Title
Saliva: A Determining Factor in Caries Distribution

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Publication Date
2017

Peer reviewed|Thesis/dissertation

SALIVA: A DETERMINING FACTOR IN CARIES DISTRIBUTION

by

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THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Oral and Craniofacial Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

[redacted]

ACKNOWLEDGEMENTS

To the people who have helped me through this project:

Stanford: Dr. Daniel Relman, Dr. Diana Proctor, Meredith Millman, Samuel Walker

UCSF: Dr. Mark Ryder, Dr. Yvonne Kapila, Jing Cheng, Dr. Shanne Sastiel, Dr. Jonathan Weng

NIDCR Grant: R01-DE23113-001

ABSTRACT

SALIVA: A DETERMINING FACTOR IN CARIES DISTRIBUTION IN SJOGREN'S SYNDROME

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BACKGROUND: Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease with lymphocytic infiltrate of the salivary and lacrimal glands and reduced salivary flow. Increased incidence of caries and candidiasis, impaired ability to chew and speak, and reduced quality of life are all associated with reduced salivary flow. Although studies show that SS patients tend to have higher caries rates than non-SS patients, less is known about how low vs. high salivary flow rates relate to caries incidence in SS. The purpose of this study was to test the hypothesis that caries incidence is inversely proportional to the rate of salivary flow in patients with SS as well as in otherwise healthy controls.

METHODS: A cross-sectional, prospective study of 30 SS patients and 105 controls was undertaken to evaluate salivary flow rates and caries incidence. Unstimulated whole salivary flow rates (UWS-FR; mL/min) were measured over 5 minutes, and caries incidence was evaluated using the decayed-missing-filled-surfaces (DMFS) index by calibrated clinicians. Mean values, distributions across subjects and teeth, and scatter plots of UWS-FR vs. caries rate for data covariates, such as age, gender, and race, were obtained.

RESULTS: SS subjects exhibited a mean DMFS score of 45 and a mean UWS-FR of 0.113 whereas the controls exhibited a mean DMFS score of 9 and a mean UWS-FR of 0.459. Within the SS group, subjects with low UWS-FR (N= 19; mean; 0.030) had a DMFS score of 51 while those with high UWS-FR (N= 11;mean 0.257) had a DMFS score of 35. Control subjects with low UWS-FR (N = 3; mean 0.070) had a DMFS score of 16 and those with high UWS-FR (N = 102; mean 0.472) had a DMFS score of 8.8. Thus, although low-flow controls had a lower UWS-FR (N = 3; mean 0.070) than high-flow SS patients (N = 11; mean 0.257), low-flow controls still had lower DMFS scores than high-flow SS subjects. Scatter plot data further showed an interaction between age, salivary flow rates, and DMFS scores. In age-matched controls and SS subjects, lower UWS-FR predicted higher DMFS across all decades of life. Notably, this relationship was most pronounced for the 60-69 year olds, followed by the 50-59 year olds, and the 40-49 year olds. In terms of the spatial distribution of DMFS across teeth, in both control and SS subjects there was a lower to higher average DMFS score gradient from anterior to posterior teeth. In the control subjects there were no major discernable differences in the magnitude or pattern of this gradient. In the SS subjects there were higher mean DMFS scores in the low salivary group vs. the high salivary group along the entire anterior to posterior gradient.

CONCLUSIONS: SS subjects exhibited higher levels of DMFS scores compared to controls in relation to UWS-FR levels. The results of this study should be watched closely as age and sample size are major limitations.

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INTRODUCTION

Background

Sjogren's syndrome (SS) is a chronic inflammatory autoimmune disease that is characterized by a lymphocytic infiltration of the salivary and lacrimal glands. Primary SS is defined as the disease developing in isolation, whereas secondary SS occurs in conjunction with other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematous. Disease prevalence is 0.6%.[1] SS affects primarily women in their forties and fifties, with the diagnosis occurring much later than the actual initial onset of disease. One of the most common symptoms for patients with SS is xerostomia. Saliva is important because it not only protects the oral mucosa and teeth through its buffering capacity and remineralization properties, but it also controls the composition of the oral microflora and thereby exhibits antibacterial, antifungal, and antiviral properties.[2] With decreased amounts of saliva, SS patients develop a decreased ability to chew and speak, caries, and candidiasis,[3] and they experience an overall decreased quality of life. Treatment for SS is focused on palliative care, which translates to keeping the oral mucosa hydrated and treating associated symptoms; however, immunosuppressive, anti-inflammatory, and anti-rheumatic drugs are used when there are systemic manifestations.[4]

There have been numerous studies on caries incidence in SS patients.[6] These studies show that SS patients tend to have higher caries rates[5,7] than non-SS patients. However, these studies do not specify the amount of saliva a SS patient may produce. In fact, approximately 12% of SS patients indeed have normal salivary flow,[8] regardless of the symptoms they experience. If caries incidence correlates with the amount of salivary flow, then sequentially there should be a lower incidence of caries in SS patients with high or normal salivary flow.

Another thing to note is that caries distribution in the mouth may differ. In normal healthy patients, caries tend to occur on occlusal and proximal surfaces of teeth.[9,10] However, in SS patients, caries tend to predominantly occur on the cervical or root surfaces.[5,12,13,14,15] This difference may be attributed to SS patients having low salivary production in the three salivary glands, which are located near the maxillary buccal and mandibular lingual tooth surfaces. However, there has been no paper to date exploring whether the amount of salivary flow in SS patients affects the spatial distribution of caries in the mouth.

To date, there have been no studies that correlate the amount of salivary flow to the caries incidence and spatial distribution in the mouth. Thus, the purpose of this study was to test the hypothesis that caries incidence levels and caries spatial distribution are related to the level of salivary flow rate in SS patients. These hypotheses were tested in the following specific aims.

Specific Aims

- Aim 1: Determine the difference in caries incidence in Control subjects with low versus high salivary flow rates
- Aim 2: Determine the difference in caries incidence in SS subjects with low versus high salivary flow rates
- Aim 3: Determine whether caries incidence correlates with salivary flow in age-matched SS and Control subjects
- Aim 4: Determine whether a spatial distribution pattern exists in caries incidence in SS and Control subjects with low versus high salivary flow rates

METHODS

Recruitment and Informed Consent Process

The data collection for 30 SS subjects and 105 otherwise healthy controls took place at the UCSF Dental Center, Periodontics Clinic (San Francisco, CA) from 2015 to 2017. Subjects were pre-screened by phone interview to determine initial eligibility. Informed consent form was given to the subject at the beginning of appointment.

Study Sample

SS subjects were included in the study if they were adults over 18 years old, complained of dry mouth, and had been diagnosed at least three months ago with Sjogren's Syndrome as per the American European Consensus Criteria[37] or the American College of Rheumatology Classification Criteria.[38] The diagnosis was confirmed with doctor's note at a later appointment. The diagnosis date of SS was also collected verbally and verified with subjects' documentation. Otherwise healthy control subjects were included in the study if they were healthy, non-smoking adults over the age of 18.

Exclusion criteria for the SS group were: 1) having fewer than 15 non-implant teeth, 2) smoke or use chewing tobacco or snuff or quit using tobacco products within the 6 months preceding enrollment, 3) being treated by a physician for an uncontrolled chronic medical condition, 4) have symptoms of or treatment of asthma or acid reflux in the last 3 months, 5) history of radiation therapy to the head or neck, 6) history of oral, systemic antibiotics or antifungals use within the 6 month period preceding enrollment, 7) required to take antibiotics before dental treatment, 8) history of stimulant or heroin abuse or of eating disorders, 9) lactating, pregnant, or intending to become pregnant, 10) any dental treatment during the one

month period preceding enrollment and cannot or will not abstain from dental treatments during their enrollment, 11) have fixed dental appliance (retainers, fixed dentures, braces, orthodontic wires), 12) periodontitis, candidiasis, halitosis, tooth pain, or any other disease in the mouth (to patient's knowledge), 13) diagnosed with Sjogren's syndrome by the American European Consensus Criteria [37] or the American College of Rheumatology Classification Criteria[38] fewer than 3 months prior to the date of enrollment.

Exclusion criteria for the control group were: 1) having fewer than 15 natural, non-implant teeth. 2) missing both central incisors, both canines, or both first molars in either the maxilla or the mandible, 3) crown or implant replacing both central incisors, both canines, or both first molars in either the maxilla or the mandible, 4) currently being treated by a physician for any chronic medical condition, including asthma and acid reflux, 5) history of radiation therapy to the head or neck, 6) take any medication on a daily basis other than birth control, 7) history of oral, systemic antibiotics or antifungals use within the 6 month period preceding enrolment, 8) required to take antibiotics before dental treatment, 9) history of stimulant or heroin abuse or of eating disorders 10) lactating, pregnant, or intending to become pregnant, 11) any dental treatment during the 1 month period preceding enrollment and cannot or will not abstain from dental treatments during their enrollment, 12) fixed dental appliance (retainers, fixed dentures, braces, orthodontic wires), 13) experienced dry mouth for a full week at any time in the past 6 months, 14) periodontitis, candidiasis, halitosis, tooth pain, or any other disease in the mouth (to patient's knowledge).

Ethics, HIPAA, and Institutional Review Board Approval

IRB was obtained (#14-13115). All procedures followed the ethical and HIPAA protocol.

Sialometry

Unstimulated whole salivary flow rate (UWS-FR) was obtained. Subjects refrained from taking food and drinks for at least 2 hours before saliva collection. Unstimulated saliva was expectorated into pre-weighed 50 mL sterile tubes (Falcon®) every minute for a total of five minutes. Salivary output was expressed as milliliters per minute (mL/min).

Clinical Examination

Five calibrated examiners performed the clinical examinations. Prior to commencing examination of participants, a periodontist/calibrator (MR) conducted a training/calibration for each of the examining dentists. The training calibration included a demonstration of techniques to examine and measure for oral soft tissue health and lesions/changes, dental caries, bleeding on probing, probing depths, and position of the gingival margin to the CEJ (in order to calculate clinical attachment levels). Following this demonstration, each examiner was assessed with the calibrator (MR) on a volunteer subject to calibrate measures for caries, probing depths and gingival margin levels. A minimum concurrence of 90% for caries detection, probing depths and gingival margin position was required. All examiners successfully met the concurrence requirement for the first examined volunteer, thereby not requiring a second calibration exam. The examinations included a clinical evaluation of decayed, missing, and filled surfaces (DMFS). The presence of cavities was confirmed by drying the tooth surface and using a dental explorer. If the site had a sticky catch with an explorer, it was recorded as having a decayed surface. DMFS score was calculated utilizing the WHO DMFS index.[36] Third molars, fractured teeth, congenitally missing teeth, and teeth missing from orthodontic treatment, trauma, or other non-disease related cause were excluded. Anterior teeth were counted as having four surfaces

(mesial, distal, buccal, lingual) and posterior teeth as having five surfaces (mesial, distal, buccal, lingual, occlusal), for a total of 128 surfaces for 28 teeth. Teeth with full coverage crowns were considered "filled" for all surfaces. Dental implants were considered "missing" for all surfaces. Teeth with sealants were considered sound. If a tooth had decayed and filled surfaces concurrently, the DMFS score was computed for the decayed surface only.

Statistical Analysis

The difference in DMFS scores between SS and control subjects were evaluated using the Wilcoxon Two-Sample Test and the Spearman correlation test. Scatter plots for DMFS scores in relation to age and UWS-FR in SS and control subjects were obtained. Spatial distribution of DMFS was mapped.

RESULTS

A total of 135 subjects were included in this study. For gender distribution, there were 90 females and 45 males (*Table 1*). The majority subjects in the control group were in their 20s and 30s, whereas the majority of SS group subjects were in their 50s and 60s (*Table 2*).

Sex	SS	Control	Total
Female	29	61	90
Male	1	44	45
Total N	30	105	105

Table 1: Sex distribution in SS and Control groups.

Table of group by Age								
Group	Age Group							
Frequency (%)	<20	20-29	30-39	40-49	50-59	60-69	70-	Total
Control	5 (3.7)	50 (37.0)	29 (21.5)	8 (5.9)	10 (7.4)	3 (2.2)	0 (0.0)	105 (77.8)
SS	0 (0.0)	1 (0.7)	0 (0.0)	3 (2.2)	9 (6.7)	11 (8.2)	6 (4.4)	30 (22.2)
Total	5 (3.7)	51 (37.8)	29 (21.5)	11 (8.2)	19 (14.0)	14 (10.4)	6 (4.4)	135 (100)

Table 2: Age distribution in SS and Control groups.

SS subjects (n=30) exhibited a mean DMFS score of 45 and a mean UWS-FR of 0.113, whereas the controls (n=105) exhibited a mean DMFS score of 9 and a mean UWS-FR of 0.466 (*Table 3*). There was a statistically significant difference in DMFS scores between SS and the control group.

Group	N	Variable	N	Mean	S.D.	Median (Q1, Q3)	Range
Control	105	Age	105	32.4	11.6	29.0 (24, 37)	18-68
		DMFS	93	9.01*	10.77	6.00 (1, 13)	0-46
		UWS-FR	105	0.47	0.28	0.41 (0.27, 0.61)	0.03-1.80
SS	30	Age	30	60.0	10.7	61.5 (54, 66)	29-77
		DMFS	30	45.30*	31.71	43.50 (17, 65)	0-101
		UWS-FR	30	0.11	0.14	0.07 (0.00, 0,15)	0-0.52

*P <0.0001 in DMFS between Control and SS.

Table 3: Distribution of DMFS and UWS-FR in SS and Control groups.

Low UWS-FR was defined as less than 0.1 mL/min for both the SS and control group. Overall, patients with high UWS-FR had a lower DMFS score than that with low UWS-FR; this

difference was statistically significant (*Table 4*). The correlation between DMFS and UWS-FR was -0.357. Within the SS group, subjects with low UWS-FR (n= 19; mean 0.030) had a DMFS score of 51 while those with high UWS-FR (n= 11; mean 0.257) had a DMFS score of 35 (*Table 5*). The difference in DMFS scores for high vs. low UWS-FR in the SS group was statistically insignificant. The correlation between UWS-FR and DMFS score in SS subjects was 0.147. Control subjects with low UWS-FR (n= 3; mean 0.070) had a DMFS score of 16 and those with high UWS-FR (n = 102; mean 0.477) had a DMFS score of 8.8. The difference in DMFS scores for high vs. low UWS-FR in the control group was statistically insignificant. The correlation between UWS-FR and DMFS score in control subjects was 0.100. Interestingly, although low-flow controls had a lower UWS-FR (mean 0.070) than high-flow SS subjects (mean 0.257), low-flow controls still had a lower DMFS score (mean 16) than high-flow SS subjects (mean 35).

Overall	High UWS-FR (> 0.1 mL/min; n = 113)				Low UWS-FR (< 0.1 mL/min; n = 22)				P
	Mean	S.D.	Median (Q1, Q3)	Range	Mean	S.D.	Median (Q1, Q3)	Range	
DMFS	11.62	14.13	6.0 (1, 17)	0-65	46.50	36.37	45.5 (13, 81)	0-101	0.0002

*P = 0.0002 in DMFS between High vs. Low UWS-FR.

Table 4: DMFS values in High vs. Low UWS-FR in all subjects.

Characteristic	High UWS-FR (> 0.1 mL/min)				Low UWS-FR (< 0.1 mL/min)				P
	Mean	S.D.	Median (Q1, Q3)	Range	Mean	S.D.	Median (Q1, Q3)	Range	
Control	n = 102				n = 3				
Age	32.3	11.3	29.0 (24, 37)	18-68	35.3	23.1	23 (21, 62)	21-62	
DMFS	8.77	10.25	6.0 (1, 13)	0-46	16.33	24.09	5.0 (0, 44)	0-44	0.91
UWS-FR	0.48	0.28	0.41(0.29, 0.61)	0.11-1.80	0.07	0.04	0.09 (0.03, 0.10)	0.03-0.10	
SS	n = 11				n = 19				
Age	56.3	13.3	61 (45, 66)	29-73	62.2	8.63	62 (55, 70)	46-77	
DMFS	35.0	19.66	36 (17, 54)	8-65	51.3	36.1	49 (13, 92)	0-101	0.29
UWS-FR	0.26	0.14	0.23 (0.14, 0.32)	0.11-0.52	0.03	0.03	0.02 (0, 0.07)	0-0.08	

Table 5: Distribution of DMFS and UWS-FR according to High vs. Low UWS-FR in SS and Control groups.

Scatter plot data further showed an interaction between age, salivary flow rates, and DMFS scores. Overall, as UWS-FR decreased, the higher DMFS scores were (*Fig 1*). In control subjects, lower UWS-FR predicted higher DMFS for ages 40 and beyond (*Fig 2*). Notably, this relationship was most pronounced (steepest slope) for the 60-69 year olds (n= 3), followed by the 50-59 year olds (n= 10) and the 40-49 year olds (n= 8). For SS subjects, this negative correlation existed only for 70+ year olds (n= 6). 60-69 year old SS subjects (n= 11) showed almost no relationship between UWS-FR and DMFS scores. Interestingly, in 50-59 year olds (n= 9) and 40-49 year olds (n= 3) a positive relationship prevailed. (*Fig 3*).

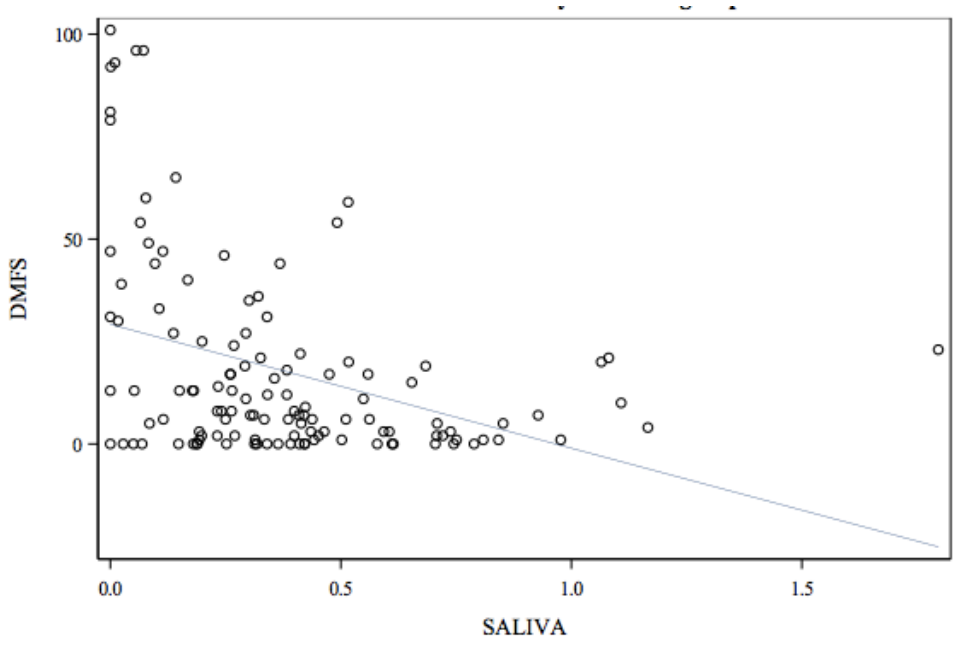

Fig 1: DMFS in relationship to UWS-FR in all subjects.

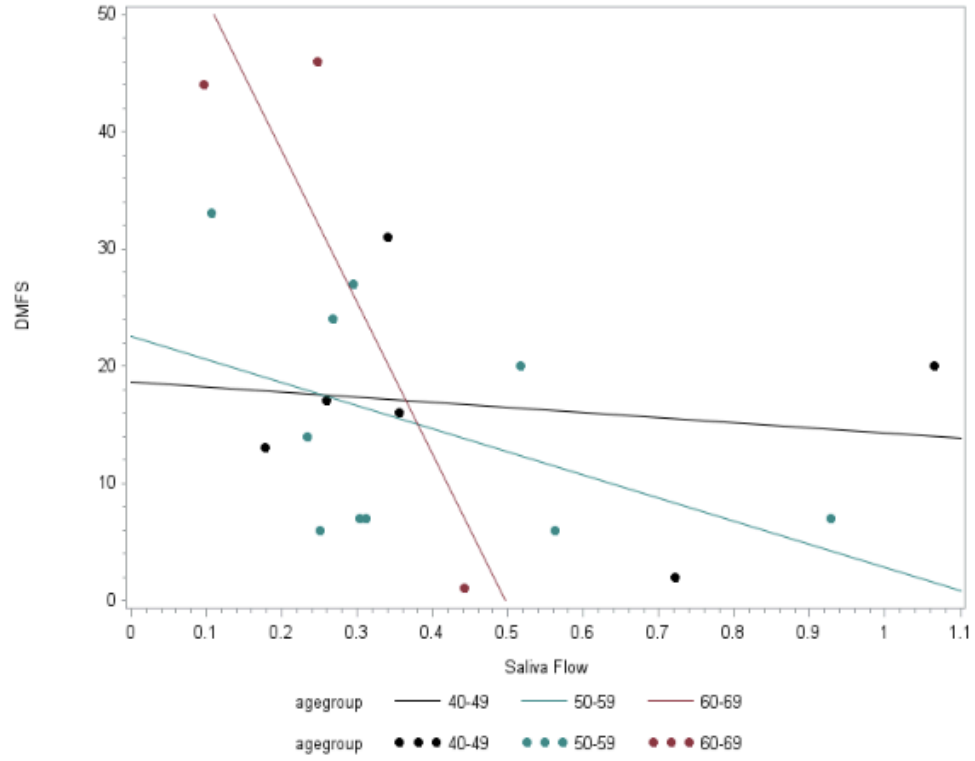

Fig 2: Scatter plot of DMFS in Control subjects 40 years old and above.

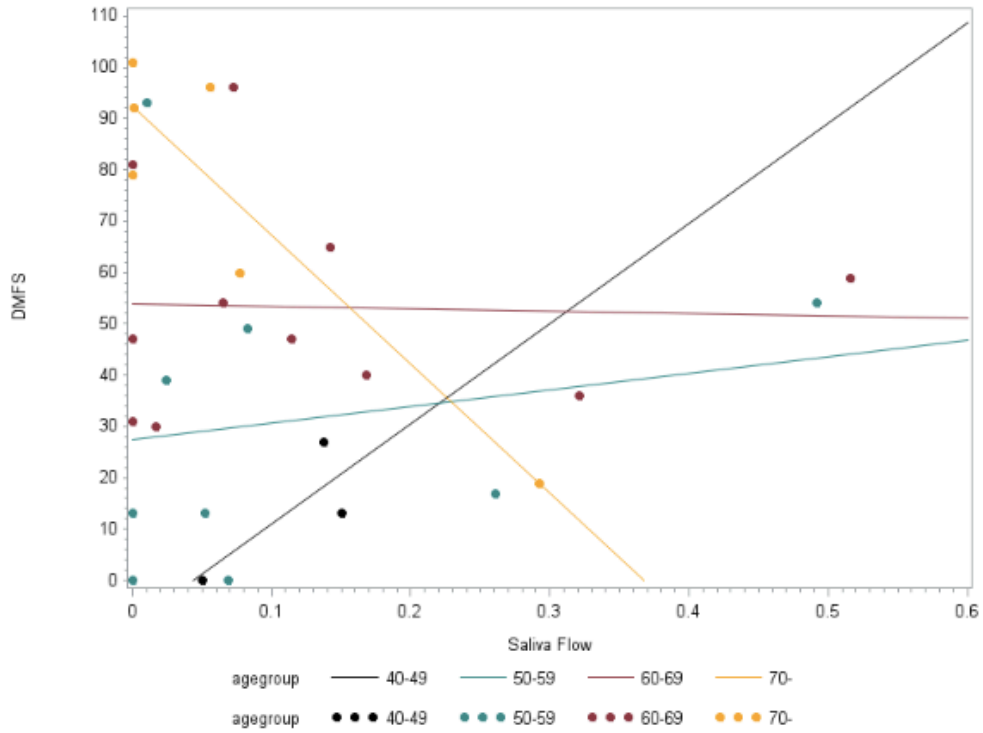

Fig 3: Scatter plot of DMFS in SS subjects 40 years old and above.

These age-stratified control data did not represent the whole sample set. By performing the scatter plot data for all ages, we can see that younger subjects did not show a negative relationship between DMFS and UWS-FR; in fact, it was reversed.

In terms of DMFS distribution patterns (*Fig 4*), in both control and SS subjects there was a lower to higher average DMFS score gradient from anterior to posterior teeth. In the control subjects there were no major discernable differences in the magnitude or pattern of this gradient. In the SS subjects there were higher mean DMFS scores in the low salivary group vs. the high salivary group along the entire anterior to posterior gradient.

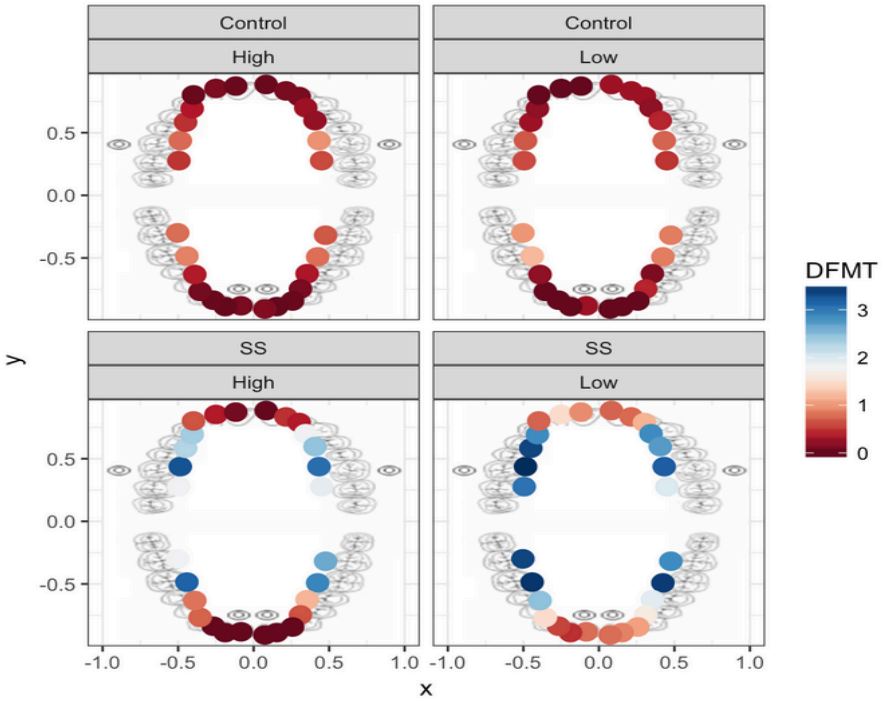

Fig 4: DMFT distribution in SS and Control subjects in the mouth.

DISCUSSION

In this cross-sectional, prospective study of 30 SS patients and 105 controls, we made several key observations.

We confirmed previous observations[5,7] that SS patients tend to have higher caries incidence than otherwise healthy controls. Many studies indicate that SS patients have a higher mean DMFT than otherwise healthy controls[35] due to hyposalivation, which contributes to increased number and frequency of cariogenic microorganisms *Lactobacillus* spp, and *Streptococcus mutans* in supragingival plaque,[32] and poorer saliva buffering capacity.[35]

Furthermore, this study found that the level of UWS-FR correlated to caries activity in

both SS and otherwise healthy controls. UWS-FR of 0.1 mL/min or lower is considered abnormal.[19,20,21,28] In our study sample, 19 SS subjects and 3 Control subjects exhibited UWS-FR of 0.1 mL/min or lower.

There have been many studies in the past that suggests a negative relationship between caries incidence and UWS-FR in otherwise healthy subjects.[22] This study confirms those findings, despite having a low correlation (0.147). Scatter plot data showed that this relationship was most pronounced for 60-69 year olds, followed by the 50-59 year olds, and the 40-49 year olds. This may be partly due to the fact that older patients tend to have reduced production of saliva from loss of acinar cells,[40] tendency to intake increasing medications that cause hyposalivation,[41,42] and history of possible radiation therapy.[43,44]

In contrast, to date, studies that correlated the amount of salivary flow to caries incidence in SS subjects are limited. Jorkjend et al.[39] compared secondary SS subjects to age-matched controls and found that there was no difference in DMFT between SS and control subjects in both low and high UWS-FR. Our results indicate that caries incidence correlates negatively with salivary flow rate in SS subjects, albeit having a low correlation (0.100). Scatter plot data shows that in 40-49 year olds there is almost no relationship between UWS-FR and caries incidence. By contrast, in 50-59 year olds and 60-69 year olds, the data showed that higher UWS-FR predicted lower DMFS scores. Possible reasons for the difference in results may be due to the fact that Jorkjend's study recruited secondary SS subjects, whereas this study included predominantly primary SS subjects. Also, Jorkjend's study did not include decayed teeth, which indicates current disease activity.

Interestingly, our age-match data indicates that low-flow Control subjects had a lower

DMFS score than that of high-flow SS subjects. This may be contributed to the fact that our SS subjects were predominantly in the 50-70 year old range, whereas the control group was mostly in the 20-30 year old range. Since the UWS-FR in un-medicated healthy individuals tend to decrease with age,[22] the age alone may play a significant confounding factor in the difference in caries incidence in this study. Older subjects would have had more exposure to caries risk and a history of more dental treatments, which can increase the DMFS scores.

In terms of tooth distribution patterns (*Fig 5*), the DMFS scores were consistently higher for posterior teeth than anterior teeth in control subjects. However, in SS subjects with low salivary flow showed high DMFS scores on posterior than anterior teeth, whereas SS subjects with high salivary flow showed high DMFS scores on all teeth except mandibular anterior teeth. To date this is the first study that demonstrates caries distribution in the full mouth. Previous studies claimed that in normal healthy patients, caries tend to occur on occlusal and proximal surfaces of teeth,[9,10] whereas in SS patients, caries tend to predominantly occur on the cervical or root surfaces.[5,12,13,14,15] The difference in caries spatial distribution shown in this study may be may be attributed to SS patients having low salivary production in the three salivary glands, particularly the submandibular and parotid glands which are known to produce approximately 65% and 20% of unstimulated salivary production.[45]

The results of this study should be interpreted with caution as this study has several limitations. This study has a small population size for SS subjects. Also, using individual age brackets and age-stratification further decreased the number of subjects in each category. Additionally, SS subjects were older as a group than control subjects, so age-stratification was limited. This study recruited subjects via pre-screening over the telephone before performing clinical examination and salivary flow collection, which can exclude potential outliers not

included in this study.

Fortunately, from this study, we learned that SS patients are more susceptible to caries than otherwise healthy controls, with increasing incidence as the salivary flow amount decreased. In addition, caries are more prone to be seen in posterior teeth in SS patients. Astute clinicians should not underestimate the possible presence or development of SS in patients presenting hyposalivation, as the date to diagnosis of SS can be delayed. Future research should specify preventative measures to minimize the risk of caries incidence in SS patients, as well as possible therapeutic methods to target areas in the mouth that are more prone to caries development.

CONCLUSIONS

SS subjects exhibited higher levels of DMFS scores compared to controls in relation to UWS-FR levels. The results of this study should be watched closely as age and sample size are major limitations.

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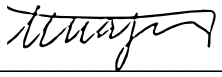
Author Signature  Date 6/13/17