

## Oral health of Chinese people with systemic sclerosis

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**Abstract** The aim was to study oral health status, salivary function, and oral features of Chinese people with Systemic Sclerosis (SSc). Chinese people with SSc attending a university specialist clinic were invited for a questionnaire survey and a clinical examination. Ethics approval was sought (UW 08-305). Gender- and age-matched individuals without SSc who attended a university dental hospital were recruited for comparison. Forty-two SSc patients with a mean age of  $54.0 \pm 12.2$  were examined. This study found no Chinese people with systemic sclerosis were periodontally healthy and many (76%) had periodontal pockets despite most of them (93%) practiced daily tooth-brushing. They all had caries experience (DMFT=10.5) and many (65%) had untreated decay. Mucosal telangiectasia was a common oral feature (80%). They had lower resting salivary flow rates ( $0.18 \pm 0.17$  ml/min vs.  $0.31 \pm 0.21$  ml/min;  $p=0.003$ ) and pH values ( $6.90 \pm 0.40$  vs.  $7.28 \pm 0.31$ ;  $p<0.001$ ) and reduced maximal mouth opening ( $40.1 \pm 6.5$  mm vs.  $43.6 \pm 7.0$  mm) than people without SSc.

**Keywords** Scleroderma · Systemic Sclerosis · Caries · Periodontal status · Chinese

### Introduction

Scleroderma is a symptom of a group of diseases that involve the abnormal growth of connective tissue, which supports the skin and internal organs [1]. It has two broad categories which are localized scleroderma (LS) and systemic sclerosis (SSc) [2]. LS is a disorder of the skin and sometimes the deeper tissues. The most visible effects of the disease are skin lesions which are often referred as morphea. Morphea may only cause cosmetic problems, but generalized morphea or linear scleroderma has widespread skin lesions in which scarring spreads down to the underlying structures. SSc indicates a more extensive skin involvement and even internal organ diseases. It is a clinically heterogeneous, systemic disorder which affects the connective tissue of the skin, internal organs, and the walls of blood vessels.

Diagnosis of SSc is largely dependent on medical history and physical examination. The signs included changed skin appearance and texture, calcium deposits developing under the skin and changes in the tiny blood vessels at the base of the fingernails. Hematological screening may also be employed to confirm the diagnosis [1]. Patients suffering from SSc usually exhibit CREST syndrome. The acrostics CREST stands for calcinosis—calcium deposition in soft tissue, Raynaud's phenomenon—color change in fingers and toes, esophageal dysfunction—decreased mobility of esophagus, sclerodactyly—deformity of extremities, and telangiectasia—dilation of terminal vessels. CREST syndrome also has various degree of connective tissue fibrosis.

The etiology of Systemic Sclerosis remains uncertain. It is believed that SSc is of autoimmune origin that leads to fibrosis of the skin and various internal organs and thus it has been grouped under the subject of rheumatology [1]. The prevalence of SSc ranged from 4 to 286 per million

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and the incidence reported varied from 0.6 to 22.8 per million per year [3–12]. It affects more female and mean age of SSc people reported by many studies was in the range of 46 to 54 years of age (Table 1).

Constriction of the oral orifice is a common finding among people with SSc [13]. Clinical findings such as periodontal disease, widening of periodontal ligament space (Fig. 1), loss of tongue mobility, oral mucosal telangiectasia (Fig. 2), and salivary hypofunction were reported (Table 1). People with SSc are at risk of dental caries, oral ulcers, and fungal infections [14]. Erosion of facial bones may be found. Individual studies and case reports have shown osseous resorption at mandibular angles, coronoid processes, and zygomatic arches [15, 16].

Studies on oral health status and oral features of people with SSc were limited and mainly conducted on Caucasians. So far, there is no study in English reporting the oral features of Chinese people with SSc. This study aims to investigate the oral health status and oral features of Chinese people with SSc.

## Methods

### Study sample

All Chinese people with SSc attending the Rheumatology Clinic of the Queen Mary Hospital, The University of Hong Kong in Hong Kong were invited to participate in this study by telephone. A group of people without SSc who had records in the Prince Philip Dental Hospital, The University of Hong Kong during the study period was selected as control. The participants with and without SSc were gender- and age-matched. In case the participant with SSc is edentulous, a sex- and age-matched edentulous person was recruited for comparison. The study was approved by the Institutional Review Board (UW 08-305). It was carried out from April to July 2008 in the Prince Philip Dental Hospital. The purpose and the protocol were individually explained to all invited patients; and written informed consent was obtained from each participant prior to admission to the study. The study was composed of two parts. The first part was a questionnaire survey. The second part was a clinical assessment which consisted of a salivary function test and an oral examination.

### Questionnaire survey

The participant's personal data, oral hygiene habits (toothbrushing and use of other oral hygiene aids) and satisfaction with oral health were asked in the questionnaire survey. Subjective dry-mouth symptoms were assessed by Xerostomia Inventory (XI) [17]; which comprised 11 questions

to assess the negative impacts of xerostomia. Respondents were asked to choose one of five responses ("never", scoring 1; "hardly ever", 2; "occasionally", 3; "fairly often", 4; and "very often", 5) to the following statements referring to the previous 4 weeks: "My mouth feels dry"; "I have difficulty in eating dry foods"; "I get up at night to drink"; "My mouth feels dry when eating a meal"; "I sip liquids to aid in swallowing food"; "I suck sweets or cough lollies to relieve dry mouth"; "I have difficulties swallowing certain foods"; "The skin of my face feels dry"; "My eyes feel dry"; "My lips feel dry"; and "The inside of my nose feels dry". Each individual's responses were scored and summed to give a single XI score. A higher XI score indicates more severe subjective symptoms of xerostomia. Completed questionnaire forms were checked immediately when they were returned so that there was no missing or unclear answers.

### Sialometric assessment

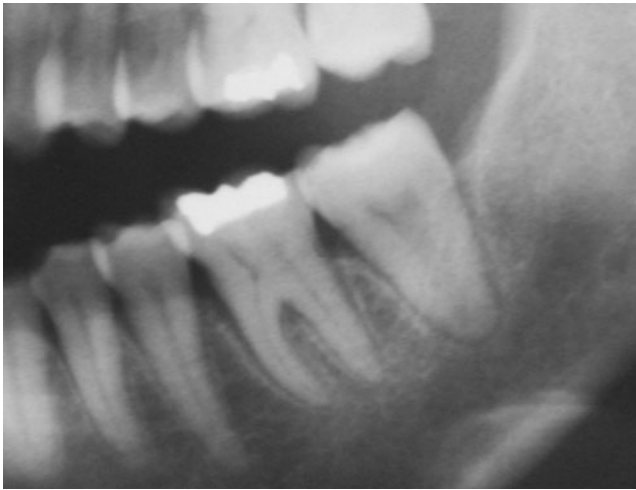
Sialometric assessment was performed on the resting and stimulated whole salivary flow rate and acidity of saliva to assess the salivary function. Assessment of salivary flow rate was performed following the method described by Navazesh and Christensen [18]. Participants who were suffering from sialadenitis were excluded. The participants were asked not to eat, drink, and smoke within an hour before the sialometric assessments. After rinsing their mouth with 10 ml phosphate-buffered saline for 30 s, they were asked to expectorate their saliva for 10 min. This procedure was repeated to study the whole salivary flow rate by chewing on a piece of 15-mm sterilized silicone rubber tubing (Masterflex 964DD-14, Cole-Parmer, Illinois, USA) for 5 min while they expectorated all saliva stimulated. The salivary pH was measured with a pH meter (Sentron 501Pocket FET pH meter, Sentron, Washington, USA). All measurements were made at the chairside immediately after saliva collection.

### Clinical examination

Two calibrated examiners were involved in assessing the caries status and the periodontal status in the study. The maximum mouth opening was measured by the inter-incisal distance plus the overbite, as described by Wood and Branco [19]. The overbite was obtained with teeth in centric occlusion. The inter-incisal distance was measured by the distance between maxillary and mandibular central incisors in the midline when the mouth was maximally opened. Participants with missing central incisors were excluded from this part of investigation. Oral mucosal, periodontal, and tooth conditions were examined under optimal lighting using the World Health Organization

**Table 1** Main findings of clinical studies on people with Systemic Sclerosis

Investigators (year)	Study site	Sample size	Mean age (range)	Main findings
Vincent et al. (2009) [31]	Nantes, France	30; 4 M, 26 F	59±14	Skin atrophy Peribuccal rhagades Telangiectasia Decreased mouth opening Xerostomia Xerophthalmia Periodontal ligament space widening Bone resorption Trigeminal neuralgia
Poole et al. (2005) [29]	Pennsylvania, USA	22; 1 M, 21 F	–	Decreased mouth opening Poor oral hygiene
Scardina et al. (2005) [46]	Palermo, Italy	15; 3 M, 12 F	62±8 (35–72)	Abnormalities in periodontal microcirculation
Scardina and Messina (2004) [41]	Palermo, Italy	31; 31 F	52±12	Trigeminal neuropathy Telangiectasia Retraction of oral frenulum Atrophy of oral mucosa Candidal infection Increased gingival bleeding Decreased mouth opening Salivary hypofunction Increased caries experience Mandibular resorption
Rout et al. (1996) [15]	UK	21; 6 M, 15 F	64 (36–81)	Widening of periodontal ligament space Tooth resorption Bone resorption
Nagy et al. (1994) [42]	Debrecen, Hungary	32; 3 M, 29 F	49±11	Telangiectasia of oral mucosa Decreased mouth opening
Wood et al. (1988) [21]	Canada	31; 31 F	52±12	Decreased mouth opening Increased caries experience Xerostomia Increased mobility of teeth Thickening of periodontal membrane Erosion of mandible
Alexandridis and White (1984) [35]	Los Angeles, USA	26	48 (30–85)	Thickening of periodontal ligament space
Eversole et al. (1984) [30]	San Francisco, USA	19; 2 M, 17 F	62 (25–80)	Symptoms referable to the TMJ Crenation of the buccal mucosa Hypomobility of the tongue
Marmary et al. (1981) [36]	Jerusalem, Israel	21	46±12 (27–63)	Elevated blood sedimentation rate Elevated antinuclear factor Limited mouth opening Gross jaw bone changes Widening of periodontal ligament space



**Fig. 1** Widening of periodontal ligament space in tooth 36

criteria [20]. Oral mucosal features were recorded. Diascopy test was used to examine blanching of telangiectasia lesions. Community periodontal index (CPI) was used to assess the periodontal condition and decayed, missing, filled teeth (DMFT) index for tooth status. The assessments were performed by two calibrated examiners using ruler, dental mirror, straight probe, and CPI probe. During the survey, about 10% of the dentate participants were randomly selected for re-examination by another examiner to assess the inter-examiner agreement.

#### Statistical analysis

Inter-examiner agreement on caries and periodontal assessment were computed using Cohen's Kappa statistics. The data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, USA). Chi-square test and Fisher exact test were used to study the oral hygiene habits (tooth-brushing and use of other oral hygiene aids), periodontal status, dental visit



**Fig. 2** Oral mucosal telangiectasia on lateral border of tongue

behavior, and dental satisfaction of people with and without SSc. Parametric *t* test was used to study resting and stimulated salivary flow rate and pH values, maximum mouth opening, caries experience (DMFT score), and the severity of subjective dry-mouth symptoms (summated XI score) of the participants. The cut-off point for statistical significance was set at 0.05.

#### Results

All 77 people (4 male, 73 female) with SSc registered in the Rheumatology Clinic were invited by telephone for this study. Eighteen hospitalized patients were not able to participate in this study. A total of 42 individuals with SSc, 1 male and 41 female, were examined. The response rate was 55%. Two examined participants with SSc were edentulous. These two participants, together with two age- and sex-matched participants without SSc, were excluded in assessments such as of periodontal examination and caries experience. Duplication examination was carried out in eight randomly selected participants. The Kappa statistics in the assessment of caries and periodontal status were 0.98 and 0.75, respectively.

The age of the 42 participants with SSc ranged from 29 to 79 and their mean age was  $54.0 \pm 12.2$ . Nine participants with SSc (including two edentulous SSc participants) did not have central incisors and were excluded in the study of maximal mouth opening. An age- and gender-matched group of 42 people without SSc were recruited as control for this study. All participants except one with SSc were non-smoker. They were examined in the Prince Philip Dental Hospital and all of them were provided with an orthopantomogram for dental check up purpose on request. The two groups of participants had no significant difference in education, employment status, family income, marital status, and number of family members.

#### Oral hygiene habits

Comparing patients with or without SSc, most practiced daily tooth-brushing (93% vs. 98%;  $p=0.59$ ). However, less patients practiced dental flossing (45% vs. 60%;  $p=0.43$ ). About one third of them used mouthrinses (33% vs. 40%;  $p=0.06$ ).

#### Salivary function

Among the 42 SSc participants, the mean resting salivary flow rate was  $0.18 \pm 0.17$  ml/min and the mean stimulated whole salivary flow rate was  $0.60 \pm 0.52$  ml/min (Table 2). They had significantly lower stimulated and resting salivary flow rate than people without SSc. In addition, they had

**Table 2** Sialometric assessment, Xerostomia Inventory score, and selected oral features of respondents

	People with SSc (N=42)	People with no SSc (N=42)	<i>p</i> value
Resting salivary flow rate (ml/min)	0.18±0.17	0.31±0.21	0.003
Stimulated salivary flow rate (ml/min)	0.60±0.52	0.81±0.43	0.048
Resting salivary pH value	6.90±0.40	7.28±0.31	<0.001
Stimulated salivary pH value	7.12±0.41	7.39±0.26	0.001
Xerostomia Inventory score	25.1±10.0	24.3±6.3	0.641
TMJ tenderness	3 (7%)	1 (2%)	0.317
Presence of telangiectasia (no.,%)	34 (81%)	0	<0.001
Maximal mouth opening <sup>a</sup> (mm)	40.1±6.5	43.6±7.0	0.038

<sup>a</sup> Total number of gender- and age-matched respondents for analysis was 66 (i.e., 33+33) as nine SSc respondents with missing incisors were excluded

significantly lower stimulated and resting salivary pH values. Although the XI score of participants with SSc was higher than that of the control group, the difference is not statistically significant.

#### Dental features

Erosion of coronoid processes was detected in one SSc participant. However, there was similar prevalence of participants with tenderness upon palpation on TMJ (Table 2). However, oral mucosal telangiectasia was commonly observed in SSc but not in non-SSc participants. The common sites were the lateral border of the tongue (Fig. 1) and buccal mucosa. No clinical evidence of common oral mucosal lesions such as candidal infection, recurrent aphthous ulceration, and lichen planus was found in all participants. Two edentulous SSc participants and 7 SSc participants who had at least one reference central incisor missing were excluded in measurement of mouth opening. The maximum inter-incisal mouth opening of SSc participants was significantly less than the control group.

#### Caries status

The number of teeth present between people with and without SSc was similar. (Table 3) There was no significant difference in the decayed (DT), missing (MT), filled (FT) teeth, and caries experience (DMFT) on the two groups of people. There was no statistically significant association found between caries experience of SSc people with salivary flow rate and extent of mouth opening.

#### Periodontal status

In this study, none of the participants was found to have healthy gum, i.e., scored CPI=0 as the highest score among the six sextants examined (Table 4). Most of the SSc participants (97%) had calculus and many of them (76%) had periodontally involved teeth (CPI>2). Despite more SSc people had pockets (76% vs. 55%) and required advanced

periodontal care, the difference was not statistically significant. There was no statistically significant difference between the presence of periodontal pocket with salivary flow rate or with extent of mouth opening for SSc people. There was also no significant difference of maximal mouth opening according the participants with highest CPI score.

#### Dental visit behavior and dental satisfaction

There were significantly less SSc people attending dental visits within a year than, but there was no significant difference between dental satisfaction between people with or without SSc (Table 5). There was no significant relationship between their satisfaction of oral health and the caries experience and the presence of advanced periodontal disease. Satisfaction of oral health also had no significant association with their subjective dry-mouth symptoms in this study.

#### Discussions

The Queen Mary Hospital, which has a specialist Rheumatology Clinic, serves about 0.6 million people living on the western Hong Kong Island. Since SSc is not a common systemic disease in Hong Kong, many physicians would refer their patients with SSc to Queen Mary Hospital for treatment and follow-up. There is no registered list of people with SSc in Hong Kong, but we might estimate the prevalence of SSc among Chinese people in Hong Kong is about 130 per million (77/600,000). This estimated rate is within the range of 4 to 286 per million reported in the literature [10, 12]. This study selected age- and sex-matched people who were registered in Prince Philip Dental Hospital for comparison. Both the Prince Philip Dental Hospital and the Queen Mary Hospital are located in the western part of the Hong Kong Island. Results showed that the two groups of participants had no significant difference in education, employment status, family income, marital status, and number of family members.

**Table 3** Number of teeth present and caries experience of respondents

	People with SSc ( <i>N</i> =40 <sup>a</sup> )	People with no SSc ( <i>N</i> =40 <sup>a</sup> )	<i>p</i> value
No. of teeth present	27.9±5.5	27.1±5.5	0.542
Decayed teeth (DT)	2.1±2.4	1.5±2.5	0.313
Missing teeth due to caries (MT)	4.1±5.5	4.9±5.5	0.542
Filled teeth (FT)	4.3±4.2	5.2±4.2	0.371
Caries experience (DMFT)	10.5±7.8	11.6±7.0	0.528

<sup>a</sup> Two patients were edentulous and excluded

The sample sizes of the ten reports found in the English literature search were between 15 and 32 (Table 1). This study invited all 77 registered people and 42 patients accepted our invitation. Despite a larger sample recruited in this study, the studied participants were by no means a representative sample. Hospitalized and institutionalized people with SSc might have had physical difficulties which hindered them to join this study. Despite this limitation, this study provides useful information of oral health status of Chinese people with SSc. It allows a rational understanding of the oral health status of people with SSc in Hong Kong.

The lower salivary pH value and flow rate of people with SSc might give rise to an increased risk of caries, difficulties in wearing denture, altered taste sensation, and pathological conditions such as burning mouth syndrome. Dry mouth is common among people with SSc and is a common cause of halitosis. Dentist should provide longitudinal assessment to monitor dry mouth for people with SSc. Salivary hypofunction is a disease symptom of scleroderma [21, 22]. Reduction in salivary flow will shift the balance of the oral microflora causing diseases. Dentist should suggest daily use of sugar-free chewing gum to increase the salivary flow rate [23]. Patients should be informed that chemical salivary stimulants are not very effective and pilocarpine can only increase salivary secretions for 1 to 2 h after administration [24].

Despite that the study had no SSc patient diagnosed with Sjögren's syndrome, dentist should check for Sjögren's syndrome as studies reported a 17% to 29% prevalence of Sjögren's syndrome in scleroderma patients [25–27]. The

decreased salivary flow rate may partly be due to fibrotic processes in salivary glands. Bertram [28] proposed resting whole saliva rate less than 0.1 ml/min was regarded as a sign of salivary hypofunction. Protection from saliva is impeded by salivary hypofunction. Therefore, prevention of caries and periodontal disease is the prime concern in the treatment plan for SSc patients. Their oral hygiene can also be compromised due to impaired manual dexterity and difficulties in handling oral hygiene aids [29]. Dentist should monitor and reinforce a tailor-made oral hygiene practice to patient with SSc. A helper-assisted tooth-brushing is helpful for those who cannot perform effective tooth-brushing. Topical fluorides such as 5% sodium fluoride varnish can be regularly applied by dentist to those SSc patients with high caries risk.

This study did not find that SSc has a significant impact on xerostomia because the XI score for SSc people was only slightly higher than people without SSc. The prevalence of xerostomia found is lower than that reported in previous studies (25% vs. 42% to 70%) [21, 30]. About one third of the people with SSc in this study showed a XI score equal to or more than 30. This could mean that SSc has a larger effect on some Chinese people with SSc in Hong Kong or more severe self-reported symptoms of dry mouth could be resulted from more severe scleroderma. Further clinical studies of these patients can be done to provide more information about possible correlation between SSc and oral health-related quality of life. Vincent et al. [31] reported SSc patients would have dental pain including trigeminal neuralgia. From the patient's view, this is one, if

**Table 4** Highest CPI score and periodontal treatment needed of respondents

	People with SSc ( <i>N</i> =40 <sup>a</sup> )	People with no SSc ( <i>N</i> =40 <sup>a</sup> )	<i>p</i> value
Highest CPI score (no., %)			0.176
0—Healthy	0	0	
1—Gingivitis	1 (3%)	3 (8%)	
2—Calculus	8 (20%)	15 (37%)	
3—Shallow pockets 4–5 mm	16 (40%)	13 (33%)	
4—Deep pockets ≥6 mm	15 (37%)	9 (22%)	
Periodontal treatment needed			0.058
Scaling and prophylaxis (CPI<3)	9 (23%)	18 (45%)	
Advanced periodontal care (CPI≥3)	31 (77%)	22 (55%)	

<sup>a</sup> Two patients were edentulous and excluded

**Table 5** Dental satisfaction and dental visit behavior of respondents

	People with SSc (N=40)	People with no SSc (N=40)	<i>p</i> value
Dental satisfaction			0.098
Satisfied	33 (79%)	25 (60%)	
Not satisfied	9 (21%)	17 (40%)	
Last dental visit			0.002
Within 1 year	14 (33%)	23 (55%)	
1 to 3 years	11 (26%)	16 (38%)	
More than 3 years or never	17 (41%)	3 (7%)	

not the most important symptom of severe SSc. However, no clinical pain parameter was recorded in this study.

This study found people with SSc had a significantly smaller maximum mouth opening. This is probably due to pathological changes in connective tissue resulting in a constricted oral orifice. Dentist should measure the maximum mouth opening during the oral examination. A maximum incisal opening of 40 mm or less would appear to warrant investigation as to its etiology [32]. A clinical study found the ability to open the mouth as shown by the oral and incisor aperture was significantly decreased in patients with poor oral hygiene [29]. Limited mouth opening makes dental treatment difficult and sometimes impracticable [13]. Dentist may recommend stretching exercises by placing the thumbs in opposite corners of the mouth and pulling outwards [29, 33, 34]. In addition, oral augmentation using tongue depressors between the back molars may increase oral aperture.

Wood et al. [21] suggested the poor periodontal health may be related to the reduced vascularity with resulting tissue ischemia in scleroderma individuals. This study found more people with SSc had periodontal pockets than people without SSc, but the difference is no significant. Studies reported a widening of PDL space in SSc patients [21, 31, 35, 36]. SSc is an autoimmune disease of collagen-vascular disorder characterized by increased collagen production and tissue fibrosis. Auluck [37] and Haers and Sailer [38] hypothesized the increased collagen production leads to hypertrophy of masticatory muscles. This produces excessive biting force and causes occlusal trauma to teeth, resulting in the widening of the periodontal ligament space in the absence of palpable periodontal disease. Gonzale and Coleman [39] suggested increased collagen synthesis in the periodontal ligament leads to increase in the bulk of the ligament. This is accommodated at the expense of alveolar bone, causing an increase in the width of the periodontal ligament space. Mehra [40] suggested the increased fibrosis of masticatory muscles and associated blood vessels of SSc people can cause ischemia and atrophy of masticatory muscles, which can reduce but not increase the biting forces. In addition, signs of occlusal trauma, such as

angular bone defect and mobility of teeth, were not seen in patients with systemic sclerosis. Further investigations are needed to identify the underlying reason of such radiographic observations.

This study also did not find an association of maximal mouth opening and the severity of periodontal disease despite some studies suggested there may be an association of reduced mouth opening and presence of periodontal disease [21, 41]. Oral mucosal telangiectasia was prevalent amongst the SSc people in this study. The common sites were lateral border of tongue and buccal mucosa of cheek. This finding agrees with previous reports [41, 42]. It was also reported that telangiectasia was commonly seen on the face, lips, tongue, and fingers [43]. Telangiectasia manifests as small red spots by swelling of tiny blood vessels beneath the skin. It could cause cosmetic problems if it appears on the hands and faces [1]. Previous studies found this group of patients had restricted tongue mobility [30, 44, 45]. Fibrotic changes of the tongue or lingual frenum may attribute to this phenomenon. In this study, it was observed that some participants had hypomobility of the tongue. Despite some mucosal lesions reported amongst people with SSc [14, 41], no common oral mucosal lesions such as candidal infection, recurrent aphthous ulceration, or lichen planus were observed in this study.

The dental satisfaction of people with SSc was similar to people without SSc. The oral hygiene practice of Chinese people with SSc in Hong Kong was generally good as almost all brushed their teeth at least twice a day. However, this study found that only a low percentage of people with SSc had regular dental visit to dentists, and was significantly less than the people without SSc. It is noteworthy that the control group was composed of patients who received or were receiving dental care in dental hospital, and thus could be biased in dental care utilization. Compared to the caries experience of the people without SSc, a similar caries experience among people with SSc was observed. This study found they had more untreated decay than the people without SSc but the difference was not significant. Since some oral changes may complicate dental treatment, it is essential for these people to receive

regular dental service for optimal oral health and prevention of oral diseases.

This study did not find that people with SSc had a poorer periodontal status than people without SSc. But it is noteworthy that none of our participants had healthy periodontium, and almost all of them had calculus deposits. The majority of them had periodontal pockets and needed advanced periodontal care. This study showed that periodontal disease was very prevalent and severe among Chinese people with SSc in Hong Kong.

## Conclusions

According to the results of this study, most of the Chinese people with SSc in Hong Kong had calculus on their teeth and the majority required advanced periodontal treatment. The caries risk would be high because of low salivary flow rate and salivary pH value. Many of them also had untreated decay. Periodontal and restorative treatment and tight recall for prevention and maintenance is essential. Mucosal telangiectasia was a very common oral feature. They also had a reduced mouth opening that might complicate dental care.

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**Conflicts of interest** The authors declare that they have no conflicts of interest and/or any financial interests in any of the used products.

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