



# Minor salivary glands function is decreased in hyposalivation-related diseases



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## ABSTRACT

**Objectives:** The aim of this cross-sectional study was to investigate the relationship between minor salivary gland (MSG) flow rates and oral dryness degrees in patients with xerostomia induced by primary Sjögren's syndrome (pSS), IgG4-related sialadenitis (IgG4-RS), radiation therapy-induced dry mouth (RTDM), or Steven–Johnson syndrome (SJS).

**Design:** 160 patients with pSS, IgG4-RS, RTDM, or SJS and their age- and sex-matched healthy control subjects were enrolled. The whole saliva flow rates and MSG flow rates were measured in four locations, including the upper labial, lower labial, buccal, and palatal mucosae. The degree of oral dryness was assessed in patient groups using the summated xerostomia inventory (SXI).

**Results:** The flow rates of whole saliva and most MSGs in patient groups were significantly lower than the flow rates in healthy control groups ( $P < 0.05$ ). The mean relative percentage of decrease in saliva flow rates was smaller in MSGs than in whole saliva in patient groups ( $P < 0.05$ ), indicating that these disorders have less impact on MSGs. Among the four MSG locations (the upper labial, lower labial, buccal, and palatal), buccal glands showed the highest flow rates in patient groups ( $P < 0.05$ ). SXI scores were significantly higher in pSS and RTDM patients than in IgG4-RS and SJS patients ( $P < 0.05$ ). The degree of xerostomia varied among different patient groups ( $P < 0.05$ ) and there was no clear correlation between MSG flow rates and SXI scores ( $P > 0.05$ ).

**Conclusions:** MSG function is significantly reduced in pSS, RTDM, IgG4-RS, and SJS patients, but this reduction is more pronounced in the major salivary glands.

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## 1. Introduction

The oral cavity has 600–1000 minor salivary glands (MSGs) scattering beneath the labial, buccal, palatal, and lingual mucosa. The saliva secreted by MSGs accounts for less than 10% of the whole saliva (Dawes & Wood, 1973). However, due to their close proximity to the oral mucosa, continuous supply of small amounts of saliva, and high concentration of protective substances such as mucins and IgA, MSGs play a significant role in oral functions, including protection and lubrication of the oral mucosa, as well as maintaining taste and oral mucosal immunity (Eliasson & Carlen,

2010). Moreover, MSGs play a major role in saliva production during sleep; therefore, a decreased MSG flow rate appears to account for night-time dry mouth (Dijkema et al., 2012). A correlation between MSG flow rates and the thickness of the residual saliva film on the oral mucosa has been observed, suggesting that MSG saliva secretion is important for the subjective sensation of dry mouth (Won, Kho, Kim, Chung, & Lee, 2001). This view is further supported by observations that local areas of dry mucosa can trigger dry sensation (Dawes, 1987). Satoh-Kuriwada et al. proposed that dry mouth is more strongly related to reduction in labial saliva flow than to decrease in stimulated whole saliva (Satoh-Kuriwada, Iikubo, Shoji, Sakamoto, & Sasano, 2012). However, hyposalivation is generally defined as an unstimulated whole saliva flow rate of  $< 0.1$  ml/min or a stimulated rate of  $< 0.7$  ml/min, and very few studies have focused on MSG flow rates in patients with dry mouth (Ericsson & Hardwick, 1978; Satoh-Kuriwada et al., 2012).

**Abbreviations:** pSS, primary Sjögren's syndrome; IgG4-RS, IgG4-related sialadenitis; RTDM, radiation therapy-induced dry mouth; SJS, Steven–Johnson syndrome; HNC, head and neck cancer; MSG, minor salivary gland; SXI, summated xerostomia inventory.

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Severe hyposalivation caused by Sjögren's syndrome (SS) and radiation therapy (RT) for head and neck cancer (HNC) is frequently confronted in the clinic of oral medicine. Flow rates of the labial glands in pSS and RT patients were reportedly lower than in control subjects (Eliasson, Almstahl, Lingstrom, Wikstrom, & Carlen, 2005). IgG4-related sialadenitis (IgG4-RS), which has main characteristics of enlarged salivary and lacrimal glands and decreased saliva secretion, is a component of IgG4-related diseases. Considering its close relationship with Mikulicz disease, IgG4-RS was once considered identical to primary SS, which are now recognized as separate diseases (Himi, Takano, Yamamoto, Naishiro, & Takahashi, 2012; Masaki, Sugai, & Umehara, 2010).

In 1997, Murube-del-Castillo proposed transplantation of MSGs as a treatment for severe dry eyes secondary to Steven-Johnson syndrome (SJS) (Geerling, Raus, & Murube, 2008). SJS, also known as erythema multiforme major, is a life-threatening reaction of the skin to particular types of medication. Not only skin and mucosal membranes, but also salivary and lacrimal glands are often involved, resulting in dry eye and dry mouth (Sant', Hazarbassanov, de Freitas, & Gomes, 2012; Saeed, Mantagos, & Chodosh, 2016). However, no previous study has evaluated MSG functions in IgG4-RS and SJS patients.

Although the underlying pathogenesis appears different, all four conditions exhibit certain levels of salivary gland hypofunction. Previously, we investigated the characteristics of MSG flow rates in healthy individuals (Wang, Shen, Liu, Si, & Yu, 2015). The present study was designed to further investigate the characteristics of MSG flow rates in patients with hyposalivation-related diseases and to examine the potential relationship between MSG flow rates and the degree of oral dryness.

## 2. Materials and methods

### 2.1. Subjects and study design

As the main objectives of this study is to compare flow rates of MSGs between patient groups and healthy controls, the formula for comparison between independent quantitative samples was used to calculate the sample size. Based on our preliminary study, a sample size of 26–37 patients or healthy subjects was needed (Wang et al., 2015). From June 2014 to May 2015, 160 patients with pSS, IgG4-RS, RTDM, or SJS were enrolled in this study. All patients were referred to the Department of Oral and Maxillofacial Surgery or Department of Oral Medicine at the Peking University School of Stomatology or the Department of Ophthalmology at the Beijing Tong Ren Hospital, Capital University of Medical Science. Information pertaining to age, sex, disease duration, smoking, allergies, comorbidities, drug consumption, number of remaining major salivary glands, and radiation dose received was recorded. Disease duration was defined as the period from the initial observation of dry mouth or enlargement of major salivary glands to first visit. Measurements were performed in all patients before

possible submandibular/labial gland biopsy in the pSS and IgG4-RS groups. The inclusion/diagnostic criteria for each patient group were described below.

SS patients were required to meet the American-European Consensus Group criteria for pSS (Vitali et al., 2002). None of the patients were receiving treatment with steroids or immunosuppressive agents.

IgG4-RS was diagnosed according to the following criteria: (1) persistent (> 3 months) swelling in more than one major salivary glands; (2) elevated serum IgG4 level (> 135 mg/dl); and (3) infiltration of IgG4-positive plasma cells in the tissue (IgG4-positive plasma cells/IgG-positive plasma cells ratio > 0.4 according to immunostaining). In addition, it was necessary to rule out other disorders such as sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer (Li et al., 2015).

RTDM was diagnosed according to the following criteria: (1) history of head and neck cancer originating in the oral cavity, oropharynx, or nasopharynx; (2) history of treatment with surgery and postoperative radiotherapy or radiotherapy alone; (3) total radiation dose received was above 40 Gy; (4) no past history of RT or malignancies; and (5) absence of local recurrence or distant metastases.

The inclusion criteria for patients in the SJS group were as follows: (1) history of SJS caused by allergy to drugs or an infectious process; (2) persisting symptom of dry eyes despite previous ophthalmologic treatment including application of artificial tears and punctal plugs, and (3) ophthalmologic evaluation: Schirmer test < 2 mm, break-up time (BUT) < 5 s, and fluorescence staining (+) (Qin et al., 2013).

Each disease group had the same number of patients: pSS group: 40 women (median age 55.5 years; age range, 26–71 years); IgG4-RS group: 16 women and 24 men (median age 56 years; age range, 23–81 years), RTDM group: 15 women and 25 men (median age, 55.5 years; age range, 27–83 years), and SJS group: 21 women and 19 men (median age, 25 years; age range, 7–62 years). The control group for each patient group consists of 40 age- and sex-matched individuals without dry mouth, dry eye, or clinical evidence of any systemic disease (Table 1). The study was designed and conducted in complete accordance with the World Medical Association Declaration of Helsinki (version 2002), and it was approved by the Ethics Committee of the Peking University School of Stomatology (PKUSSIRB: 201412003). All experiments were undertaken with the understanding and written consent of each subject.

### 2.2. Dry mouth questionnaire

The intensity of mouth dryness in patients was assessed using the summated xerostomia inventory (SXI), which included the following five questions: "my mouth feels dry," "I have difficulty in eating dry foods," "my mouth feels dry when eating a meal," "I have difficulties swallowing certain foods," and "my lips feel dry". The

**Table 1**  
Basic information in pSS, IgG4-RS, RTDM and SJS groups and healthy controls.

		N	Sex (M/F)	Median age (years)	Age range (years)	Median duration (months)	Num	Total RT dose (Gy)
pSS	Control	40	0/40	50.5	26–74	0	6	0
	Patients	40	0/40	55.5	26–71	40	6	0
IgG4-RS	Control	40	24/16	57.5	23–83	0	6	0
	Patients	40	24/16	56	23–81	12	6	0
RTDM	Control	40	25/15	57	27–83	0	6	0
	Patients	40	25/15	55.5	27–83	10	4.9 ± 0.3	58.2 ± 10.4
SJS	Control	40	19/21	26	5–62	0	6	0
	Patients	40	19/21	25	7–62	54	6	0

N represents number of patients in each group; num represents the number of remaining major salivary glands.

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