

Semi-quantitative evaluation of salivary gland function in Sjögren's syndrome using salivary gland scintigraphy

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Abstract This retrospective study is designed to evaluate the diagnostic value of semi-quantitative parameters of salivary gland scintigraphy (SGS) in Sjögren's syndrome (SS) and explore the relationship between SGS parameters and salivary gland histopathologic manifestations. SGS and labial salivary gland biopsy were performed on 95 SS patients and 36 healthy age-matched and sex-matched volunteers. Uptake ratios at 15 min (UR_{15}) and stimulated excretion fraction (EF) of each parotid and submandibular gland were calculated automatically from SGS; histopathologic grades were classified based on focal lymphocytic infiltration, and biopsy focus scores were calculated simultaneously. As a result, the UR_{15} and EF of each salivary gland in SS patients were significantly lower than that in controls. Multivariate logistic regression equation was: $\text{logit } p = 6.965 - 1.680 \times UR_{15} \text{ of left submandibular gland} - 0.040 \times \text{EF of left parotid gland} - 0.050 \times \text{EF of right submandibular gland}$. The receiver operating characteristic (ROC) curve validated high efficiency of this model with

the area under curve of 0.911. And logistic regression analysis on combined original and validation cohorts confirmed its diagnostic value. Moreover, the EF of right parotid gland and both submandibular glands was correlated with histopathologic changes. Consequently, the semi-quantitative parameters of SGS may be helpful for diagnosing SS; UR_{15} of left submandibular gland, EF of left parotid gland, and EF of right submandibular gland are more powerful predictor of SS. Besides, SGS parameters reflect the degree of salivary gland involvement, severe patients with low parameters would have high histopathologic grades and biopsy focus scores.

Keywords Labial salivary gland biopsy · Salivary gland scintigraphy · Semi-quantitative parameters · Sjögren's syndrome

Introduction

Sjögren's syndrome (SS) is an inflammatory autoimmune disease characterized by focal lymphocytic infiltration and the destruction of exocrine glands, especially the salivary and lachrymal glands [1]. Xerostomia is the major manifestation resulting from the dysfunction of salivary glands. As for most patients lacking distinguishing signs and symptoms, evaluating salivary glands function is necessary and important to help in the early diagnosis of SS. Several measurements have been proposed to assess salivary gland functions, such as salivary flow rate, contrast sialography, salivary gland ultrasonography, and labial salivary gland biopsy [2–4]. These methods are either invasive or complex, which are not suitable for usual use. Compared with other methods, salivary gland scintigraphy (SGS) is a noninvasive, sensitive, safe, and objective technique. Not only the location and morphology of salivary glands can be obtained, but also quantitative parameters can be calculated. However, traditional SGS technique

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took too long and focused on qualitative measuring, such as delayed uptake, reduced concentration, and/or delayed and diminished excretion of the tracer [5]. Even though the procedure and quantitative parameters of SGS were explored widely, so far, there is no consensus on which SGS methods and parameters were more sensitive in evaluating salivary gland function [1, 6, 7]. Further efforts are still necessary to establish a sensitive and quantitative method using SGS in discriminating between SS patients and normal controls.

In this study, we aim to assess the function of salivary glands qualitatively and semi-quantitatively in SS patients and healthy volunteers using modified short time SGS with determined sensitive semi-quantitative parameters. By analyzing these data, we set a logistic regression equation for helping in the diagnosis of SS by using these parameters. Furthermore, the correlation between semi-quantitative parameters of SGS and histopathologic changes of labial biopsy in SS was also investigated.

Materials and methods

Subjects

Ninety-five patients with clinically diagnosed SS in our department were enrolled in this retrospective study. All patients met the classification criteria for SS (2002 American–European Consensus Criteria) [3]. It consisted of 75 primary SS patients and 20 SS patients associated with other autoimmune diseases including rheumatoid arthritis ($n=13$) and systemic lupus erythematosus ($n=7$). SGS and minor salivary gland biopsy were performed on all patients. Main characteristics of SS patients are summarized in Table 1.

Table 1 Main characteristics of the Sjögren's syndrome (SS) patients in this study

Features	SS patients
Number	95
Age (years), median (range)	49 (14–83)
Female/male	85/10
Xerostomia (+)/(-)	89/6
Xerophthalmia (+)/(-)	73/22
ANA (+)/(-)	80/15
Anti-Ro/SSA (+)/(-)	70/25
Anti-La/SSB (+)/(-)	40/55
Ocular tests (+)/(-)	81/14
Salivary gland biopsy (+)/(-)	48/47
Extraglandular features (+)/(-)	73/22
Rheumatoid factor (+)/(-)	55/35

ANA anti-nuclear antibody

Thirty-six healthy volunteers (29 females and seven males, age 12–68 years, median age 36 years) with no evidence of salivary gland dysfunction or no history of autoimmune diseases were also enrolled as a control group. Another 26 SS patients (20 females and six males, age 24–77 years, median age 47 years), 10 healthy subjects (nine females and one male, age 16–63 years, median age 31 years), and 22 patients with no-SS sicca syndrome (20 females and two males, age 15–74 years, median age 47.5 years) were included as validation subjects.

Salivary gland scintigraphy

Patients were in supine position with chin raised. After intravenous injection of 370 MBq ^{99m}Tc pertechnetate ($^{99m}\text{TcO}_4^-$), SGS was performed with single-photon emission computed tomography (SPECT) (Millennium VG, GE, USA), using a low-energy, high-sensitivity, parallel-hole collimator at 2 min per frame. The duration of the scan was 30 min with salivary secretion stimulated by oral administration of 0.1 g vitamin C at 15 min. The head was kept stationary during scintigraphy. Images were recorded in 64×64 matrix with 2.5 magnification. The energy window around 140 keV photopeak of ^{99m}Tc was 15 %.

Images and data analysis

Regions of interest (ROI) of each parotid and submandibular gland were drawn manually, with background ROI painted on the right temporal region. UR_{15} was defined as (salivary gland count at 15 min–background count)/background count and EF as (maximum salivary count before stimulation–minimum salivary count after stimulation)/(maximum salivary count before stimulation–background count)×100 %. In the absence of a gland visualization, a value of zero was given for the UR_{15} and EF. The images of SGS were analyzed by two experienced nuclear physicians independently.

Labial salivary gland biopsy

The minor salivary glands of the lower lip were routinely sectioned following the informed consent. The biopsy material was fixed in formaldehyde, embedded in paraffin, serially sliced, and stained by hematoxylin–eosin. All slices were carefully examined and then graded by an experienced pathologist. Histopathologic changes were classified from 0 to 4 according to the focal lymphocytic infiltration following Chisholm and Mason's grading criteria (grades 3 and 4 were defined positive) [3, 8]. On the other hand, we calculated the biopsy focus score on the basis of the number of lymphocytic foci every 4 mm² tissue, which reflected the histopathologic changes quantitatively.

Statistical analysis

All the scintigraphy parameters were expressed as means \pm SD. Initially, differences of parameters between patients and controls were compared using Student's *t* test. Multivariate stepwise binary logistic regression analysis was used to establish a logistic regression model helping in the diagnosis of SS by applying the parameters of SGS ($\alpha=0.05$, $\beta=0.10$). ROC analysis was performed and the area under curve (AUC) was calculated to evaluate the diagnostic efficiency of the model. The 26 SS patients and 10 healthy subjects were included as an independent validation group to confirm the predictive efficiency of SGS parameters. And the 22 patients with no-SS xerostomia were used to verify the diagnostic accuracy of the model in patients affected by no-SS sicca syndrome. In addition, the relationship between functional parameters of SGS and histopathologic grades, SGS parameters, and biopsy focus scores was assessed by Spearman rank correlation test. All statistical analyses were employed using statistical product and service solutions version 13.0 and $p < 0.05$ was considered statistically significant.

Results

Analysis of images in SGS

After intravenous injection of $^{99m}\text{TcO}_4^-$, images of parotid and submandibular glands became clear gradually in healthy volunteers and faded rapidly after oral administration of 0.1 g vitamin C at 15 min. Then, imaging agents were excreted into mouth. In contrast, images of patients with SS were not clear or could not be visualized, and the imaging agents are still located in parotid and submandibular glands after oral administration of vitamin C; the changes of oral images were not obvious (Fig. 1).

Comparison of SGS parameters between SS patients and controls

First, we made comparison of SGS parameters between primary SS patients and patients associated with other autoimmune diseases and found that there were no statistical differences in UR_{15} of each parotid and submandibular gland and EF of each parotid and left submandibular ($p > 0.05$), other than EF of right submandibular ($p = 0.01$). Then, the comparison of SGS parameters between patients with SS and healthy volunteers was made and results were shown in Table 2. The UR_{15} and EF of each parotid and submandibular gland in patients with SS were significantly lower than those in controls ($p \leq 0.001$). There was no statistical difference in bilateral scintigraphy parameters ($p > 0.05$). The

UR_{15} of the submandibular glands was significantly lower compared with parotid glands ($p < 0.05$), but not in the EF.

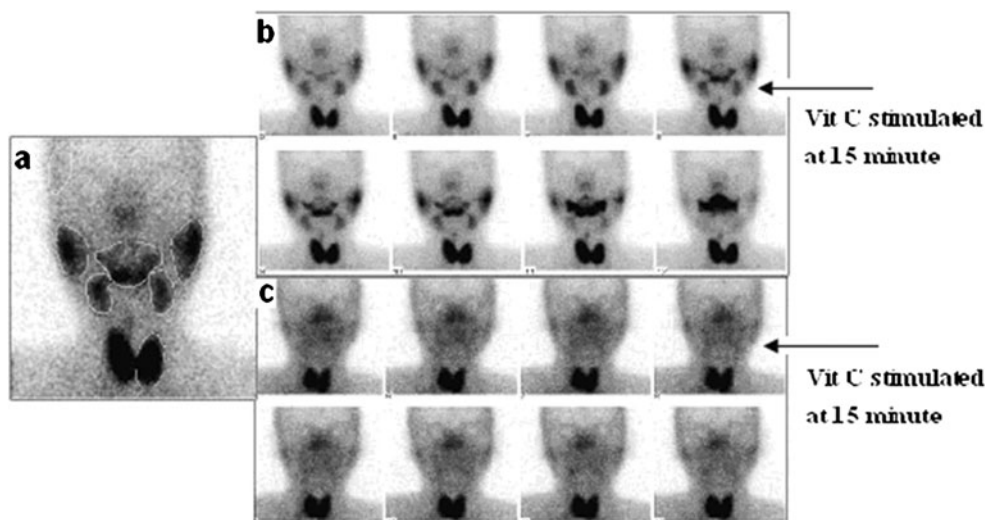
Logistic regression model and ROC analysis

We established a binary logistic regression model, determining diagnosis of SS as response variable and parameters of SGS as independent variable. Finally, UR_{15} of left submandibular gland (X1, $p = 0.004$), EF of left parotid gland (X2, $p = 0.001$), and EF of right submandibular gland (X3, $p = 0.023$) entered the model. The logistic regression equation was $\text{logit } p = 6.965 - 1.680 \times X1 - 0.040 \times X2 - 0.050 \times X3$, with odds ratio (OR) and 95 % confidence interval (CI) of 5.366 (1.711–16.834), 1.041 (1.017–1.066), and 1.051 (1.007–1.097), respectively. We evaluated the efficiency of the logistic regression model using ROC analysis (Fig. 2). The AUC was 0.911 ± 0.024 , with 95 % CI (0.863–0.959), which verified the diagnostic value of logistic regression model we established. The validation group is age and sex matched, and there was no statistical difference of SGS parameters between validations and previous subjects. Then, we performed the multivariate logistic analysis in the combined original and validation cohorts and found that X1 ($p = 0.002$), X2 ($p < 0.001$), and X3 ($p = 0.016$) have more sensitive diagnostic value for this combined cohorts, with OR and 95 % CI of 4.839 (1.748–13.394), 1.043 (1.021–1.066), and 1.046 (1.008–1.086), respectively. In the ROC analysis, AUC was 0.911 ± 0.022 , with 95 % CI (0.869–0.953). To verify the diagnostic accuracy of the model in SS patients and patients affected by no-SS sicca syndrome, we performed a validation analysis using the 95 SS patients and 22 patients with no-SS sicca syndrome. It showed that only X2 was statistical significant ($p = 0.031$); but not for X1 and X3.

Correlation between parameters of SGS and histopathologic changes

The relationships between parameters of scintigraphy and minor salivary gland histopathologic changes are demonstrated in Table 3. The EF of right parotid gland and both submandibular glands significantly decreased corresponding to the histopathologic grades ($p < 0.05$). These indicated that the tracer excretion ability of right parotid gland and both submandibular glands weakened along with higher histopathologic grades. There was no significant correlation between histopathologic grades and UR_{15} of each salivary gland or EF of left parotid gland ($p > 0.05$). Furthermore, the minor salivary gland biopsy focus scores of these 95 patients ranged from 0 to 6 with median of 1. The EF of right parotid gland and both submandibular glands was also negatively connected with the biopsy focus score, which reflected

Fig. 1 Salivary gland scintigraphy (SGS) images of Sjögren's syndrome (SS) patients and controls. **a** Regions of interest in SGS images. **b** SGS images of healthy volunteers. These images represent the normal pattern. **c** SGS images of patients with SS



histopathologic changes influencing the parameters of scintigraphy to a certain extent.

Discussion

SGS was a safe and sensitive method for assessing functions of salivary glands, and recent report showed that SGS even offered valuable clinical information for prognosis and outcome of the primary SS [9]. SGS has been suggested for diagnosing SS in 2002 American–European criteria with positive qualitatively described as delayed uptake, reduced concentration, and/or delayed and diminished excretion of the tracer [5]. Over the past decades, a variety of different quantitative parameters obtained from SGS such as percent uptake counts, gland to background ratio, time elapsed to peak counts, and magnitude of stimulated salivary excretion have been proposed; however, there has been no consensus

on which parameters will be more valuable and sensitive for the diagnosis of SS [1, 6, 7, 10, 11].

Previous researches took more than 40 min for SGS and analyzed peak uptake SGS parameters of salivary glands. However, the time of uptake peak ranged from 15 to 40 min, or even longer, and most traditional SGS took long to make patients uncomfortable. For this reason, we shortened the examination time to 30 min by modifying scintigraphic procedure and calculated UR_{15} and EF stimulated by vitamin C at 15 min. The UR_{15} of parotid and submandibular gland reflected the ability of uptaking imaging agent, and EF reflects ability of excreting imaging agent. In our study, semi-quantitative parameters of each parotid and submandibular gland are valuable indications for patients with SS, especially UR_{15} of left submandibular gland and EF of left parotid gland and right submandibular gland.

The results of our study showed that the parameters of each salivary gland were significantly different between

Table 2 Comparison of salivary gland scintigraphy parameters between Sjögren's syndrome (SS) patients and controls

Parameters SS (means \pm SD)		Patients, $n=95$	Controls, $n=36$	SS validations, $n=26$	Control validations, $n=10$
UR_{15}	LP*	1.68 \pm 1.09	2.89 \pm 1.07	1.53 \pm 0.94	2.50 \pm 0.86
	RP*	1.80 \pm 1.14	2.98 \pm 1.13	1.80 \pm 1.01	2.76 \pm 0.94
	LS*	0.87 \pm 0.50	1.49 \pm 0.56	0.72 \pm 0.44	1.09 \pm 0.20
	RS**	0.99 \pm 0.73	1.45 \pm 0.48	0.80 \pm 0.48	1.10 \pm 0.86
EF (%)	LP*	27.25 \pm 27.22	63.66 \pm 18.05	20.68 \pm 25.14	69.23 \pm 29.72
	RP*	27.93 \pm 25.24	64.45 \pm 19.96	18.56 \pm 25.42	64.32 \pm 23.48
	LS*	29.17 \pm 18.25	52.81 \pm 11.77	24.59 \pm 18.58	49.89 \pm 18.93
	RS*	29.03 \pm 17.26	51.97 \pm 12.66	19.05 \pm 17.01	47.63 \pm 16.41

UR_{15} uptake ratio at 15 min, EF excrete fraction, LP left parotid gland, RP right parotid gland, LS left submandibular gland, RS right submandibular gland, n number of patients

* $p<0.001$, between patients and controls

** $p=0.001$, between patients and controls

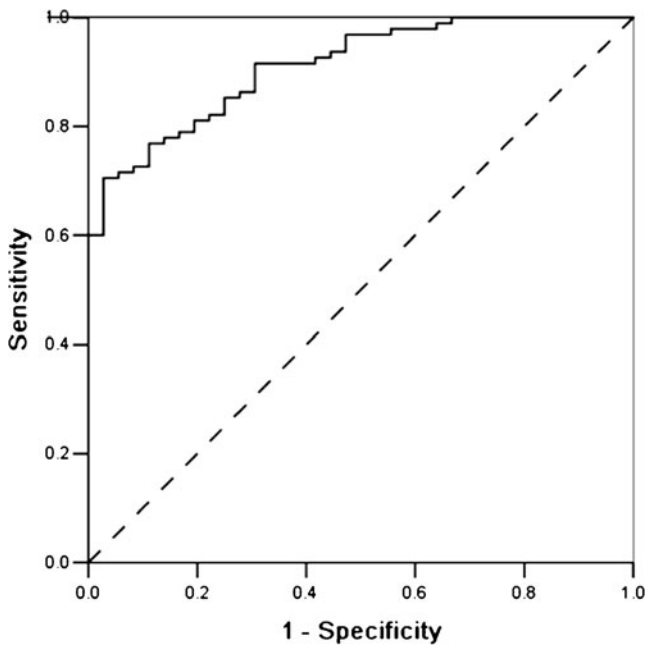


Fig. 2 Receiver operating characteristic curve for salivary gland scintigraphy parameters in discriminating between SS patients and controls

patients and the control group, and no statistical differences were found between primary SS patients and SS patients associated with other autoimmune diseases. The parameters of patients decreased in varying degrees, indicative of dysfunction of parotid and submandibular glands in patients with SS. The results were consistent with previous studies, indicating that our modified SGS is a sensitive method to evaluate salivary function [10, 12, 13]. Further investigation of these parameters by multivariate regression analysis showed that decreased UR_{15} of left submandibular gland and EF of left parotid and right submandibular were more

sensitive parameters for helping in the diagnosis of SS. These asymmetric changes may reflect the uneven nature of the inflammatory process. Adams and Seval also reported these asymmetric changes of salivary glands in patients with SS [14]. The logistic regression model showed that the parameters of submandibular glands contributed more for the diagnosis of SS, which indicated that the dysfunction of submandibular glands was more often in SS. Several researchers reported that the function of submandibular gland was more often affected than parotid gland in SS [15–17]. The mechanism of these asymmetric changes was still unknown. This might attribute to the differences in structure and function of these two salivary glands. Diagnosing SS is a complex procedure. We did not consider that UR_{15} of left submandibular gland and EF of left parotid gland and right submandibular gland together were enough to diagnose SS. Our results indicated that these parameters were more sensitive in evaluating the function of salivary glands. Patients affected by no-SS sicca syndrome were similar with SS patients for xerostomia, and with the same diminished salivary flow, which might become false positive [18]. However, these two kinds of patients have different pathophysiological changes in salivary glands, which might result in different semi-quantitative parameters. The results of our study show that the equation we formed has the ability to differentiate between these two kinds of patients.

Minor salivary gland biopsy for SS first proposed by Chisholm was believed to be the most sensitive diagnostic approach and has been regarded as “gold standard” in diagnosing SS [8, 19, 20]. The histopathologic hallmark was focal lymphocytic infiltration of the salivary glands, and the grading standard and focus score reflected the degree of inflammatory infiltration which indicated the damages of

Table 3 Correlation between salivary gland scintigraphy parameters and histopathologic changes in Sjögren's syndrome

Parameters	Histopathologic grades (means ± SD)						Biopsy focus score		
	1 (n=20)	2 (n=27)	3 (n=24)	4 (n=24)	p	r	p	r	
UR_{15}	LP	1.85±0.89	1.81±1.35	1.43±0.91	1.66±1.08	0.166	-0.143	0.193	-0.135
	RP	2.14±1.01	1.92±1.27	1.39±0.98	1.80±1.17	0.075	-0.183	0.096	-0.172
	LS	0.90±0.43	1.01±0.54	0.79±0.47	0.78±0.52	0.093	-0.173	0.051	-0.201
	RS	0.98±0.51	1.07±0.56	0.82±0.48	1.11±1.15	0.321	-0.103	0.174	-0.141
EF (%)	LP	30.78±28.77	29.48±31.73	24.13±21.33	24.92±26.82	0.572	-0.059	0.507	-0.069
	RP ^{*, **}	35.72±22.58	31.41±30.51	26.95±23.45	18.50±20.49	0.022	-0.235	0.024	-0.232
	LS ^{*, **}	32.84±14.36	31.94±18.60	29.81±18.01	22.35±20.16	0.032	-0.220	0.021	-0.236
	RS ^{*, **}	37.36±11.49	29.95±18.50	29.51±18.21	20.58±15.92	0.001	-0.325	0.002	-0.309

UR_{15} uptake ratio at 15 min, EF excrete fraction, LP left parotid gland, RP right parotid gland, LS left submandibular gland, RS right submandibular gland, n number of patients, r correlation coefficient

* $p < 0.05$, in histopathologic grades

** $p < 0.05$, in biopsy focus score

normal salivary gland formation. Even though labial biopsy provided definite evidence of the specific inflammation in SS, it did not give immediate functional information of salivary glands [21, 22]. In addition, the nature of invasion hampered its wide application. However, evaluating function of salivary glands distinctly was the greatest advantage of SGS. This character attracted interest of some researchers to explore the relationship between SGS parameters and histopathologic grades. There were controversies over association between inflammatory manifestations of labial biopsy and SGS parameters. An early study from Schall suggested that the quantitative parameters of SGS were not correlated with histopathologic grades [5]. However, with the development of SPECT and data analysis system, several authors reported that SGS characteristics connected well with histopathologic changes [1, 19, 21, 23, 24]. Our study demonstrated that the EF of right parotid gland and bilateral submandibular gland was correlated with minor salivary gland inflammation grades and focus scores. Conversely, the UR₁₅ of both parotid gland and submandibular gland was not correlated with the histopathologic grades. This indicated that SGS parameters reflected the degree of salivary gland involvement to some extent, and the excretion function parameters may be more sensitive than uptake parameters in diagnosing SS.

In summary, we believe that the modified semi-quantitative SGS is a safe and reliable method to evaluate salivary glands function in SS patients and can be suitable for clinical use for its noninvasive, sensitive, and objective merits. But it should be noted that this research still had several limitations. First, we just calculated semi-quantitative parameter; absolutely quantitative has not been achieved yet for patients' weight was not being recorded. Secondly, we drew the ROI of parotid and submandibular glands manually which increase the variability. When the images of the salivary glands were not clear enough, we could not draw the ROI accurately, leading to inaccurate parameters. Finally, our results show that there were overlap among SS patients and normal controls for the values of semi-quantitative parameters. The sample size in this study was not big enough and the results should be confirmed by further studies.

Conclusions

Salivary gland scintigraphy is a sensitive and noninvasive method to evaluate the function of salivary glands. Modified salivary gland scintigraphy with sensitive semi-quantitative parameters is valuable and essential for diagnosing Sjögren's syndrome, which is more convenient than traditional technique for its time-saving merit. The UR₁₅ of left submandibular gland and the EF of left parotid gland and right

submandibular gland are more sensitive parameters for evaluating the function of salivary glands in patients with SS, and the EF of right parotid gland and both submandibular glands are correlated with histopathologic manifestations.

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