Risk factors for caries development in primary Sjogren syndrome

Nicola Berman, MD,[a] Frederick Vivino, MD, MS,[a,b] Joshua Baker, MD, MSCE,[a,c] Jonathan Dunham, MD,[d] and Andres Pinto, DMD, MPH, MSCE, MBA[e]

Objectives. The aim of this study was to compare the risk factors for caries between patients with primary Sjogren syndrome (SS) and those with non-Sjogren syndrome (NSS) salivary hypofunction and to identify the prevalence of incisal or cervical/root caries in each group.

Study Design. This was a retrospective, cross-sectional study conducted at a single center between 2012 and 2015 for assessment of patients with possible SS. Two-hundred and twenty-five (225) patients (99 SS and 126 NSS) participated in the study.

Results. Student *t* test and Wilcoxon's rank sum test were used to evaluate group differences in continuous variables and the χ^2 test was used to determined differences in categorical variables. Significant univariate associations were further assessed by using multivariate ordinal regression models. Patients with SS were more likely to have a greater number of total caries (odds ratio [OR] 1.72 [1.03−2.88]; $P = .04$). And a focus score greater than 1/4 mm^2 was associated with greater number of total caries (OR 2.88 [1.05, 7.93]; $P = .04$]. Adjusted analysis for salivary flow did not show a significant association between stimulated or unstimulated salivary flow or glandular-specific salivary flow and the total number of carious lesions.

Conclusions. Patients with salivary hypofunction secondary to SS do have a greater caries risk compared with patients with salivary hypofunction caused by other factors. In this study cohort, this finding was not associated with salivary flow rates. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:117−122)

Patients with Sjogren syndrome (SS) experience salivary dysfunction, which may significantly affect oral health. Poor oral health has been shown to also adversely influence overall patient quality of life.[1] Patients with SS experience higher levels of caries, more tooth extractions, and higher dental expenses over a lifetime compared with healthy controls.[2,3] Despite these known dental complications, the precise mechanism causing them is unknown. Although patients with SS generally have lower salivary flow rates (salivary hypofunction) compared with healthy individuals, it remains unclear whether this factor alone is enough to account for the high rate of caries in this population.

There are data supporting a link between low salivary flow rates and increased risk for dental caries among those with SS and other causes of salivary hypofunction. One systematic review suggested that a chronically low stimulated whole-mouth salivary flow rate less than 0.8 to 1 mL/min was the strongest predictor of a greater risk for caries.[4] Recently, a national panel of oral medicine experts, under the auspices of the Sjogren's Syndrome Foundation, published clinical practice guidelines for caries prophylaxis in SS. The committee strongly recommended the use of topical fluoride in all patients with SS and dry mouth. For refractory cases, the additional use of nonfluoride remineralizing agents, chlorhexidine antimicrobial rinses, and stimulation of salivary flow was suggested.[5] The recommendation for stimulation of salivary flow was based on consensus expert opinion that "the oral health community generally accepts that increasing saliva may contribute to decreased caries incidence." This statement is supported by data from 2 prior animal studies that demonstrated that treatment with pilocarpine can significantly alter caries development in murine models of dry mouth.[6,7] However, the oral medicine working group also stressed that currently, "no studies link improved salivary flow to caries prevention" in humans and, therefore, rated the overall strength of this recommendation as "weak."[5]

In addition to low salivary flow, a variety of changes in sialochemistry that could potentially play a role in

Statement of Clinical Significance

This study is the largest study, to date, to compare the association between salivary hypofunction in patients with primary Sjogren syndrome (SS) and those with caries, but not SS. Increasing or supplementing salivary flow may be insufficient to prevent caries onset in patients with SS.

[a]Assistant Professor, Hofstra School of Medicine, Lennox Hill Hospital, Northwell Health, NY, NY.
[b]Professor of Clinical Medicine and Chief, Division of Rheumatology, Penn Presbyterian Medical Center, Philadelphia, PA, USA.
[c]Assistant Professor of Rheumatology and Epidemiology, Perelman School of Medicine Perelman School of Medicine.
[d]Associate Professor of Clinical Medicine and Rheumatology, Perelman School of Medicine Perelman School of Medicine.
[e]Professor and Chair, Oral and Maxillofacial Medicine and Diagnostic Sciences, University Hospitals Cleveland Medical Center, Assistant Dean for Graduate Studies, Case Western Reserve University, School of Dental Medicine, Cleveland, OH, USA.

Received for publication Nov 23, 2018; returned for revision Mar 25, 2019; accepted for publication Apr 20, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.04.011

caries risk are noted in patients with SS.[4,8-11] These include alterations in the contents of proteins, glycoproteins, electrolytes, small molecules, and specific salivary immunoglobulin A and in the buffering capacity of saliva. Altered sialochemistry could potentially increase caries risk through several mechanisms, including alteration of the antimicrobial properties of saliva and/or alteration of calcium and phosphate concentration, which affects tooth mineralization and integrity.

The identification of additional risk factors for cariogenesis in SS could facilitate more targeted and effective strategies to prevent dental complications in this population. The aim of this study was to compare the risk factors for caries between patients with primary SS salivary hypofunction (SS group) and those without SS (non−Sjogren syndrome [NSS] group) salivary hypofunction. We also sought to identify the prevalence of incisal or cervical/root (as a single variable that includes cervical and/or root surfaces) caries in each group because these anatomic locations are most often affected in patients with dry mouth, including those with SS.[11-14]

MATERIALS AND METHODS

Patients

This retrospective cross-sectional study occurred at a single center (Penn Sjogren's Center) and included over 200 patients seen between 2012 and 2015 for assessment of possible SS. The Institutional Review Board of the University of Pennsylvania approved this project. All patients in this study underwent a comprehensive assessment, which included complete history and physical examination, serology/lip biopsy, whole mouth unstimulated sialometry, parotid stimulated sialometry, technetium^{99} pertechnetate salivary scintigraphy, Schirmer test without anesthesia, ocular surface staining with vital dyes, review of recent medical and dental records, and a dental examination.[15,16] The dental examination was performed by trained and calibrated oral medicine evaluators. The whole-mouth unstimulated salivary flow rates and the parotid stimulated salivary flow rates were measured after a 1-hour fast. A low whole-mouth unstimulated salivary flow rate was defined as a rate less than 0.05 mL/min. An abnormally low stimulated parotid salivary flow rate was defined as less than 0.150 mL/minute.[17] All seronegative (Anti-Ro autoantibodies/Anti-La autoantibodies negative) patients with objective evidence of dry mouth and/or dry eyes underwent a labial minor salivary gland biopsy for histologic staining and estimation of a focus score. A biopsy with a focus score greater than 1/4 mm^2 was considered a positive result.[18] Patients were classified as primary SS and NSS groups, according to the 2002 American European Consensus Group (AECG) criteria.[19] Results based on alternative criteria sets for the classification of SS were also analyzed. For ordinal regression models, 3 categories of caries were defined (none, 1−2 caries, or ≥3 caries).

Data analysis

The Student *t* test and Wilcoxon's rank sum test were used to evaluate group differences in continuous variables, and the χ^2 test was used to determine differences in categorical variables. Differences in the number of cervical/root, incisal, and total caries between the SS and NSS groups were compared. Univariate associations between the clinical factors and the total caries were assessed in ordinal regression models. Independent associations between the clinical factors identified in univariate analyses and the total number of caries were measured with parsimonious mutivariable ordinal regression models. Because of a prehypothesized relationship between salivary flow and total number of caries, measurements of unstimulated and stimulated salivary flow were forced into multivariable models.

RESULTS

A total of 225 consecutive patients were included in the primary analysis. Ninety-nine were classified as having SS and 126 were classified as NSS, according to AECG criteria. Diagnoses for patients with NSS sicca included chronic sialadenitis, sclerosing chronic sialadenitis, undifferentiated connective disease, radiation-induced salivary hypofunction, and medication-induced salivary hypofunction. Clinical information and the results of laboratory, ocular, and oral assessments for both groups are summarized in Table I.

The SS group had a significantly higher mean and median number of cervical/root, incisal, and total caries compared with patients with NSS hypofunction (Figure 1). No significant differences in the whole-mouth unstimulated salivary flow rates and the parotid stimulated salivary flow rates were observed between the SS and NSS groups. There were no significant differences in demographic characteristics, symptom prevalence, use of anticholinergic medications, use of secretogogues, tooth loss, or history of dental visits or oral examinations within the last year between the 2 groups.

In the overall cohort, the only factors significantly associated with a greater number of total caries in univariate ordinal regression models were greater age (per 1 year) (odds ratio [OR] 1.023 [1.00, 1.04] $P = .01$) and a focus score greater than 1/4 mm^2 (2.168 [1.289, 3.648]; $P < .004$) (Table II). There was also a trend toward a greater prevalence of caries among those reporting use of anticholinergic medications (1.63 [0.96, 2.73]; $P = .07$). In univariate analyses, the association between caries experience and low whole-mouth unstimulated (OR 1.01 [0.60, 1.71]; $P = 0.75$)

Table I. Demographic and clinical characteristics of patients with primary Sjogren syndrome and non-Sjogren syndrome patients

	Sjogren syndrome	*Other sicca*	*P value*
Number of patients	99	126	
Age	54.1 (13.8)	51.5 (13.1)	.14
Females	87.8%	89.8%	.64
Currently smoking, N (%)	5 (5%]	7 (5%)	.90
Duration dry mouth sx	40 (17, 93)	36 (12, 91)	.55
Duration of dry eye sx	48 (22, 115)	48 (14, 120)	.55
ANA or RF+, N (%)	64 (65%)	29 (23%)	<.001
SSA +, N (%)	62 (63%)	9 (7%)	<.001
Schirmer's test <5 mm/5 min, N (%)	44 (44%)	46/125 (37%)	.25
Focus score > 1/4 mm^2, N (%)	1 (1, 1)	0 (0, 0)	<.001
Anticholinergic drugs, N (%)	51 (52%)	71 (56%)	.47
Cholinomimetic drugs, N (%)	24 (24%)	22 (17%)	.19
Antimalarial drugs, N (%)	34 (35%)	24 (19%)	.007
Current corticosteroid use, N (%)	20 (20%)	17 (13%)	.16
Number of incisal caries	0 (0, 2)	0 (0, 0)	.004
Number of cervical root caries	0 (0, 2)	0 (0,1)	.05
Total number of caries	1 (0,4)	0 (0,2)	.02
Any caries, N (%)	55 (56%)	55 (44%)	.08
Dentures, N (%)	11 (11%)	12 (10%)	.70
Missing teeth, N (%)	57 (58%)	64 (51%)	.31
Oral examination in last year, N (%)	81 (82%)	106/125 (85%)	.55
Dentist visit in last year, N (%)	79 (80%)	106/126 (85%)	.33
Restoration last 12 months, N (%)	45 (45%)	57/125 (46%)	.98
Unstimulated whole-mouth SFR*	0.62 (0.26,1.16)	0.75 (0.28, 1.40)	.33
Abnormal USFR, N (%)	12 (12%)	12 (10%)	.51
Parotid stimulated SFR*	0.001 (0, 0.002)	0.001 (0, 0.003)	.96
Abnormal stimulated SFR, N (%)	68 (69%)	95/125 (76%)	.22

ANA, antinuclear antibodies; RF, rheumatoid factor; SFR, stimulated flow rate; SSA, Anti-Ro autoantibodies; sx, symptoms; USFR, unstimulated flow rate.
*(mL/min)

salivary flow rates or abnormally low stimulated parotid salivary flow rates (OR 1.06 [0.60, 1.90]; $P = .83$) was not significant. Univariate ordinal regression models demonstrated no association with the number of caries for either low unstimulated salivary flow rates (OR 1.15 [0.70, 1.89]; $P = .59$) or low

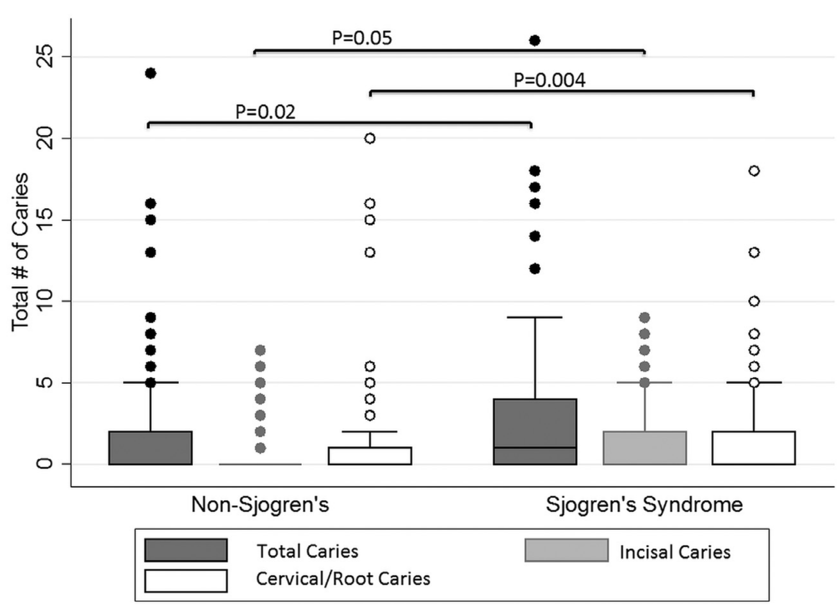

Fig. 1. Differences in the number of total, incisal, and cervical/root caries among patients with Sjogren syndrome and non-Sjogren syndrome salivary hypofunction.

Table II. Factors associated with greater total caries among all patients and those diagnosed with primary Sjogren syndrome

	All patients *B (95% CI)*	*P*	*Sjogren's syndrome only* *B (95% CI)*	*P*
Age	1.02 (1.00, 1.04)	0.02	1.03 (1.00, 1.06)	.07
Focus Score > 1/4 mm^2	2.16 (1.28, 3.64)	0.004	2.88 (1.05, 7.93)	.04
Anticholinergic drugs	1.62 (0.96, 2.73)	0.07	1.24 (0.56, 2.73)	.59
Low parotid stimulated salivary flow	0.99 (0.54, 1.75)	0.92	1.28 (0.54, 3.04)	.57
Low whole-mouth unstimulated salivary flow	0.94 (0.55, 1.58)	0.80	1.03 (0.45, 2.33)	.95

RF, ANA, SSA, abnormal Schirmer's test, and current smoking status.
ANA, antinuclear antibodies; CI, confidence interval; RF, rheumatoid factor; SSA, Anti-Ro autoantibodies.
*Also tested and not significant: Sex, duration of xerostomia, duration of dry eyes, abnormal ocular staining.

stimulated salivary flow rates (OR 0.98 [0.56, 1.70]; $P = .94$]. The absolute focus score correlated significantly with the number of caries present in the overall group (Rho: 0.20; $P = .002$) but was not statistically significant in the SS group (Rho: 0.17; $P = .09$). There was also a significant association between the number of caries and advancing age in the SS group in univariate analyses (Rho 0.24; $P = .02$).

In multivariable ordinal regression models, adjusted for group differences in age, abnormal unstimulated salivary flow, abnormal stimulated flow rates, and the use of anticholinergic drugs, individuals with a diagnosis of SS were more likely to have a greater number of total caries (OR 1.72 [1.03, 2.88]; $P = .04$] compared with the NSS group. In the SS group, the only factor associated with a greater number of total caries was a focus score greater than 1/4 mm^2 (see Table II). Within the SS cohort, there was no significant correlation between the total number of caries and a low whole-mouth unstimulated salivary flow rate or a low parotid stimulated salivary flow rate in univariate or multivariable analyses (see Table II).

DISCUSSION

SS is a chronic, systemic, inflammatory disease characterized by mononuclear cell infiltration of the exocrine glands and other organs. It may cause a variety of clinical manifestations, most notably salivary hypofunction and keratoconjunctivitis sicca, and is associated with a high burden of illness.[20] SS is now considered the second most commonly prevalent autoimmune rheumatic disease after rheumatoid arthritis.[21] At the present time, because no cure exists, treatment is primarily palliative.

Because of the lack of ability to effectively prevent progression of the underlying exocrine gland dysfunction, salivary hypofunction persists and leads to the development of numerous oral health complications.[13,22] The development of caries on the incisal and cervical/root tooth surfaces in SS represents a particularly costly and devastating problem. In most patients, low salivary flow is considered the most important risk factor for caries.[4]

The present study is the largest study, to date, to compare the rates of caries in SS with NSS types of salivary hypofunction and to investigate the risk factors for the development of caries in these groups. Significant differences in the prevalence of incisal, cervical/root, and total caries exist in the SS population, compared with the NSS population with salivary hypofunction caused by other factors. These differences in caries were observed despite a lack of statistically significant differences between the 2 groups in either parotid stimulated salivary flow or whole-mouth unstimulated salivary flow. This implies that qualitative differences, rather than quantitative changes, in saliva flow may serve as important additional risk factors for caries development in the SS population.

Several smaller studies have assessed the risk factors for caries in this population. A study by Boutsi et al.[23] found no significant differences in the occurrence of periodontal disease or cervical caries in 24 patients with SS vs other patients with other autoimmune disorders and controls with NSS sicca. Those authors did report an inverse correlation between "cervical decay lesions" and whole-mouth unstimulated salivary flow in SS.[23] Another small study reported a significantly higher score for decayed, missing, and filled tooth surfaces (DMFS) in 20 patients with SS who met the AECG criteria compared with 20 age-matched controls. The DMFS score also was inversely correlated with salivary flow, especially, the unstimulated whole-mouth salivary flow rate.[11]

Studies of sialochemistry in patients with SS vs healthy controls have reported a number of significant differences, including changes in electrolytes, salivary immunoglobulins, antimicrobial proteins, lipids, glycosylated mucins, and other salivary constituents.[8-11,24] Unfortunately, these results sometimes conflict with each other and may be difficult to interpret across studies because of differences in the type and technique of saliva collection, patient selection criteria, and methods of sialochemical assay. The most frequently reported sialochemical findings in SS include heterogeneous electrolyte levels in whole-mouth unstimulated salivary flow (i.e., increased Na, K, and immunoglobulin levels) vs stimulated parotid salivary flow (i.e., increased Cl, decreased phosphate, increased lactoferrin).The heterogeneity of major salivary gland involvement in SS could also explain the differences in the results of sialochemical analyses. Additionally, it remains unclear whether findings in patients with SS who produce some saliva are universally applicable to the entire SS population, including patients with late-stage disease and "no flow," who are typically unable to participate in sialochemical studies.

More recently, investigators studied the relationship between salivary mucins and salivary rheology.[24] This study found similar concentrations of the mucins MUC5 B and MUC7 in patients with SS and healthy controls but noted a statistically significant decrease in MUC7 glycosylation in the SS group. Because mucins also play a role in antimicrobial defense by selectively modulating the adhesion of microbes to oral tissue surfaces, further qualitative analyses of these and other salivary constituents could potentially yield additional information regarding caries risk in SS.

In contrast to data from other studies, our data support a more complex relationship between salivary flow, salivary quality, and risk of dental caries. We found no statistically significant association between caries prevalence and abnormally low salivary flow rates among the SS and NSS sicca groups. Differences between the SS and NSS groups were present even in multivariable models that adjusted for salivary flow and considered the number of missing teeth, used as a proxy for the caries/periodontal disease experience.

After multivariate analysis, the only risk factor associated with the total number of caries in the SS group was a focus score greater than 1/4 mm^2. Thus, it is conceivable that the underlying inflammatory mechanism that causes autoimmunity and exocrine gland dysfunction in SS may indirectly contribute to the development of caries as well. A recent study of salivary biomarkers in SS unstimulated whole-mouth salivary flow examined proteonomic multianalyte profiles and observed profound differences in SS-related protein patterns vs healthy controls.[25] The findings in that study reflected changes in immunologic domains affecting B cell−dominated immune responses, macrophage differentiation, and T-cell chemotaxis. Those authors suggested that utilization of this technique could enhance SS diagnosis or be used to assess response to therapy. Furthermore, at least one study documented a positive correlation between SS biopsy focus scores and changes in sialochemistry (increased sodium and chloride) in patients with SS vs healthy controls.[11]

There are several limitations to the present study. Although differences in subject classification sometimes influence the results of SS studies, reclassification of our SS patient cohort according to the 2012 American College of Rheumatology−Sjogren's International Collaborative Clinical Alliance classification criteria did not significantly alter the results or change the study conclusions. A similar effect was seen with reclassification per the 2016 European League Against Rheumatism criteria[26,27] In addition, differences in caries prevalence between the patients with SS and the NSS controls could not be explained by differences in the number of missing teeth or self-reported dental visits and restorations within the last 12 months. This observation is further supported by 2 prior studies that documented better compliance with tooth brushing and dental visits among patients with SS compared with healthy controls.[2,11]

In a retrospective cross-sectional study, it is difficult to ascribe causality to any relationship. Furthermore, it is not possible to assess the temporal relationships. There may also be a lack of external validity, given that the study was conducted at a single SS center. Further studies to assess these relationships, with larger databases, would be of interest. This study also did not control for other important risk factors for caries development, including presence of fluoridated water, routine fluoride use, oral hygiene, and dietary intake of fermentable carbohydrates. However, given the geographic distribution of the sample, it seems likely that exposure to fluoridated water would have been equally distributed in both groups.

CONCLUSIONS

Our study findings suggest that patients with SS have a greater risk of caries compared with individuals with salivary hypofunction resulting from other causes. Although most patients with SS exhibited diminished salivary flow, the measured flow rate was not sufficient to explain the observed excess risk of caries. The risk of caries in patients with SS may be influenced by host factors and/or quantitative or qualitative differences in sialochemistry related to the underlying inflammatory process. Further research to compare sialochemistry, buffering capacity, and microbial flora in SS cohorts vs other groups with salivary hypofunction may reveal significant differences that affect caries risk and thereby facilitate targeted and effective strategies for caries prophylaxis in the SS and other patient populations in the future.

REFERENCES

1. Stewart C, Berg K, Cha S, Reeves W. Salivary dysfunction and quality of life in Sjogren syndrome: a critical oral−systemic connection. *J Am Dent Assoc*. 2008;139:291-299.
2. Christensen L, Petersen PE, Thorn JJ, Schiødt M. Dental caries and dental health behavior of patients with primary Sjögren syndrome. *Acta Odontol Scand*. 2001;59:116-120.
3. Fox PC, Bowman SJ, Segal B, et al. Oral involvement in primary Sjögren syndrome. *J Am Dent Assoc*. 2008;139:1592-1601.

4. Leone CW, Oppenheim FG. Physical and chemical aspects of saliva as indicators of risk for dental caries in humans. *J Dent Educ*. 2001;65:1054-1062.
5. Zero TD, Brennan MT, Daniels TE, et al. for the Sjogren's Syndrome Foundation Clinical Practice Guidelines Committee. Clinical practice guidelines for oral management of Sjogren disease: dental caries prevention. *J Am Dent Assoc*. 2016;147:295-305.
6. O'Connell A, Pearson S, Bowen W. Pilocarpine alters caries development in partially desalivated rats. *J Dent Res*. 1994;73:637-643.
7. Leach S, Connell R. Reversal of fissure caries in the albino rat by stimulating saliva flow with pilocarpine. *Caries Res*. 1990;24:127-129.
8. Thorn JJ, Prause JU, Oxholm P. Sialochemistry in Sjögren's syndrome: a review. *J Oral Pathol Med*. 1989;18:457-468.
9. Featherstone J. The science and practice of caries prevention. *J Am Dent Assoc*. 2000;131:887-899.
10. Kalk W, Vissink A, Spijkervet F, et al. Sialometry and sialochemistry: diagnostic tools for Sjogren's syndrome. *Ann Rheum Dis*. 2001;60:1110-1116.
11. Pedersen AML, Bardow A, Nauntofte B. Salivary changes and dental caries as potential oral markers of autoimmune salivary gland dysfunction in primary Sjögren's syndrome. *BMC Clin Pathol*. 2005;5:4.
12. Atkinson J, Fox P. Sjogren's syndrome: oral and dental considerations. *J Am Dent Assoc*. 1993;91:838-845.
13. Mathews S, Kurien B, Scofield R. Oral manifestations of Sjogren's syndrome. *J Dent Res*. 2008;87:308-318.
14. Mavragani C, Moutsopoulos N, Moutsopoulos H. The management of Sjogren's syndrome. *Nat Clin Pract Rheumatol*. 2006;2:252-261.
15. Hermann GA, Vivino FB, Shnier D, et al. Variability of quantitative scintigraphic salivary indices in normal patients. *J Nucl Med*. 1998;39:1260-1263.
16. Hermann GA, Vivino FB, Goin JE. Scintigraphic features of chronic sialadenitis and Sjögren's syndrome: a comparison. *Nucl Med Commun*. 1999;20:1123-1132.
17. Kaplan I, Zuk-Paz L, Wolff A. Association between salivary flow rates, oral symptoms, and oral mucosal status. *Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;106:235-241.
18. Daniels T, Cox D, Shiboski CH. For the Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome (SS) among 1726 registry participants. *Arthritis Rheum*. 2011;63:2021-2030.
19. Vitali C, Bombardieri S, Jonsson R, et al. European Study Group on Classification Criteria for Sjögren's Syndrome Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002;61:554-558.
20. Vivino F. Sjogren's syndrome: clinical aspects. *Clin Immunol*. 2017;182:48-54.
21. Helmick C, Felson D, Lawrence R. National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis Rheum*. 2008;58:15-25.
22. Humphrey SP, Williamson RT. A review of saliva: normal composition, flow and function. *J Prosthet Dent*. 2001;85:162-169.
23. Boutsi E, Dafni U, Moutsopoulos H, Skoupouli F. Dental and periodontal status of Sjogren's syndrome. *J Clin Periodontol*. 2000;27:231-235.
24. Chaudhury NM, Proctor GB, Karlsson NG, Carpenter GH, Flowers SA. Reduced mucin-7 (Muc7) sialylation and altered saliva rheology in Sjögren's syndrome associated oral dryness. *Mol Cell Proteomics*. 2016;15:1048-1059.
25. Delaleu N, Mydel P, Kwee I, Brun JG, Jonsson MV. High fidelity between saliva proteomics and the biologic state of salivary glands defines biomarker signatures for primary Sjogren's syndrome. *Arthritis Rheum*. 2015;67:1084-1095.
26. Shiboski S, Shiboski C, Criswell L, et al. American College of Rheumatology Classification Criteria for Sjogren's syndrome: a data driven, expert consensus approach in the Sjogren's international collaborative clinical alliance cohort. *Arthritis Care Res*. 2012;64:475-487.
27. Shiboski C, Shiboski S, Seror R. The International Sjogren's Syndrome Criteria Working Group. American College of Rheumatology/European League Against Rheumatism Classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheum Dis*. 2017;69:35-45.

Reprint requests:

Andres Pinto
Oral and Maxillofacial Medicine and Diagnostic Sciences
University Hospitals Cleveland Medical Center
Assistant Dean for Graduate Studies
Case Western Reserve University
School of Dental Medicine
Room 1190
2124 Cornell Road
Cleveland
OH 44106
USA.
Andres.Pinto@UHhospitals.org