Effect of Xerostomia on the Functional Capacity of Subjects with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the intensity of xerostomia and hyposalivation in subjects with rheumatoid arthritis (RA) as well as the effects of these conditions on functional incapacity and disease activity.
Methods. The study sample comprised 236 individuals of both sexes who had RA. All the individuals were submitted to clinical evaluation and unstimulated sialometry. Functional capacity was determined by using the Health Assessment Questionnaire (HAQ), xerostomia was assessed using the Xerostomia Inventory, and disease activity was evaluated with the 28-joint Disease Activity Score (DAS28). The effect of Sjögren syndrome (SS) was analyzed, and the sample was divided into 2 groups: RA (191 subjects) and RA/SS (45 subjects).
Results. The Xerostomia Inventory showed positive and significant correlation with fatigue ($r = 0.243$; $p < 0.0001$), number of painful joints ($r = 0.218$; $p = 0.001$), HAQ ($r = 0.279$; $p < 0.0001$), and DAS28 ($r = 0.156$; $p < 0.0001$). On regression analysis, both xerostomia (OR 3.89, 95% CI 1.84-8.23, $p < 0.001$) and DAS28 (for severe disease activity: OR 13.26, 95% CI 3.15-55.79, $p < 0.001$) showed influence on functional incapacity. Forty-five individuals (19.1%) presented with secondary SS, and having this diagnosis was not associated with disease activity or functional capacity.
Conclusion. Xerostomia demonstrated an adverse effect on quality of life of subjects with RA, being associated with a reduction in functional capacity. In this clinical setting, xerostomia can be monitored as a marker of worse clinical evolution. (First Release September 1 2016; J Rheumatol 2016;43:1795–1800; doi:10.3899/jrheum.151211)

Key Indexing Terms:
XEROSTOMIA
SJÖGREN SYNDROME
RHEUMATOID ARTHRITIS
FUNCTIONAL CAPACITY

Xerostomia is defined as a subjective complaint of dry mouth usually associated with qualitatively or quantitatively changed saliva production. In addition to the dry mouth, xerostomic subjects frequently mention symptoms such as burning mouth; increasing thirst; losing taste sensation; difficulty swallowing, chewing, and speaking; mouth-breathing; tooth sensitivity; gastroesophageal reflux; and poorly fitting removable dentures[1,2,3]. The prevalence of xerostomia may vary widely, ranging from 4% to 29% in the general population, and is more commonly observed in women and older individuals[4].

Although the reduced salivary flow rates are an important aspect of xerostomia, some subjects complain of dry mouth in spite of having normal salivary flow[5]; therefore we need to evaluate adequately both subjective and objective questions in this group. An instrument called the Xerostomia Inventory has been introduced to determine the effect of xerostomia on day-to-day activities. To our knowledge, it is the first scientifically validated instrument for investigating the prevalence of xerostomia[6]. On the other hand, the analysis of hyposalivation is based on the objective assessment of the salivary flow rate through sialometry, commonly accepted as a simple and reproducible diagnostic method[7].

Rheumatoid arthritis (RA) is a multisystemic, progressive, chronic inflammatory disease, associated with a series of extraarticular manifestations. Xerostomia and hyposalivation are more prevalent in individuals with rheumatic diseases, and may significantly limit the patient's quality of life[8,9,10]. Particularly in RA, studies have considered xerostomia and hyposalivation extraarticular manifestations of the disease, although studies have demonstrated that these conditions

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Funded by Pernambuco State Research Foundation (FACEPE – APQ 1978–4.02/12) and the Brazil National Council for Scientific and Technological Development/CNPq (481469/2012-5).

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Accepted for publication June 30, 2016.

usually point toward the diagnosis of secondary SS (sSS)[3,11,12,13,14].

In addition to oral symptoms, subjects with RA experience high levels of pain, functional incapacity, reduced capacity for work, and premature death[15]. They develop more constant and higher levels of fatigue in comparison with the population in general[16]. Even in its initial stage, RA and its extraarticular manifestations have a considerable effect on health-related quality of life, promoting a broad spectrum of functional limitations that may alter daily life activities. Different indicators describe functional capacity of subjects with RA; among them, the Health Assessment Questionnaire (HAQ) has been widely used and scientifically approved[17,18]. It can provide support for planning alternative strategies for treatment of the disease, thus making it possible to improve quality of life and well-being.

The aim of our study was to evaluate the effect of xerostomia, hyposalivation, and SS diagnosis in subjects with RA and the association of these conditions with functional incapacity and disease activity.

MATERIALS AND METHODS

Sample characterization. An observational epidemiologic study was conducted from March to September 2014, with 236 individuals of both sexes, over the age of 18 years, and with a diagnosis of RA. The sample size was estimated based on the prevalence of xerostomia in subjects with RA, defined as 18.6% in a study conducted by Haga, *et al*[19]. The set CI was 95%, with a sampling error of 5%, and an estimated prevalence of 18.6%, resulting in a sample of at least 233 subjects. All the subjects came from the Rheumatology Unit of Hospital das Clínicas — Universidade Federal de Pernambuco (HC-UFPE). Those involved in the research previously consented to their inclusion in the study by signing the Term of Free and Informed Consent, after the study was approved by the Research Ethics Committee of UFPE, protocol No. CCAE 10221112.3.0000.5208.

The diagnosis of RA was based on the criteria determined by the American College of Rheumatology[20], and the diagnosis of sSS was established by the criteria of the American-European Consensus Group[21]. Subjects excluded from the study were those with a history of radiotherapy in the head and neck region, human immunodeficiency virus infection, sarcoidosis, amyloidosis, graft-versus-host disease, hepatitis C virus infection, and use of anticholinergic drugs. All the subjects in the sample were initially evaluated, without separating the subjects with RA only from those with RA/SS.

Functional capacity evaluation. Functional capacity was determined using the HAQ. The instrument developed by Fries, *et al*[17], and translated and validated for Portuguese by Ferraz, *et al*[22] evaluates the functional status of subjects with RA by detecting the level of difficulty the subjects experience when performing day-to-day activities, and their need for assistance to perform them. For each of the 8 categories, the subject indicated the degree of difficulty using 4 possible responses ranging from "no difficulty = 0" to "incapable of doing it = 3". The score for each category was the highest result of any of its items. The final HAQ score was determined by the mean score of the 8 categories.

Visual analog scales (VAS) were also used, ranging from 0 to 100 mm to evaluate the self-perception of general status (VAS of a general state of disease) and fatigue in the previous week, informed by the subject[23].

Xerostomia evaluation. Xerostomia was evaluated by using the Xerostomia Inventory proposed by Thomson, *et al*[5], and validated in Portuguese[24]. The inventory is composed of 11 items evaluated through a Likert scale ranging from 1 to 5. The sum of the subject's responses could range from 11 to 55, and higher values corresponded to a more pronounced perception of xerostomia.

Salivary flow rate evaluation. Saliva to evaluate resting salivary flow (RSF) was collected by obtaining whole nonstimulated saliva. Collection occurred according to the previously developed method[25]. The examination was performed in the afternoon, between 2 PM and 5 PM, and the subjects were instructed not to eat, drink, or smoke for a minimum period of 90 min before saliva collection. After being comfortably seated, the subjects were directed to move the head slightly forward, swallow, and then allow saliva to run from the mouth into a plastic receptacle marked in millimeters, for 15 min. The RSF rate was determined by the total value, divided by 15, and was expressed in milliliters per minute. Values below 1.5 ml (or 0.1 ml/min) were considered positive.

Disease activity evaluation. Disease activity was evaluated using the Disease Activity Score 28 (DAS28). DAS28 uses 28 articulations to count the number of painful and edematous joints, with the erythrocyte sedimentation rate or C-reactive protein as an inflammatory marker, in addition to the overall patient-performed evaluation of health or disease activity, on a scale from 0 to 100[26].

According to the result obtained, the subject was considered in remission (< 2.6), low activity (≥ 2.6 to ≤ 3.2), moderate activity (> 3.2 to ≤ 5.1), or intense RA activity (> 5.1).

Statistical analyses. For data analysis, the absolute distributions, percentages, and statistical measures were obtained from the following: mean ± SD and median (descriptive statistics techniques). The Mann-Whitney U test was used for independent samples and the Pearson correlation coefficient for measurement of the linear relationship between the continuous variables.

Regression analysis included all subjects and was performed to evaluate the variables associated with functional incapacity. Functional capacity (HAQ) was introduced as a dependent variable. These were introduced as independent variables: age, duration of disease, VAS of the general state of disease, VAS of fatigue, painful articulations, edematous articulations, disease activity (DAS28), SS diagnosis, xerostomia, Xerostomia Inventory, and salivary flow. Logistic regression was performed by backward LR method. Composing the model involved the variables that had significance ≤ 0.20 in the bivariate analysis, and all tests were applied with 95% CI.

The data obtained for each variable evaluated were recorded, tabulated, and analyzed in a spreadsheet in the SPSS (Statistical Package for the Social Sciences) Software program, version 20.0 for Windows. The level of significance used in the decision of statistical tests was 5.0%.

RESULTS

Clinical characteristics. Two hundred thirty-six subjects were included in the study, of whom the majority were women (94.6%). The median age was 53.32 years (SD 11.93), with a minimum age of 22 years and a maximum of 80 years. The mean disease duration up to the time of interview was 9.47 years (SD 7.98), and a large portion of subjects (38.1%) presented with moderate disease activity. The mean RSF was 0.36 ml/min (SD 0.3 ml/min), ranging from 0.0 to 1.60 ml/min. A mean HAQ value of 1.25 (SD 0.83) was measured, ranging from 0 to 3.0. The mean xerostomia score was 23.62 (SD 10.57), ranging from 11.0 to 53.0. Forty-five individuals (19.1%) presented with the diagnosis of sSS. Table 1 shows the clinical data of the participants in our study. Table 2 describes the drug consumption according to the diagnosis of SS. Antihypertensives and antidepressants were more commonly reported among RA/SS individuals (p = 0.001 and p = 0.033, respectively).

Effect of salivary flow and xerostomia. Salivary flow dimin-

Table 1. Clinical characteristics of sample of 236 patients with rheumatoid arthritis. Results are mean (± SD) unless otherwise indicated.

Clinical Characteristics	Results
Age, yrs	53.32 (11.93)
Duration of disease, yrs	9.47 (7.98)
Xerostomia inventory	23.62 (10.57)
Salivary flow, ml/min	0.36 (0.29)
VAS of general state of disease	52.13 (31.88)
VAS of fatigue	48.74 (33.76)
No. painful joints	6.38 (8.07)
No. edematous/swollen joints	2.07 (3.90)
HAQ	1.25 (0.83)
DAS28	4.34 (1.60)
Remission (< 2.6)	15.7%, n = 37
Light activity (≥ 2.6 to ≤ 3.2)	10.6%, n = 25
Moderate activity (> 3.2 to ≤ 5.1)	38.1%, n = 90
Intense activity (> 5.1)	35.6%, n = 84

VAS: visual analog scale; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score.

Table 2. List of reported drugs according to the diagnosis of Sjögren syndrome. Patients with inadequate information regarding medication intake were not included.

Drug Class	RA/SS		RA		p
	n	%	n	%	
Disease-modifying drugs					
Yes	36	92.3	146	90.12	0.676
No	3	7.7	16	9.88	
Steroidal antiinflammatories					
Yes	26	66.7	103	63.6	0.718
No	13	33.3	59	36.4	
Antihypertensives					
Yes	15	38.5	24	14.8	0.001
No	24	61.5	138	85.2	
Antidepressants					
Yes	6	15.4	8	4.9	0.033
No	33	84.6	154	95.1	
Antidiabetics					
Yes	5	12.8	10	6.2	0.725
No	34	87.2	152	93.8	
Total	39	100.0	162	100.0	

RA: rheumatoid arthritis; SS: Sjögren syndrome.

Table 3. Correlation between variables of rheumatoid arthritis and xerostomia.

Variables	Coefficient of Correlation**	p
Xerostomia Inventory (XI) × age	0.522	0.42
XI × duration of disease, yrs	–0.35	0.609
XI × salivary flow	–0.234	< 0.0001*
XI × VAS of general state of disease	0.124	0.061
XI × VAS of fatigue	0.243	< 0.0001*
XI × no. painful joints	0.218	0.001*
XI × no. edematous joints	0.060	0.362
XI × HAQ	0.279	< 0.0001*
XI × DAS28	0.156	< 0.0001*
Salivary flow × age	–0.160	0.014*
Salivary flow × duration of disease, yrs	0.005	0.940
Salivary flow × VAS of general state of disease	–0.033	0.681
Salivary flow × VAS of fatigue	–0.006	0.929
Salivary flow × no. painful joints	–0.051	0.522
Salivary flow × no. edematous joints	–0.022	0.734
Salivary flow × HAQ	–0.062	0.348
Salivary flow × DAS28	–0.020	0.762
HAQ × age	0.113	0.085
HAQ × duration of disease, yrs	0.91	0.186
HAQ × VAS of general state of disease	0.401	< 0.0001*
HAQ × VAS of fatigue	0.347	< 0.0001*
HAQ × no. painful joints	0.492	< 0.0001*
HAQ × no. edematous joints	0.334	< 0.0001*
HAQ × DAS28	0.595	< 0.0001*
DAS28 × age	0.113	0.086
DAS28 × duration of disease, yrs	–0.049	0.482
DAS28 × VAS of general state of disease	0.633	< 0.0001*
DAS28 × VAS of fatigue	0.427	< 0.0001*
DAS28 × no. painful joints	0.711	< 0.0001*
DAS28 × no. edematous joints	0.578	< 0.0001*

* Statistically significant. ** Pearson correlation coefficient. VAS: visual analog scale; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score.

ished with increase in age (r = –0.160; p = 0.014), and with an increase in the Xerostomia Inventory scores (r = –0.234; p < 0.0001). The Xerostomia Inventory showed positive and significant correlation with the variables: fatigue (r = 0.243; p < 0.0001), number of painful joints (r = 0.218; p = 0.001), HAQ (r = 0.279; p < 0.0001), and DAS28 (r = 0.156; p < 0.0001; Table 3). In addition, 70 individuals (29.7%) complained of xerostomia despite of presenting a normal salivary flow rate (p < 0.0001).

Effect of sSS diagnosis. Age was not shown to differ between the groups evaluated (RA 52.7 yrs, SD 12.3; RA/SS 56.0 yrs, SD 10.8; p = 0.111). Similarly, the time of RA diagnosis did not vary between the groups (RA 9.3 yrs, SD 7.9; RA/SS 10.6 yrs, SD 7.9; p = 0.217).

Subject resting salivary flow was shown to be significantly reduced in Group RA/SS (RA/SS 0.1 ± 0.1 ml/min × RA 0.4 ± 0.3 ml/min, p < 0.0001), as shown in Table 4. Subjects with RA/SS presented higher Xerostomia Inventory scores (RA 21.7 ± 9.5; RA/SS 31.6 ± 11.2; p < 0.0001).

Functional capacity evaluation. The regression model was capable of demonstrating the risk of developing moderate to severe functional incapacity, represented by HAQ > 1. Xerostomia, the number of painful joints, and disease activity (DAS28) remained in the model and were related to HAQ (Table 5). Patients with xerostomia presented an OR 3.89 of developing a moderate to grave functional incapacity (p < 0.001). In addition, the risk of developing HAQ > 1 was increased according to the rise of disease activity, so that patients with elevated RA activity had an OR of developing moderate to severe functional incapacity of 13.26 (p < 0.001).

Table 4. Effect of Sjögren syndrome (SS) diagnosis on clinical presentation of rheumatoid arthritis (RA).

Variable	Diagnosis	N	Mean ± SD	p**
Age, yrs	RA	191	52.7 ± 12.3	0.111
	RA/SS	45	56.0 ± 10.8	
Duration of disease, yrs	RA	183	9.3 ± 7.9	0.217
	RA/SS	32	10.6 ± 7.9	
Xerostomia Inventory	RA	191	21.7 ± 9.5	< 0.0001*
	RA/SS	45	31.6 ± 11.2	
Salivary flow, ml/min	RA	191	0.4 ± 0.3	< 0.0001*
	RA/SS	45	0.1 ± 0.1	
VAS of general state of disease	RA	191	53.2 ± 31.7	0.232
	RA/SS	39	46.7 ± 32.9	
VAS of fatigue	RA	191	49.3 ± 33.5	0.532
	RA/SS	37	45.7 ± 35.5	
No. painful joints	RA	191	6.2 ± 7.9	0.559
	RA/SS	45	7.1 ± 8.8	
No. edematous/swollen joints	RA	191	1.9 ± 3.9	0.179
	RA/SS	45	2.6 ± 3.7	
HAQ	RA	188	1.2 ± 0.8	0.104
	RA/SS	45	1.4 ± 0.9	
DAS28	RA	190	4.3 ± 1.6	0.441
	RA/SS	42	4.5 ± 1.7	

* Statistically significant. ** p value of Mann-Whitney Independence Test. VAS: visual analog scale; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score.

Table 5. Final regression analysis model highlighting the association between HAQ and RA clinical markers.

Variable	OR	95% CI	p
DAS28			0.002
Remission	1.00	—	
Mild activity	3.02	0.71–12.75	0.133
Moderate activity	4.94	1.27–19.14	0.021
Severe activity	13.26	3.15–55.79	< 0.001
Xerostomia			
Negative	1.00	—	< 0.001
Positive	3.89	1.84–8.23	
Painful joints			
Negative	1.00	—	0.070
Positive	2.49	0.93–6.69	

Logistic regression by backward LR method. Initial variables: age, duration of disease, VAS of general state of disease, VAS of fatigue, painful articulations, edematous articulations, disease activity (DAS28); SS diagnosis, xerostomia, xerostomia inventory and salivary flow. VAS: visual analog scale; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; RA: rheumatoid arthritis; SS: Sjögren syndrome.

DISCUSSION

Undeniably, studies about the diagnostic and prognostic indicators of RA have progressed considerably in the last few years. In spite of this, few studies have related the functional incapacity present in RA to oral symptoms. Our study evaluated the clinical significance of assessing the intensity of xerostomia and resting salivary flow and their effect on the functional capacity of subjects with RA, as well as the correlation between these indicators and the diagnosis of SS. We verified that functional incapacity in the subjects with RA was related to their perception of dry mouth.

RA, because of its chronic inflammatory nature, is a disease that can cause significant morbidity and mortality associated with joint damage, in addition to extraarticular manifestations[27]. Its symptoms mainly manifest in individuals from 30 to 40 years, although individuals of any age may be affected, including children. The disease may be incapacitating and painful, and may substantially affect mobility as a result of edema, pain, and articular destruction if not treated adequately[28]. The chief extraarticular manifestations include vasculitis, neuropathy, pericarditis, keratoconjunctivitis sicca, scleritis, episcleritis, peripheral ulcerative keratitis, nephritis, rheumatoid lung disease, amyloidosis, and rheumatoid nodules[29]. These manifestations appear to represent an indicator of damage or a marker of disease activity, in addition to worse prognosis, greater functional incapacity, and increased mortality[30,31]. Among the extraarticular manifestations, the symptoms of dry mouth are related to disease activity and subject health status[27].

Xerostomia is defined as a subjective perception of dry mouth frequently associated with an accentuated reduction in salivary flow[32,33]. In this context, resting salivary flow varies according to the presence of xerostomia, so that the Xerostomia Inventory score increased with the reduction in flow[24], as we observed. However, many subjects with RA complain of xerostomia in spite of presenting a normal salivary flow rate[27,34,35], similar to our findings.

In spite of being considered an extraglandular manifestation of RA, xerostomia may occur owing to additional

causes such as sSS[32,36,37]. SS is a chronic systemic inflammatory disorder that mainly affects the endocrine glands, leading to xerostomia and xerophthalmia. It is characterized by the infiltration of mononuclear cells into the exocrine glands and acinar and ductal destruction, with consequent glandular hypofunction[38]. The prevalence of SS in subjects with RA has varied from 4% to 40%[19,39,40], with this variation possibly being related to the diagnostic criteria, the nationality of the subjects, and tests used. In any event, SS has been associated with a more severe presentation and worse prognosis of RA[41,42].

In addition to the symptoms of dryness, studies have shown evidence that the presence of SS demonstrated a possible increased risk of non-Hodgkin lymphoma[43], and increased mortality in subjects with RA[42,44]. Studies have also suggested that the symptoms of dryness are associated with high activity of RA[41], and have demonstrated a correlation between hyposalivation and increase in RA activity[27]. Our present study found an association between RA activity, xerostomia, and the diagnosis of sSS, so that subjects with RA/SS showed a higher number of painful and edematous joints and higher HAQ scores. These findings reinforce the need for diagnosis of SS, to characterize a more aggressive phenotype of RA.

However, few studies have evaluated the risk factors associated with the development of dry mouth and dry eyes in subjects with RA. Wolfe and Michaud reviewed a population of 9921 subjects with RA and observed that the disease activity and treatment contributed to the establishment of oral and ocular symptoms, and that these were related to an increase in HAQ, the number of painful articulations, and fatigue[45]. The present study observed a correlation between HAQ and the general state, fatigue, number of painful and edematous joints, DAS28, and the Xerostomia Inventory, but only the latter variables accounted for about 40% of the variation in HAQ. Nevertheless, the intensity of xerostomia has a limited influence on this process, as opposed to the greater influence exerted by disease activity as measured through DAS28. Correlation of the HAQ values with improvement in various physical variables in RA allows us to determine the concept of minimally clinical important difference. In our study, we observed that the change of 1 point in DAS28 is capable of promoting a clinically significant change of 0.26 points in HAQ, because the reduction of 0.22 points is indicative of an improvement in the functional status[46,47].

Extraarticular manifestations demonstrated an adverse effect on quality of life and prognosis of subjects with RA, with a more steady evolution of the disease, intensification of disease activity, and reduction in functional capacity. Therefore, when implementing actions with the aim of improving the quality of life of these subjects, not only functional capacity but also the intensity of xerostomia and hyposalivation, as well as early diagnosis of SS, should be considered. Also, we emphasize the importance of using self-reported questionnaires, such as the Xerostomia Inventory and HAQ, to guide clinical management, document changes in the subject's health status, and evaluate the results of treatments.

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