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Experimental Oral Medicine

Salivary flow and its relationship to oral signs and symptoms in patients with dry eyes

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OBJECTIVES: The aim of this study was to investigate oral symptoms and clinical parameters in dry eye patients. Subjective reports of the sensation of a dry mouth, salivary flow rates, and clinical parameters of oral disease related to three different types of dry eye patients were examined.

SUBJECTS AND METHODS: There were 224 individuals, including dry eye patients and control subjects. The dry eye patients were classified into three types: patients with Sjögren's syndrome (SS-DE), patients without SS-DE (non-SS-DE), and patients with Stevens–Johnson syndrome (SJS-DE). Salivary flow rates were measured using two kinds of sialometry. Subjective and objective oral symptoms and signs were also examined.

RESULTS AND CONCLUSION: Over half of the dry eye patients complained of a dry mouth. The flow rates of their stimulated whole saliva and parotid saliva were significantly lower than those of the control groups ($P < 0.05$, $P < 0.01$). The sensation of a dry mouth and changes in oral soft tissues, dental caries, and oral *Candida* frequently occurred in dry eye patients.

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Keywords: dry eye; dry mouth; salivary flow rate

Introduction

The prevalence of symptomatic associations between dry eye and dry mouth in population-based studies has already been reported (Hay *et al*, 1998; Schein *et al*, 1999; Price and Venables, 2002). Hay *et al* (1998) examined the prevalence of dry eye and dry mouth in 341 subjects and reported that 29% of subjects had dry mouth symptoms, 24% had dry eye symptoms and 14% had both. Hikichi *et al* (1995) reported that 17% of outpatients in general eye clinics have some signs or symptoms of dry eye. These patients often complain of dryness of mouth and condition of intra-oral changes.

Eye clinicians classify dry eye syndrome into three types: simple dry eye, autoimmune positive dry eye, and Sjögren's syndrome (SS) (Tsubota *et al*, 1994). Sjögren's syndrome is frequently associated with the occurrence of keratoconjunctivitis sicca and xerostomia as an autoimmune disorder (Fox *et al*, 1986). Stevens–Johnson syndrome (SJS) is also known to cause dry eye syndrome. Stevens and Johnson (1922) reported this to be a specific syndrome, which includes eruptive fever with stomatitis and ocular inflammation. Drug intake and infections can also affect the skin and mucous membranes and initiate these diseases. However, the mechanisms underlying such effects have not been identified (Coster, 1997).

As far as we know, no study has ever been undertaken to explore the relationship between dry eye and dry mouth with respect to the different types of dry eye patients. We therefore examined the relationship between the three types of dry eye patients and their oral signs and symptoms in dry eye patients.

Materials and methods

Study population

This study was conducted on dry eye outpatients at Ichikawa General Hospital, Tokyo Dental College in Chiba Prefecture, Japan. Written informed consent was obtained from each patient after the aims and methodology of the study were explained. The survey was carried out between June 1999 and August 2002. There were 141 dry eye patients, 17 men and 124 women, with a mean age of 56.01 ± 13.65 years (20–79). Dry eye patients were diagnosed based on the criteria used by the Japanese Dry Eye Research Center (Hikichi *et al*, 1995). We classified the dry eye patients into three groups: (1) dry eye patients with Sjögren's syndrome (SS-DE; $n = 54$) as diagnosed by Fox's criteria (Fox *et al*, 1986), Fox's criteria fit the recently revised EC-North

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American classification criteria (Vitali *et al*, 2002); (2) dry eye patients without Sjögren's syndrome (non-SS-DE; $n = 67$) (Lemp, 1995); and (3) dry eye patients with Stevens–Johnson syndrome, who were induced by medications (SJS-DE; $n = 20$). We also classified two control groups: (1) age-matched patients with ophthalmopathies such as cataract, myopia, keratoconus, and myodesopsia excluding dry eye symptoms [control patients (CP), $n = 32$]; (2) age-matched healthy volunteers receiving regular health checks in the Tokyo metropolitan area and in Chiba Prefecture [control (C), $n = 51$]. The mean ages of CP and C were 54.25 and 50.98, respectively (Table 1). The examinations of dry eye and dry mouth including the CP groups were carried out blind knowing that they have some ophthalmopathy. The oral health checks of healthy volunteers were also performed as blind to the examiner.

Saliva sampling
All the patients visited the dry eye clinics between 9:00 and 12:00 hours. Patients were forbidden any oral intake or smoking for at least 1 h prior to saliva collection. We examined the stimulated whole salivary secretion, followed by stimulated parotid saliva.

Sampling of stimulated whole saliva
Whole saliva was measured by stimulation using a chewing gum base (0.5 g) without sugar, flavour, or any additives. In order to soften the gum base and remove saliva from the mouth, the saliva secreted was swallowed after initial chewing for 1 min. During the subsequent 4 min, stimulated saliva was collected in a sterilized plastic tube while the subject chewed the same bolus gum base. The flow rate was recorded as ml min^{-1}. We excluded those patients who were wearing dentures. It is impossible to masticate the chewing gum base because of the adhesiveness of gum base to dentures. We excluded three patients of SS-DE, two of SJS-DE, seven of non-SS-DE, five of CP, and one-denture wearer in the control subjects.

Sampling of stimulated parotid saliva
Parotid saliva was stimulated using sour apricot candy (2.6 g; Lotte Co., Tokyo, Japan) and was collected for 5 min in a modified Lashley' cup (Lashley, 1916).

Table 1 Age distribution of subject groups

Subjects	*n*	*Mean ± s.d.*	*Range*
SS-DE[a]	54	58.09 ± 10.61	30–78
Non-SS-DE[b]	67	55.18 ± 14.50	20–79
SJS-DE[c]	20	52.85 ± 17.02	22–76
CP[d]	32	54.25 ± 13.23	25–78
C[e]	51	50.98 ± 15.03	30–78

[a]SS-DE, Sjögren's syndrome with dry eye; [b]non-SS-DE, dry eye not associated with Sjögren's syndrome; [c]SJS-DE, Stevens–Johnson syndrome with dry eye; [d]CP, control patients; [e]C, healthy volunteers as a control.

Oral examination
The examination was carried out by one of the authors (K.M.). Dental caries was registered with an explorer and mirror under standardized conditions and optimal light. Caries data were expressed as decayed, missing, and filled teeth (DMFT). The third molars were excluded from the analysis. To examine oral soft tissue (buccal mucosa, tongue mucosa and angular cheilitis), a calibration trial was conducted between the examiner and patients. Kappa statistic for the recording of oral soft tissue was more than 0.9. Buccal mucosa was examined as normal, slight redness, severe redness and leukoedema. Changes in the tongue mucosa were classified as normal, atrophy of tongue mucosa, groove of the tongue mucosa and shiny tongue. Angular cheilitis were classified as normal, slight angular cheilitis, heavy cheilitis or angular cheilitis at both corners of the mouth.

Detection of oral Candida
Oral mucosa (tongue, cheeks, pharynx), teeth and denture surfaces were swabbed using selective medium CA (Candida Color; Kanto Kagaku Co., Tokyo, Japan) (Okubo *et al*, 1997) to examine the distribution of *Candida* in the mouth. After incubation at 37°C for 48 h, the number of colonies was counted for four species (*Candida albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*) according to the manufacturer's instructions.

Questionnaire
The subjects were asked to answer a questionnaire consisting of questions relating to symptoms of their sensation of a dry mouth, their general medical condition, and usage of medication. Subjects were asked to indicate whether their symptoms were never, occasionally, or frequently experienced.

Statistical analysis
Data were statistically analysed using StatView (Version 5.0, SAS Institute, Cary, NC, USA). A two-tailed Fisher exact test and chi-square test were used to analyse the questionnaire. A one-way analysis of variance (one-way ANOVA) was used to evaluate the differences in the clinical parameters between the groups.

Results

Salivary flow rates in dry eye patients
In SS-DE, both stimulated whole and parotid saliva were the lowest volume in other subject groups and significant differences were observed between SS-DE *vs* CP and C in stimulated whole saliva ($P < 0.01$) and SS-DE *vs* non-SS-DE, CP, and C in stimulated parotid saliva ($P < 0.05$, $P < 0.01$). In non-SS-DE, there was a significant difference between CP and C in stimulated whole saliva ($P < 0.05$, $P < 0.01$). In SJS-DE, both stimulated whole and parotid saliva were lower compared with CP and C subjects. However, no significant difference was found between the groups (Table 2).

Table 2 Salivary flow rates in subject groups

Subjects	*Stimulated whole saliva (ml min^{-1})*	*Stimulated parotid saliva [ml (5 min^{-1})]*
SS-DE[a]	0.34 ± 0.35 (38)	1.74 ± 2.12 (31)
Non-SS-DE[b]	0.66 ± 0.50 (51)	3.29 ± 2.16 (46)
SJS-DE[c]	0.81 ± 0.53 (8)	2.58 ± 2.47 (10)
CP[d]	1.04 ± 0.67 (26)	3.46 ± 1.69 (21)
C[e]	1.18 ± 0.73 (47)	3.53 ± 2.23 (38)

Values are give as mean ± s.d. (*n*).
*$P < 0.05$, **$P < 0.01$.
[a]SS-DE, Sjögren's syndrome with dry eye; [b]non-SS-DE, dry eye not associated with Sjögren's syndrome; [c]SJS-DE, Stevens–Johnson syndrome with dry eye; [d]CP, control patients; [e]C, healthy volunteers as a control.

Table 3 Condition of buccal mucosa in subjects

Subjects	*n*	*Normal (%)*	*Slight redness (%)*	*Severe redness (%)*	*Other observations (%)*
SS-DE[a]	18	55.6	22.2	11.1	11.1
Non-SS-DE[b]	18	83.3	16.7	0	0
CP[c]	22	95.2	0	4.8	0
C[d]	38	94.7	2.6	0	2.6

[a]SS-DE, Sjögren's syndrome with dry eye; [b]non-SS-DE, dry eye not associated with Sjögren's syndrome; [c]SJS-DE, Stevens–Johnson syndrome with dry eye; [d]CP, control patients; [e]C, healthy volunteers as a control.

Dental caries in dry eye patients

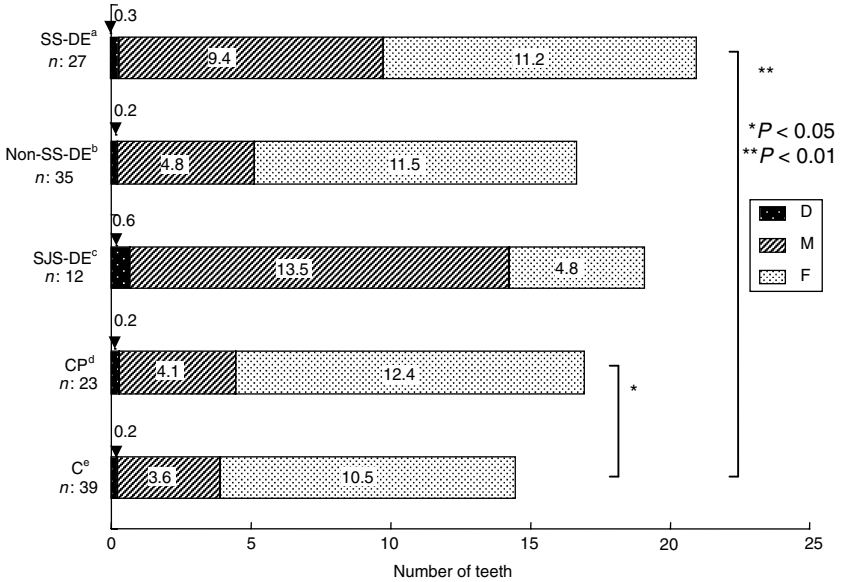
Figure 1 shows the decayed, missing, and filled teeth for the three groups of dry eye patients and the control groups. The mean DMFT index of SS-DE was significantly higher than that of C ($P < 0.01$). A significant difference was also observed in the DMFT index between CP and C ($P < 0.05$). The number of decayed and missing teeth in SJS-DE was the highest in any of the groups.

Changes in the oral soft tissue

Tables 3–5 show the condition of the oral soft tissues in subjects. We excluded SJS-DE groups because the number of patients was insufficient for statistical analysis. A significantly higher proportion of patients with dry eye had one or more oral soft tissue lesions than did both the CP and C groups ($P < 0.05$). Another characteristic of the patients with SS-DE was an association with redness of the buccal mucosa (22%), groove on the tongue (33.3%), and angular cheilitis (44.5%). Additionally, the patients with non-SS-DE were more likely to manifest atrophy on the surface of the tongue (27.8%) and groove on the tongue (27.8%) than other oral soft tissue lesions. It was also observed that CP and C groups had one or more oral soft tissue lesions, particularly, atrophy on the surface of the tongue (CP: 4.8%, C: 13.5%) and groove on the tongue (CP: 9.5%, C: 2.7%).

Detection rate of Candida *in dry eye patients*

Figure 2 shows the detection rate of *Candida* in subjects. Dry eye patients had significantly more *Candida* than CP and C groups ($P < 0.05$). The *Candida* cultures were positive in 76.0% of all the SS-DE, 56.7% of non-SS-DE, and 50.0% of SJS-DE, whereas 9.1% of CP and 28.6% of C were positive for *Candida* cultures. *C. albicans* and *C. glabrata* were the most frequent species found on tongue and denture surfaces.



a: SS-DE: Sjögren's syndrome with dry eye
b: Non-SS-DE: Dry eye not associated with Sjögren's syndrome
c: SJS-DE: Stevens-Johnson syndrome with dry eye
d: CP: control patients
e: C:healthy volunteers as a control

Figure 1 DMFT index in subject groups: SS-DE, Sjögren's syndrome with dry eye; non-SS-DE, dry eye not associated with Sjögren's syndrome; SJS-DE, Stevens–Johnson syndrome with dry eye; CP, control patients; and C, healthy volunteer controls

Table 4 Condition of the tongue in subjects

Subjects	*n*	*Normal (%)*	*Atrophy of surface of the tongue (%)*	*Groove on the tongue (%)*	*Shiny tongue (%)*	*Strawberry tongue (%)*
SS-DE[a]	18	27.8	16.7	33.3	16.7	5.6
Non-SS-DE[b]	18	44.8	27.8	27.8	0	0
CP[c]	21	85.7	4.8	9.5	0	0
C[d]	37	83.8	13.5	2.7	0	0

[a]SS-DE, Sjögren's syndrome with dry eye; [b]non-SS-DE, dry eye not associated with Sjögren's syndrome; [c]SJS-DE, Stevens–Johnson syndrome with dry eye; [d]C, healthy volunteers as a control.

Table 5 Angular cheilitis in subjects

Subjects	*n*	*Normal (%)*	*Slight angular cheilitis (%)*	*Heavy angular cheilitis or slight angular cheilitis at both corners of the mouth (%)*
SS-DE[a]	18	55.6	16.7	27.8
Non-SS-DE[b]	18	77.8	22.2	0
CP[c]	21	100	0	0
C[d]	37	94.5	2.6	0

[a]SS-DE, Sjögren's syndrome with dry eye; [b]non-SS-DE, dry eye not associated with Sjögren's syndrome; [c]CP, control patients; [d]C, healthy volunteers as a control.

Relationship between subjective symptoms of dry mouth and salivary flow rates

The patients with dry eye complained of a sensation of dry mouth than the control subjects more frequently (47.5% *vs* 4.9%; $P < 0.05$) (Table 6). Their stimulated whole and parotid salivary flow rates were lower than those of patients who complained of only an occasional sensation of a dry mouth or no symptoms of dry mouth ($P < 0.01$) (Table 7).

Table 6 Sensation of dry mouth in subject groups

Sensation of dry mouth	*n*	*Frequent (%)*	*Occassional (%)*	*No symptoms (%)*	
Dry eye patients*	141	47.52	27.66	18.44	]**
Controls	82	4.88	8.54	86.59	]**

*Dry eye patients SS-DE, non-SS-DE, and SJS-DE.
**$P < 0.05$.

Discussion

This study was conducted to compare the association of oral signs and symptoms in dry eye patients. When stimulated whole and parotid saliva was considered, lower secretion rates were observed in SS-DE. Atkinson *et al* (1990) reported that the stimulated flows of submandibular/sublingual glands were also below normal in 56 of 64 patients. In our study, patients with non-SS-DE also suffered from the sensation of a dry mouth, and the flow rates of their stimulated whole and parotid saliva were lower than those of the control groups. This study also showed that the salivary flow rates in

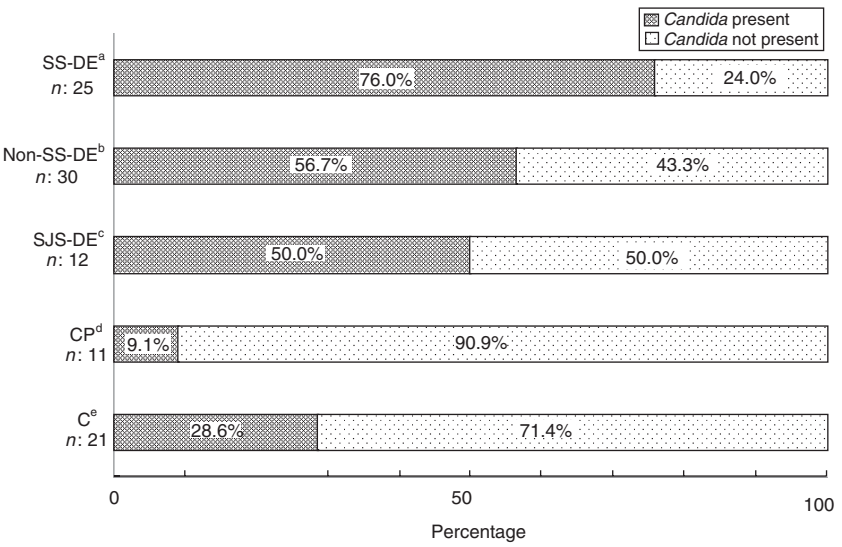


Figure 2 Condition of buccal mucosa in subject groups: SS-DE, Sjögren's syndrome with dry eye; non-SS-DE, dry eye not associated with Sjögren's syndrome; CP, control patients; C, healthy volunteer controls

Table 7 Realtionship between sensation of dry mouth and salivary flow rates in dry eye patients

	Sensation of dry mouth		
Salivary flow rates in dry eye patients	*Frequent*	*Occassional*	*No symptoms*
Stimulated whole salivary flow rate (ml min^{-1})	0.45 ± 0.48 ($n = 43$)	0.60 ± 0.48 ($n = 37$)	1.08 ± 0.67 ($n = 45$)
Stimulated whole salivary flow rate [ml (5 min^{-1})]	2.18 ± 2.03 ($n = 41$)**	2.56 ± 1.98 ($n = 28$)**	3.86 ± 2.14 ($n = 38$)**

Values are give as mean ± s.d.
**$P < 0.01$.

stimulated whole and parotid saliva in SJS-DE were lower than those in the control groups. In fact, SJS patients complained of a sensation of dry mouth and stomatitis. It might be inferred from these data that the salivary gland and oral mucosa were also damaged by an aberrant reaction. Although the ocular and skin manifestations in SJS are often reported, little information is available about the relationship of oral symptoms and salivary flow.

Dry mouth results not only from SS, but also from medical treatments such as medication, radiation, and chemotherapy, which all decrease salivary flow. Multiple medications in older patients make them more susceptible to dry mouth. Sreebny and Schwartz (1986) described how increased drug intake was positively correlated with age. Further, the total number of drugs taken was positively correlated with the prevalence of xerostomia. Wijers *et al* (2002) demonstrated that of 39 patients treated with radiation therapy between 1965 and 1995, 64% experienced a moderate to severe degree of permanent xerostomia. With respect to age and salivary flow, resting saliva was negatively correlated with age among females (Heintze, Birkhed and Björn, 1983) and stimulated saliva exhibited no diminution with increased age (Baum, 1981).

It is generally accepted that inadequate salivation is commonly associated with increased dental caries (Papas *et al*, 1993), complaints of frequent sores on the tongue, cheeks, and lips, and the growth of *Candida*. Our studies showed that dry eye patients exhibited a high DMFT index, high detection rate of oral *Candida*, and changes in oral soft tissues. The DMFT index of 27–61-year-old SS patients reported by Christensen *et al* (2001) was similar to that found in the present study. Furthermore, patients with SJS-DE suffering from dry eye also had a higher prevalence of decayed and missing teeth. These results suggest that an insufficient amount of saliva can induce dental caries. It may be difficult for such patients to visit a dental clinic alone because of the loss of their eyesight, which could therefore also affect their oral care.

Rhodus *et al* (1997) stated that 80% of all SS patients were positive for *C. albicans* but that the amount of *C. albicans* was not related to the salivary flow rate. However, other researchers have reported that the prevalence of *C. albicans* was significantly higher at almost all sites in SS patients and that there was an approximately inverse relationship between the *Candida* population and the rate of salivary flow (Tapper-Jones, Aldred and Walker, 1980; Torres *et al*, 2002). Our study also demonstrated that over half of dry eye patients had *Candida* (76% of SS-DE, 56.7% of non-SS-DE, and 50.0% of SJS-DE) but the presence of *Candida* was not correlated with a decrease in either of whole and parotid salivary flow rates.

Soft tissue changes were more prevalent in dry eye patients. These finding are not related to the volume of the stimulated salivary flow rates. Regarding oral mucosal pathology, Sweeney *et al* (1994) demonstrated that 24% of geriatric patients had denture stomatitis, 16% had angular cheilitis, and 41% had atrophic glossitis. In that study, patients with mucosal disease had significantly lower serum iron concentrations in their blood. Other researchers showed that the prevalence of *Candida*, fissured tongue, irritation fibroma, and traumatic ulcers were seen more frequently in patients with insulin-dependent diabetes (Guggenheimer *et al*, 2000).

Of the dry eye patients in this study, the volume of both stimulated whole saliva and parotid saliva were low which accounted for over half those having the sensation of dry mouth. However, 18% of dry eye patients whose volume of saliva was similar to the control group did not have the sensation of oral dryness. These results suggest that the association with the sensation of dry mouth was relatively consistent with the objective evaluation about the volume of saliva in dry eye patients.

In conclusion, a sensation of oral dryness frequently occurs in all types of dry eye patients and that the decreased salivary flow rates, changes in oral soft tissues, dental caries, and high prevalence of *Candida* are relevant in dry eye patients. When dry eye patients are treated, their oral conditions should be closely examined.

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