce SFR. In the present study, most of the patients were women, and the patients with other diseases that could affect SFR were excluded. Moreover, our findings did not show an association between hyposalivation and xerogenic drug intake. However, almost one third of the studied population presented hyposalivation. The explanation for salivary gland involvement may be the lymphocytic infiltrate, which leads to cell-mediated destruction of glandular elements; secretion of inflammatory cytokines; production of autoantibodies and their interference with muscarinic receptors; and secretion of metalloproteinases.³³⁻³⁵

The retrospective design of this study has some limitations. Some histopathologic and medical records data were missing. These factors may have affected the validation of the association between hyposalivation and some of the reported histopathologic features. The assessment of risk factors and outcomes by a prospective cohort study would likely make the results more accurate.

This study is important because it makes dentists and rheumatologists aware that SFR measurements help identify early signs and even disease activity and progression in RA patients. The scientific community should encourage studies on the role of sialometry, a quick, inexpensive and painless test, as an ancillary

tool for the diagnosis of secondary SS in RA-positive patients and for the prognosis of RA as well. Future prospective studies need to evaluate SFR over time in RA patients to verify the impact of the early diagnosis of hyposalivation on oral conditions in this population, and whether salivary flow can improve with systemic treatment.

Conclusions

The present study reinforces the importance of salivary flow assessment and salivary gland biopsy in patients with rheumatoid arthritis. Results have shown

that investigation of the salivary function represents a good screening test to predict lymphocytic foci in salivary gland histology, thus contributing to the diagnosis of Sjögren's syndrome.

Acknowledgments

We would like to thank the following colleagues for their participation in data collection during the study period: Thais Zamprogno, Tais Munhoz, Estevão Ribeiro Milanos, Fabiana da Cunha Corrêa, Renata Mendes de Sousa, Elaine Lima Amorim, Marcelle Teixeira Paulo, Silviane Franco Ruela, Fabiana da Cunha Corrêa, and Lidiane Teodoro.

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