ORAL MEDICINE

Rheumatoid arthritis patients with xerostomia have reduced production of key salivary constituents

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Objective. The aim of this study was to assess the relationship between complaints of xerostomia in patients with rheumatoid arthritis (RA) with the total output of the salivary proteins of innate and adaptive immunity.
Study Design. The salivary output and specific activity of peroxidase and specific contents of lysozyme, lactoferrin, and secretory immunoglobulin A (sIgA) were determined in xerostomic RA patients, nonxerostomic RA patients, and healthy control subjects.
Results. Compared with nonxerostomic RA and healthy control groups, xerostomic RA patients had significantly decreased output of saliva and protein, decreased peroxidase activity, and a significantly lower specific content of peroxidase and sIgA. Compared with the RA control group, xerostomic RA patients had significantly lower specific content of all salivary proteins examined.
Conclusions. The results indicate that xerostomia in patients with RA may be a harbinger of diminished saliva production regarding quantity and quality, and may be indicative of impairment of the salivary immune system of the oral cavity in xerostomic RA patients. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:483-490)

Rheumatoid arthritis (RA) is a systemic disease of connective tissue affecting ~1% of the world population, with an incidence that occurs 3 times higher in women than in men.[1] RA frequently presents with extra-articular symptoms—hematologic, neurologic, cardiovascular—as well as impairment of the lacrimal and salivary glands.[2,3] Salivary gland hypofunction is a condition in which salivary flow is significantly reduced (unstimulated <0.1-0.2 mL/min, stimulated <0.7 mL/min) and can result in alterations of the chemical composition of saliva.[4]

Xerostomia is defined as the subjective perception of dry mouth[4] and can be the outcome of a marked decrease in the salivary flow.[4,5] However, many RA patients with xerostomia have a normal salivary flow rate.[3,6-9] Xerostomia in RA patients may be due to other additional causes, such as secondary Sjögren syndrome (sSS) and/or the use of xerogenic drugs by patients.[4,10,11] sSS is an autoimmune disease characterized by inflammation of the exocrine glands, resulting in sicca symptoms and objective findings in the eyes and/or mouth in addition to the underlying disease.[12] In the initial phase of sSS, unstimulated salivary flow might not show any significant changes (>1.5 mL/15 min), whereas the saliva composition may be significantly altered.[10] Recently, it was shown that the sensation of oral dryness does not depend on the amount of water or quantity of saliva, but on the quality of saliva and presence of specific components (e.g., low sulfation of mucins, which causes low water retention).[13] It is likely that xerostomia may be the early sign of the salivary gland involvement in RA when the disease is incipient.

Given the immunologic nature of RA,[2] it may be useful to evaluate the salivary output and composition, especially the immunoregulatory components, of the saliva in RA patients with xerostomia and RA patients without this symptom.

Salivary peroxidase is one of the main salivary antioxidative enzymes. The products of peroxidase activity (hypochloride, hypobromide, hypoiodide, and hypothiocyanite) reveal strong antibacterial actions.[14-16] The antimicrobial activity of lysozyme is linked with its

Statement of Clinical Relevance

Xerostomia is not only the subjective symptom of oral dryness, but also an indicator of the profound salivary gland dysfunction. Our results indicate destruction of the salivary immunity system of the oral cavity in xerostomic rheumatoid arthritis patients.

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Table I. Age and stomatologic findings in the xerostomic RA, nonxerostomic RA, and healthy control groups (mean ± SD)

	C (n = 16)	*RA (n = 16)*	*RAX (n = 16)*	*P value, RA/C*	*P value, RAX/C*	*P value, RAX/RA*
Age (y)	53.5 ± 9.3	49.5 ± 13.43	53.22 ± 10.9	.78	.98	.76
OHI-S	0.47 ± 0.53	0.28 ± 0.44	0.35 ± 0.4	.53	.65	.56
GI	0.66 ± 0.66	0.56 ± 0.69	0.64 ± 0.65	.78	.89	.67
DMFT	16.83 ± 5.0	20.75 ± 3.9	23.28 ± 4.1	.004	.001	.09
D	2.58 ± 3.05	3.12 ± 2.65	2.22 ± 2.666	.7	.87	.64
M	3.93 ± 4.18	10.5 ± 6.0	15.22 ± 6.74	.01	.001	.001
F	10.34 ± 5.72	7.12 ± 4.41	15.22 ± 6.74	.76	.34	.23

C, Healthy control subjects; *RA*, nonxerostomic rheumatoid arthritis patients; *RAX*, xerostomic rheumatoid arthritis patients; *OHI-S*, oral hygiene index—simplified; *GI*, gingival index; *DMFT*, decayed, missing, and filled teeth.

lytic action on bacteria by facilitating the hydrolysis of the cell wall polysaccharides.[17-19] Lactoferrin is an iron-binding protein with certain similarities to transferrin. In an iron-dependent way, lactoferrin binds 2 iron atoms per molecule, and thus inhibits bacterial metabolism.[20] In an iron-independent way, lactoferrin damages the outer membranes of salivary bacteria and generates nitric oxide in macrophages, which kill the microorganisms.[21] Secretory immunoglobulin A (sIgA), the most important immunoglobulin in saliva, promotes bacterial aggregation, inhibits bacterial adherence, and thus blocks bacterial colonization of oral tissues.[22]

The aim of the present study was to assess changes in the synthesis/secretion and output of the particular proteins of innate and adaptive immunity in the saliva of xerostomic RA patients with normal unstimulated saliva production (>1.5 mL/15 min) compared with nonxerostomic RA patients and a healthy control group.

MATERIALS AND METHODS

RA patients were selected for this study from the Department of Rheumatology and Internal Diseases, Medical University Hospital, Białystok, Poland, if they fulfilled the American College of Rheumatology revised criteria for RA,[23] were aged 36-64 years, did not have complete dentures in either jaw, did not use medication that could cause oral dryness, did not smoke cigarettes, and did not have diabetes mellitus, hypertension, or hepatitis C virus or human immunodeficiency virus infection. The number of patients meeting the inclusion criteria was 90. All patients consented to participate in the study. They received a questionnaire with 6 questions on subjective symptoms of oral and eye dryness listed in the American-European classification criteria for Sjögren syndrome.[24] Inclusion criteria were no positive response to any one question associated with eye dryness. The number of patients meeting this condition was 70. The next stage of the patients selection was the performance of Schirmer-I test and unstimulated salivary flow measurement; 36 patients with a negative result of Schirmer-I test in both eyes (>5 mm/5 min) and unstimulated saliva secretion >1.5 mL/15 min were included. Patients were divided into 2 groups: experiencing dry mouth: xerostomic RA patients (RAX) (16 women); and not experiencing dry mouth: nonxerostomic RA (16 women, 4 men). Owing to the fact that xerostomic RA patients were only women and nonxerostomic RA patients were 16 women and 4 men, for further study only 16 women were included and men were excluded to avoid of the heterogeneity compared groups.

Sixteen age-matched healthy control women (C) without symptoms of oral and eye dryness, an unstimulated salivary flow >1.5 mL/15 min, and negative Schirmer-I test were selected from the Department of Conservative Dentistry Medical University, Białystok, Poland.

Clinical examinations were performed by the same experienced dentist (A.Z.) under standardized conditions in the Pedodontics Department at the Medical University in Białystok, in a dental chair with the use of portable equipment with fiber-optic light, suction device, and compressed air. All examinations were done by using diagnostic dental tools (dental mirror, probe, and periodontal probe).

Following the World Health Organization criteria,[25] the dental status of each patient was determined with the use of the decayed, missing, and filled teeth (DMFT) index. The gingival status was determined with the use of the gingival index (GI), and oral hygiene was determined with the use of oral hygiene index—simplified (OHI-S) (Table I). In 20 patients, the interrater agreements between the examiner (A.Z.) and another experienced dentist (D.W.) were assessed. The reliability was: DMFT: $r = 0.99$; GI: $r = 0.96$; OHI-S: $r = 0.94$.

Each RA patient participating in the study underwent blood tests, including laboratory markers of inflammation: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Waaler-Rose (WR) test for rheumatoid factor (RF; Table II).