Annals of Nuclear Medicine Vol. 17, No. 8, 627–631, 2003

Scoring analysis of salivary gland scintigraphy in patients with Sjögren's syndrome

Kazuya SHIZUKUISHI,* Shouhei NAGAOKA,** Yoshinori KINNO,*** Misao SAITO,*** Nobukazu TAKAHASHI,* Masami KAWAMOTO,* Aya ABE,* Lee JIN* and Tomio INOUE*

*Department of Radiology, Yokohama City University, School of Medicine
**Department of Rheumatology, Yokohama Minami Kyousai Hospital
***Department of Radiology, Yokohama Minami Kyousai Hospital

The purpose of the present study was to evaluate the validity of a scoring system based on excretion rate of salivary gland scintigraphy in patients with Sjögren's syndrome (SjS). Total scintigraphic scores were compared with the results of the Saxon test. One hundred and twenty-four subjects who were clinically diagnosed with SjS and 11 normal ones underwent salivary gland scintigraphy and the Saxon test. In salivary gland scintigraphy, the difference between maximum and minimum counts after stimulation using vitamin C divided by maximum counts was defined as the excretion rate. We then defined a scoring system with 4 grades: severe dysfunction = 3 (excretion rate < 25%), moderate dysfunction = 2 (25% ≤ excretion rate < 40%), mild dysfunction = 1 (40% ≤ excretion rate < 50%) and normal function = 0 (50% ≤ excretion rate). The summation of the total scintigraphic score (0–12) of all 4 salivary glands was used as a semi-quantitative index indicating total salivary gland function, and total scintigraphic scores were compared with the results of the Saxon test. A significant inverse linear correlation ($R^2 = 0.95$) was observed between total scintigraphic scores and mean values of the Saxon test within a range of abnormal scintigraphic scores (≥ 4). The scoring system developed in the present study is a clinically available, objective, and reproducible method for evaluation of salivary gland function in patients with SjS.

Key words: salivary gland scintigraphy, Sjögren's syndrome, Saxon test

INTRODUCTION

SJOĞREN'S SYNDROME (SjS) is an autoimmune disease characterized by a chronic inflammatory process involving the salivary and lacrimal glands. The assessment of salivary gland dysfunction is a required diagnostic criterion.

Labial salivary gland biopsy[1–4] is a reliable and useful method for diagnosing SjS; however, its invasiveness has limited the clinical use of this method. On the other hand, the Saxon test,[5] chewing gum test,[6] and salivary gland scintigraphy are equally useful alternative non-invasive methods for assessing salivary gland disease. The Saxon test and chewing gum test evaluate the amount of saliva excreted by chewing stimulation, which is a subjective examination requiring patient cooperation. Salivary gland scintigraphy with ^{99m}Tc-pertechnetate assesses salivary gland dysfunction by taste stimulation with vitamin C. Although this method appears to be objective, and has been proven to be useful for diagnosis of SjS, suitable quantitative parameters of salivary gland scintigraphy for evaluating the grades of salivary gland impairment have not been established.

In the present study, we devised and validated a patient-basis scoring system based on excretion rate of salivary gland scintigraphy, and compared the total scintigraphic scores with the results of the Saxon test in patients with SjS and normal volunteers.

Received March 5, 2003, revision accepted August 11, 2003.

For reprint contact: Kazuya Shizukuishi, M.D., Department of Radiology, Yokohama City University, School of Medicine, 3–9 Fukuura, Kanazawa-ku, Yokohama 236–0004, JAPAN.
E-mail: zeroishi@xa2.so-net.ne.jp

MATERIALS AND METHODS

Patients and normal volunteers

This retrospective study included 124 consecutive patients (122 women and 2 men; mean age 58.2 y; range 25–84 y) who were clinically diagnosed with SjS, according to the European Study Group on Diagnostic Criteria.[7] All patients and 11 normal volunteers (9 women and 2 men; mean age 60.9 y; range 33–79 y) underwent both salivary gland scintigraphy and the Saxon test at our institute. Written informed consent was obtained from all the normal volunteers.

Salivary gland scintigraphy

Patients fasted for 1 hour, and then after intravenous injection of 185 MBq ^{99m}Tc-pertechnetate, dynamic salivary gland scintigraphy was performed with a gamma camera (Stargem 3000; GE Medical), using a low-energy, high-resolution, parallel-hole collimator. Images were collected into a 128 × 128 matrix with a 140 keV photopeak for ^{99m}Tc. Anterior sequential salivary gland images were obtained at 30 s per frame for 30 min. Twenty minutes after the injection, a 5 m*l* solution containing 1 g of vitamin C was administered orally as a stimulus.

Saxon test

After the patient had swallowed the intra-orally excreted saliva, they bit and clamped down on a folded weighed piece of gauze for 2 minutes. The inserted gauze and a laboratory dish containing the remaining intra-orally saliva were weighed. The difference in weight was defined as the amount of excreted saliva. All patients underwent the Saxon test twice, and the average value of excreted saliva was defined as the result of the Saxon test for each patient.

Data analysis

After completion of the examination, regions of interest (ROIs) were drawn manually around each of the parotid and submandibular glands. Background ROI was marked in brain. Time-activity curves (TACs) over the salivary glands were generated and corrected for background radioactivity.[8] The difference between the maximum count and the minimum count after stimulation divided by the maximum count was calculated and the percentage of this value was defined as the excretion rate[9–11] (Fig. 1). A distribution of the excretion rate in the bilateral parotids and the excretion rate in the bilateral submandibular glands in each patient were estimated.

We classified the TACs of the parotid and submandibular glands into four types (normal type, poor excretion type, median type, flat type) (Fig. 2).

In addition to analysis of TAC patterns, the excretion rate was scored as belonging to one of four grades for each salivary gland. Based on the relationship between excretion rate and TAC type, we defined a scoring system with 4 grades. We employed the total scintigraphic score of all 4 salivary glands as a semi-quantitative index showing total salivary gland function for each patient.

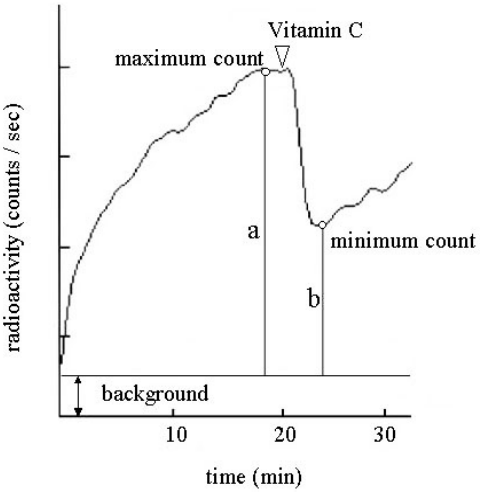

Fig. 1 Definition of excretion rate. Excretion rate was derived from time-activity curve in salivary gland scintigraphy: excretion rate = {maximum count (a) – minimum count (b)}/maximum count (a) × 100 (%)

Reproducibility study

We also assessed the reproducibility of the scoring system devised in the present study.[12,13] We selected 10 patients with varying combinations of TAC type. Two nuclear medicine technologists (M.S., S.U.) independently analyzed the scintigraphic data of these 10 patients. One technologist (M.S.) analyzed the data three times for each patient. Intraobserver and interobserver variance were then evaluated.

Statistical analysis

Differences in mean excretion rate among groups classified by TAC pattern were evaluated for statistical significance using a Student-Newman-Kuels test. The relationship between Saxon score and the total scintigraphic score was assessed using linear regression analysis. For the evaluation of reproducibility, percentage agreement and kappa were calculated for both the intraobserver and interobserber agreement.

RESULTS

Normal volunteers

The mean and standard deviation of excretion rate of the 44 glands in the 11 normal volunteers was 56.5 ± 8.9, with a range of 30.8 to 73.1 (%). The Saxon test results ranged from 3.24 to 5.03 with a mean ± SD of 4.55 ± 0.84 (g/2 min).

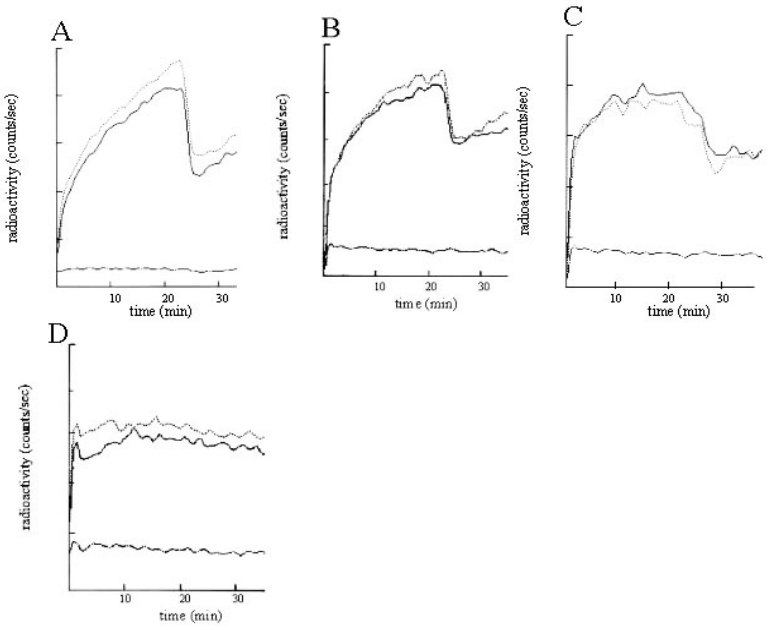

Fig. 2 Classification of time activity curve pattern. A: The normal type (N type) shows good accumulation. B: The poor excretion type (P type) shows a peak, but its excretion rate is less than 40%. C: The median type (M type) reveals lower accumulation and lower response to secretary stimulation. D: The flat type (F type) reveals weak accumulation, little secretion and little reaccumulation

Patients

No significant linear correlation was observed between the excretion rate of the parotid and excretion rate of the submandibular gland in any patient. However the excretion rate of the submandibular gland tended to be less than that of the parotid gland (Fig. 3). We classified 236 glands as Normal type with excretion rate mean ± SD of 54.9 ± 7.7 (%), 100 glands as Poor excretion type with excretion rate mean ± SD of 36.2 ± 8.0 (%), 96 gland as Median type with excretion rate mean ± SD of 31.3 ± 8.3 (%) and 64 glands as Flat type with excretion rate mean ± SD of 13.7 ± 5.7 (%). No significant difference was observed between the mean excretion rate of the 44 glands of the normal controls and that of the 236 glands classified as Normal type. The mean values of the abnormal TAC types (P type, M type and F type) differed significantly from the normal TAC type (Table 1).

Based on the results of excretion rate and TAC type, we defined a scoring system with 4 grades: severe dysfunction = 3 (excretion rate < 25%), moderate dysfunction = 2 (25% ≤ excretion rate < 40%), mild dysfunction = 1 (40% ≤ excretion rate < 50%) and normal function = 0 (50% ≤ excretion rate) (Fig. 4). The total scintigraphic score in normal volunteers ranged from 0 to 3 (total scintigraphic score 0: 5 patients, total scintigraphic score 1: 4 patients, total scintigraphic score 3: 2 patients) with a mean ± SD of 0.91 ± 1.14. Using a threshold of the mean + 2SD, we defined a normal range as less than a total scintigraphic score of 4.

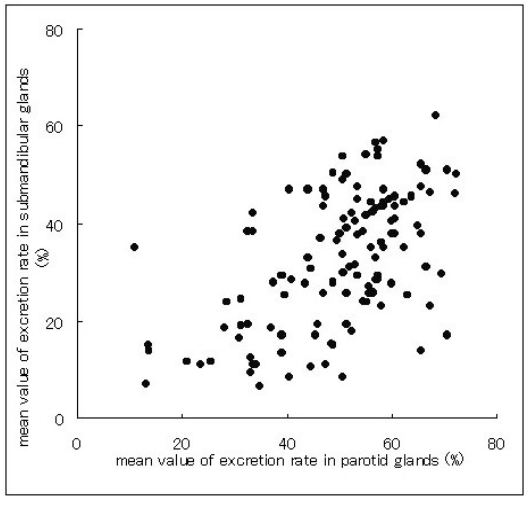

Fig. 3 Scatter plot of mean value of excretion rate in parotid glands against mean value of excretion rate in submandibular glands. The excretion rate of the submandibular glands tended to be less than that of the parotid glands

Sixty-eight of the 124 SjS patients had normal Saxon test results (more than 2 g/2 min) (Table 2). Within the range of abnormal total scintigraphic scores (≥ 4), there was a significant inverse linear correlation between total scintigraphic score and mean value of the Saxon test (Fig. 5).

We evaluated intraobserver and interobserver variance of varying combinations of TAC type by two nuclear

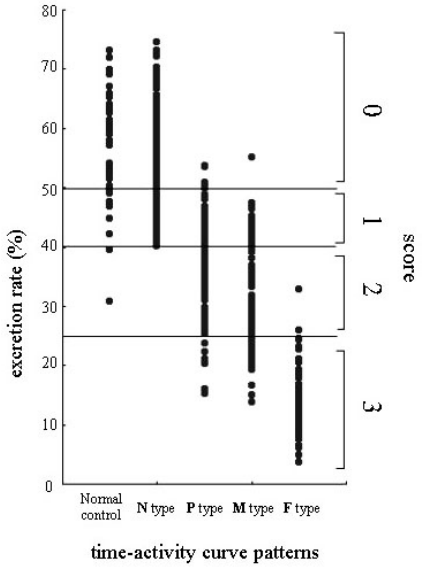

Fig. 4 Comparison of excretion rate between normal controls and four types of time-activity curves. Based on the results of excretion rate and TAC type, we defined a total scintigraphic scoring system with 4 grades.

Table 1 Results of statistical analysis of radionuclide excretion rate

	NC	N type	P type	M type	F type
NC	—	n.s.	$p < 0.01$	$p < 0.01$	$p < 0.01$
N type	—	—	$p < 0.01$	$p < 0.01$	$p < 0.01$
P type	—	—	—	n.s.	$p < 0.01$
M type	—	—	—	—	$p < 0.01$
F type	—	—	—	—	—

NC; normal control, N type; normal type, P type; poor excretion type, M type; median type, F type; flat type, n.s.; no significance

Table 2 Relationship between total scintigraphic score and mean of Saxon test

Total scintigraphic score	Mean of Saxon test	
	≤ 2 (g/2 min)	2 (g/2 min) <
7–12	26*	11
4–6	14	27
0–3	16	30
Total	56	68

*; numbers denote patient number

medicine technologists, who independently analyzed the scintigraphic data of these 10 patients.

The results of intraobserver and interobserver agreement are 0.65 in κ Statistics ($\kappa < 0.40$: poor reproducibility, $0.60 \leq \kappa < 0.75$: good reproducibility, $0.75 \leq \kappa$: excellent reproducibility, $0.55 < \kappa$: "acceptable" reproducibility). There was good reproducibility of intraobserver agreement and interobserver agreement between the two nuclear medicine technologists.

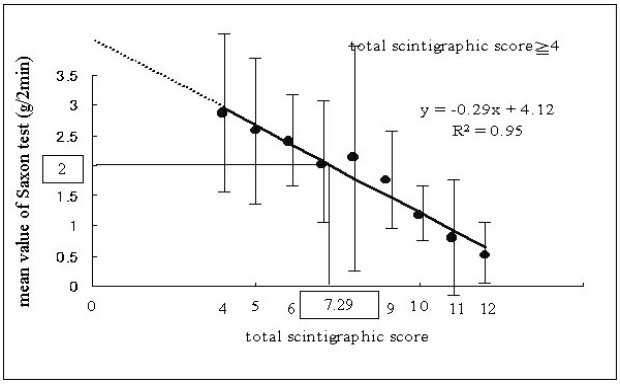

Fig. 5 Relationship between total scintigraphic score (≥ 4) and mean value of the Saxon test. Significant linear correlation was observed between total scintigraphic score and mean of the Saxon test.

DISCUSSION

In the Saxon test, a salivary excretion rate of less than 2 (g/2 min) is defined as pathological salivary dysfunction. The salivary excretion rate in the 11 normal volunteers in the present study was more than 3 (g/2 min) in the Saxon test, indicating normal salivary function. Corresponding to a normal value in the Saxon test, the mean and SD of the excretion rate was 56.45 ± 8.93 (%), similar to that previously reported.[14]

In our study, dysfunction of the submandibular gland was more severe than that of the parotid gland, as in the study by Mita et al.[15] Individual salivary gland function can be estimated using the scintigraphic scoring system, which is an advantage of this method over the Saxon test.

Referring to the classification of TACs proposed by Mita et al. and Suzuki et al., we defined 4 grades of salivary gland function, namely normal type (N type), poor excretion type (P type), median type (M type) and flat type (F type).[15,16] The range of excretion rate in normal volunteers was close to that in patients classified as N type TAC (Fig. 4). And the range of excretion rate of F type was also close to that in patients classified as M type TAC. The average excretion rate declined as N type progressed to P type, M type and then F type. Based on the distribution of excretion rate in each TAC type, we defined the range of scores to be 0, 1, 2, and 3.

When the total scintigraphic score was ≥ 4, the mean of the Saxon test in patients with the same total scintigraphic score showed a significant linear inverse correlation with the total scintigraphic score ($y = -0.29x + 4.12$, $R^2 = 0.95$) (Fig. 5). The vertical intercept of linear regression ($x = 0$, $y = 4.12$) was within the normal range derived from a study of normal volunteers. We estimated the threshold of

abnormal total scintigraphic score to be 7, corresponding to 2 (g/2 min) in the Saxon test on the formula in linear regression analysis. Eleven of 68 patients with normal Saxon test results (8.9%) had an abnormal total scintigraphic score (≥ 7). Thus, salivary scintigraphy can detect the early stage of salivary dysfunction in patients with SjS, as in the study by Daniel et al. and Bohuslavizki et al.[17,18] On the other hand, 16 of 56 patients with abnormal Saxon test results had a normal total scintigraphic score. The Saxon test is patient dependent and requires patient cooperation to obtain accurate results. The subjects included patients with false teeth and elderly persons, who we expect could not enough chew the gauze sufficiently and secrete saliva. Furthermore, the reproducibility of the Saxon test is limited. However, the total scintigraphic scoring system using in this study was reproducible.

One possible shortcoming of the total scintigraphic scoring system developed in this study is that in each patient analysis of all the time-activity curves for the four salivary glands must be performed, and thus the system may not appear to be a simple estimation. However, conventional scintigraphic analysis using time-activity curve patterns is not suitable for evaluation of overall salivary gland dysfunction, especially in cases showing varying time-activity curve patterns. This scoring system can evaluate the function in individual and overall salivary glands. The use of this scoring system in the diagnosis, management, and follow-up of patients with SjS would be more appropriate than that of time-activity curve pattern.

CONCLUSION

The scintigraphic scoring system developed in the present study is a clinically available, objective, and reproducible method for evaluation of salivary gland function in patients with SjS.

REFERENCES

1. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's syndrome. *J Clin Pathol* 1968; 21: 656–660.
2. Schall GL, Anderson LG, Wolf RO, Herdt JR, Tarpley TM, Cummings NA, et al. Xerostomia in Sjögren's syndrome: evaluation by sequential salivary scintigraphy. *JAMA* 1971; 216: 2109–2116.
3. Bunim JJ. Clinical, pathologic, and serologic studies in Sjögren's syndrome. *Ann Inten Med* 1964; 61: 509–530.
4. Bloch KJ, Buchanan WW, Wohl MJ, Bunium JJ. Sjögren's syndrome: a clinical, pathological, and serological study of sixty-two cases. *Medicine* 1965; 44: 187–231.
5. Kohler PF, Winter ME. A quantitative test for xerostomia. The Saxon Test, an oral equivalent of the Schirmer test. *Arthritis Rhem* 1958; 28: 1128–1132.
6. Miyawaki S, Torikai K, Natsume I, Nobunaga T, Ohtsuka E, Shzuki T, et al. Evaluation of two quantitative tests for salivary secretion: Chewing Gum Test and Saxon Test in normal subjects and in patients with Sjögren's syndrome. *Ryumachi* 1991; 31: 22–27.
7. Vitali C, Bombardieri S, Moutsopoulos HM, Coll J, Gerli R, Hatron PY, et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. The European Study Group on Diagnostic Criteria for Sjögren's syndrome. *Ann Rheum Dis* 1966; 55: 116–121.
8. Sugihara T, Yoshimura Y. Scintigraphic evaluation of the salivary glands in patients with Sjogren's syndrome. *Int J Oral Maxillofac Surg* 1988; 17: 71.
9. Umehara I, Yamada I, Murata Y, Takahashi Y, Okada N, Shibuya H. Quantitative evaluation of salivary gland scintigraphy in Sjögren's syndrome. *J Nucl Med* 1999; 40: 64–69.
10. Klutmann S, Bohuslavizki KH, Kröger S, Bleckmann C, Brenner W, Mester J, et al. Quantitative salivary gland scintigraphy. *J Nucl Med Technol* 1999; 27: 20–26.
11. Kosuda S, Suzuki K, Kawakami R, Akita S, Mezaki T, Inokuma S, et al. Reassessment of usefulness of salivary scintigraphy in diagnosis of Sjögren's syndrome. *KAKU IGAKU (Jpn J Nucl Med)* 1993; 30: 161–170.
12. Cicchetti DV, Sparrow SS. Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. *Am J Ment Defic* 1981; 86: 127–137.
13. Kramer MS, Feinstein AR. Clinical biostatistics. LIV. The biostatistics of concordance. *Clin Pharmacol Ther* 1981; 29: 111–123.
14. Vigh L, Carlsen O, Hartling OJ. Uptake index and stimulated salivary gland response in ^{99m}Tc-pertechnetate salivary gland scintigraphy in normal subjects. *Nucl Med Commun* 1997; 18: 363–366.
15. Mita S, Kohno M, Matsuoka Y, Matsuoka Y, Irikou S, Fujimori I, Fukuda J. Diagnostic availability of RI-sialography in Sjögren's syndrome. *Ryumachi* 1981; 21: 305.
16. Suzuki K, Hosokawa Y, Kaneko M, Omori K, Minowa K, Fukuda H, et al. Analysis on the Time/Activity curve of salivary gland scintigraphy in salivary gland diseases—The correlation between the pattern of Time/Activity curve and the amount of saliva—. *Oral Surgery Jpn* 1992; 38: 584–589.
17. Daniel TE, Powell MR, Sylvester RA, Talal N. An evaluation of salivary scintigraphy in Sjögren's syndrome. *Arthritis & Rheumatism* 1979; 22: 809.
18. Bohuslavizki KH, Brenner W, Wolf H, Sippel C, Tönshoff G, Tinnemeyer S, et al. Value of quantitative salivary gland scintigraphy in the early stage of Sjögren's syndrome. *Nucl Med Commun* 1995; 16: 917–922.