

# Correlations between histopathologic and scintigraphic parameters of salivary glands in patients with Sjögren's syndrome

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**Abstract** The aim of this study is to evaluate the diagnostic value of quantifying salivary gland scintigraphy in correlation to the labial biopsy findings of Sjögren's syndrome (SS). Thirty patients suspected of having SS referred to our clinic for salivary gland scintigraphy were included to this study. All patients underwent salivary gland biopsy as well. The severity of histopathologic changes was graded according to the Chisholm and Mason scoring system. Dynamic scintigraphy was performed and region of interests (ROI) were drawn. Time activity curves for salivary glands were generated. Count rates of maximum, minimum activity after lemon juice stimuli, and last minute activities of parotid and submandibular glands were obtained. On the basis of this ROI counts, excretion fraction (EF%) was calculated for all salivary glands. The mean EF% for normal parotid gland and pathologic parotid gland was  $54.5 \pm 13.9$  and  $45.8 \pm 18.42$ , respectively, while it was  $46.7 \pm 11.7$  for the normal submandibular gland and  $29.3 \pm 18.8$  for the pathologic submandibular gland. With progression in histopathologic grades from 0 to 4, the EF decreased in all salivary glands. Decreased EF in the salivary glands is correlated with the SS, and salivary gland scintigraphy is a sensitive and valid method for evaluation of the function of the salivary glands.

**Keywords** Ejection fraction · Labial biopsy · Salivary gland scintigraphy · Sjögren's syndrome

## Introduction

Sjögren's syndrome (SS) is an inflammatory autoimmune disease of unknown etiology characterised by lymphocytic infiltration and destruction of exocrine glands [1]. The target organs are the salivary and lacrimal glands, resulting particularly as a reduction of salivary function.

The diagnosis of SS depends not only on demonstrating an exocrinopathy, but also it is autoimmune in nature. The American/European consensus criteria are widely accepted [2] which are based on a positive response to a short questionnaire of ocular and oral symptoms, objective measurement of impaired lacrimal and salivary flow rates, and demonstration of autoimmunity by significant focal infiltrates on salivary gland biopsy and the presence of antibodies.

Reliable detection of impaired salivary function is crucial for the diagnosis of xerostomia in patients with early SS. The most specific diagnostic method for SS is still labial salivary gland biopsy, but it is invasive and causes some degree of patient discomfort.

Salivary gland scintigraphy (SGS) provides a detailed functional evaluation of salivation as it measures the amount and speed of radioisotope uptake and excretion for all four major salivary glands separately [3]. Salivary gland scintigraphy using qualitative or quantitative methods has been suggested as a sensitive, safe, easy to perform and objective alternative approach to functional and morphological evaluation of salivary/involvement in SS [4–9]. The aim of this study is to evaluate the diagnostic value of quantitative salivary gland uptake and secretion in patients with sicca symptoms in correlation to the labial biopsy of Sjögren's syndrome.

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**Table 1** Demographics of patients

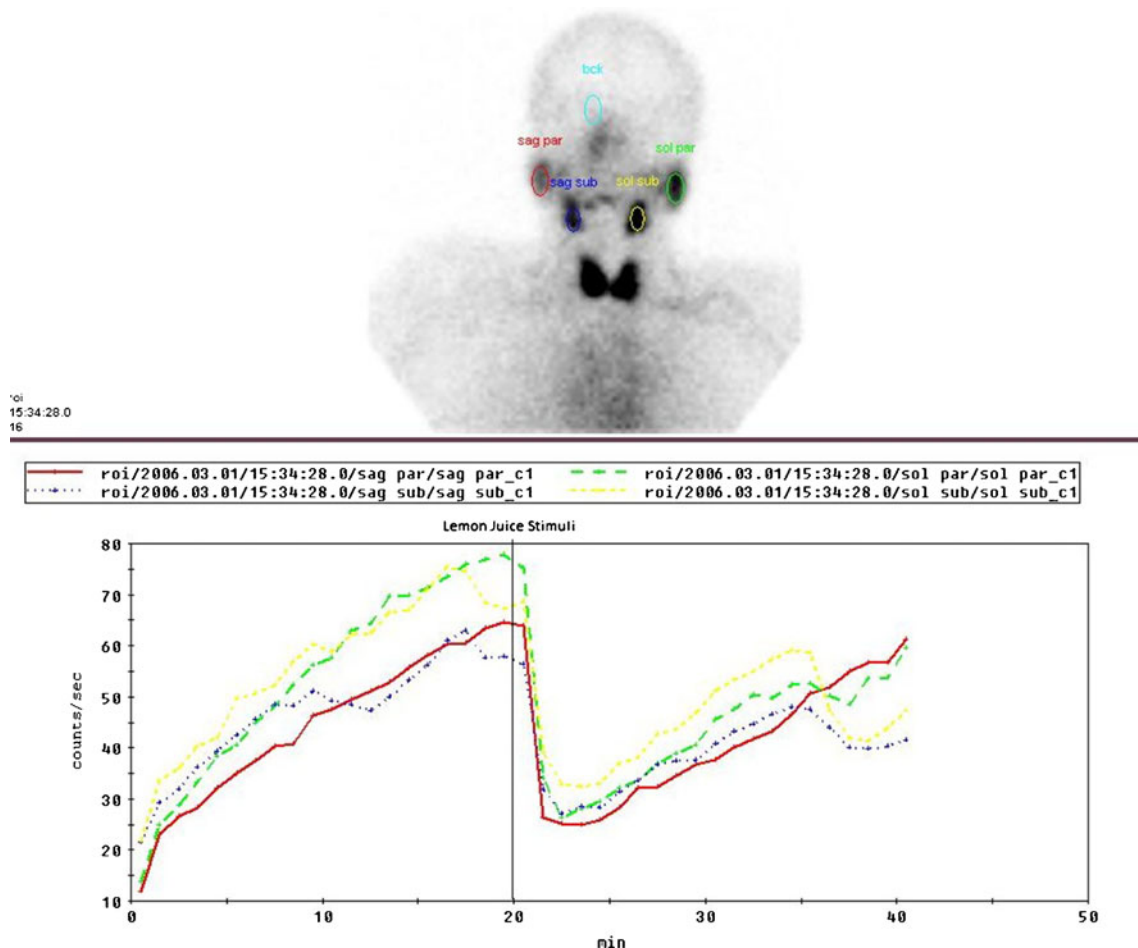
Mean age (range)	46 (25–74)	
Gender		Mean age
Female	25	39.5
Male	5	52.3
Biopsy results		
Grade 0	6	
Grade 1	9	
Grade 2	6	
Grade 3	1	
Grade 4	8	

## Material and methods

Files of 60 patients referred to the nuclear medicine department for salivary gland scintigraphy for the differential diagnosis of dry mouth were retrospectively reviewed. Thirty patients who had both salivary gland biopsy and scintigraphy

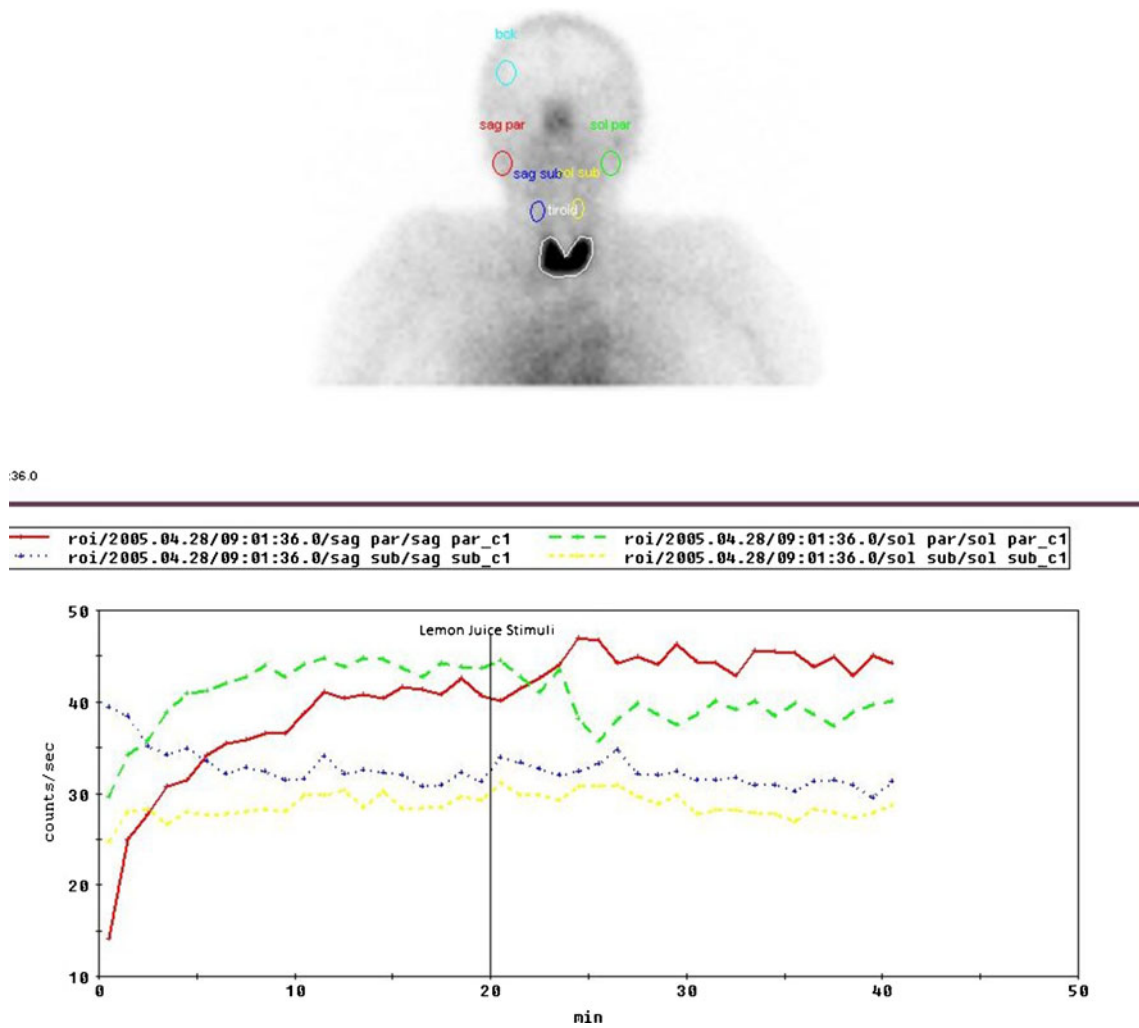
were enrolled to this study. There were 25 female and 5 male patients with a mean age of 46 years (range, 25–74) (Table 1). All had complaints of dry mouth and dry eye for a period of 12 to 36 months.

**Salivary gland scintigraphy** All patients were well hydrated before salivary gland scintigraphy. Dynamic imaging was performed in modified Water's projection after the i.v. administration of 555 mBq  $^{99m}\text{Tc}$  pertechnetate. Imaging was started immediately after injection in order not to miss the initial portion of the curve. A single-headed gamma camera (Mediso, X-Ring/R Hungary) was used with a symmetrical 20 % window around a 140-keV photopeak. Images were acquired on 128×128 pixel matrix and archived for later retrieval. After i.v. injection of  $^{99m}\text{Tc}$  pertechnetate dynamic scintigraphy was performed, with lemon juice stimulation at 20 min of the 40-min study. Regions of interests were drawn on the compressed dynamic images of the thyroid (T), parotid, and submandibular glands for both right and left sides and also to the right temporal bone as background.



**Fig. 1** Normal scintigraphic pattern of a 37-year-old female patient, who had a dry mouth complaint for 18 months, and labial biopsy result was grade 0. Good radiopharmaceutical uptake and sharp and rapid fall

of time–activity curve (TAC) after lemon juice stimuli. *Red line*: right parotid. *Green line*: left parotid. *Blue line*: right submandibular. *Yellow line*: left submandibular glands



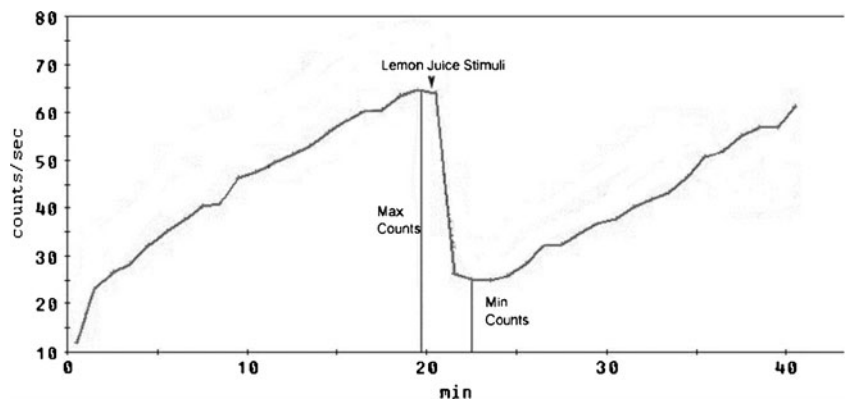
**Fig. 2** Abnormal scintigraphic pattern as diminished radiopharmaceutical uptake and no response to lemon juice stimuli on TAC in a 45-year-old female patient, who had a history of dry mouth for 2 years,

and labial biopsy was graded as 4. *Red line:* right parotid. *Green line:* left parotid. *Blue line:* right submandibular. *Yellow line:* left submandibular glands

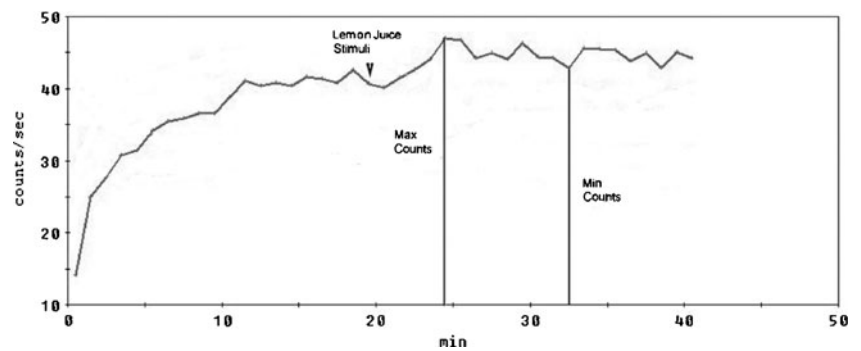
A time–activity curve for each salivary gland was generated using background subtraction. Count rates for the first minute (FM), 15 min, maximum (Max), and minimum (Min) activity after lemon juice stimuli (L) and the last

minute activities for each parotid and submandibular glands were obtained (Figs. 1 and 2). FM/Max, Max/Min, T/Max, T/15, Max/L, and 15/L were calculated as well. The difference between the maximum count and the minimum count

**Fig. 3** Normal TAC. Good radiopharmaceutical uptake and sharp–rapid fall after lemon juice stimuli are seen



**Fig. 4** Pathological TAC. Decreased uptake and nonresponsive TAC (plateau) to lemon juice stimuli are seen



after stimulation was calculated [(maximum activity–minimum activity)/maximum activity] and the percentage of this value was defined as the excretion fraction (EF%) (Figs. 3 and 4) [3, 10, 11].

**Histopathological analysis** All patients had salivary gland biopsy, which were performed by an experienced physician. The severity of histopathological changes was graded according to the Chisholm and Mason scoring system [12]. According to this scoring system, the presence of lymphocytes per 4 mm<sup>2</sup> of salivary tissue makes the basis of this scoring system where:

- Grade 0 Absence of any lymphocytes
- Grade 1 Slight infiltrate
- Grade 2 Moderate infiltrate or less than one focus, where a focus is an aggregate of 50 or more lymphocytes and histiocytes
- Grade 3 Infiltration in one focus
- Grade 4 Presence of infiltration in more than one focus

According to histopathological grading, the patients were divided into two subgroups: grade 0 and grade 1 biopsy findings were accepted as normal or with minimal changes (group I) and grades 2 to 4 were accepted as advanced stages of SS (group II).

#### Statistical analysis

The difference between the calculated semiquantitative parameters was tested using ANOVA test.

**Table 2** Mean, median, and range of EF values of the glands in group I and group II

	EF	Mean (%)		Median (%)		Range	
		Group I	Group II	Group I	Group II	Group I	Group II
RPG right parotid gland, LPG left parotid gland, RSm right submandibular gland, LSm left submandibular gland, EF excretion fraction	RPG	54.7	48.2	55.6	53.9	33.6–72.5	1.2–72–5
	LPG	54.4	43.5	64.1	45.2	29.8–70	4.6–66.5
	RSm	47.0	31.5	50.7	30.3	20.7–14.1	64.9–57.0
	LSm	46.5	27.2	48.0	22.2	29.4–8.6	63.4–93.0

## Results

Out of 30 patients, 15 were accepted in group I and 15 patients were accepted in group II. The EF values are given as mean, median (in percent), and range in Table 2 for left–right parotid and submandibular glands for both normal and pathologic sides. Excretion fraction was significantly reduced in group II patients (54.5 to 45.8 % in the parotid glands ( $p < 0.05$ ) and 46.7 to 29.3 % in the submandibular glands;  $p < 0.000$ ). With the progression in histopathologic grades, the velocity of secretion decreased in both submandibular glands.

No significant correlation was found between tracer uptake concentration and time to peak activity for parotid and submandibular glands among group I and group II. No other quantitative scintigraphic parameters were able to differentiate between group I and group II.

## Discussion

Salivary gland scintigraphy has been useful for the investigation of multiple diseases affecting salivary glands [3, 6]. In Sjögren's syndrome, pertechnetate imaging can gauge the severity of salivary gland involvement, which may not be accurately reflected by clinical symptoms (i.e., xerostomia and other features of the sicca syndrome) [4, 5]. In other clinical situations, such as iatrogenic irradiation of the salivary glands during treatment of head and neck tumours or radioiodine treatment of thyroid cancer, salivary scintigraphy helps to assess functional damage and monitor recovery [13].

Recently, salivary gland scintigraphy has been refined toward providing quantitative information on changes in gland function after parenchymal insult, whether inflammatory or radiation induced. Most attempts have used data derived from the kinetics of uptake and clearance of radioactivity in the major salivary glands [14–17]. In addition, grading and comparison of uptake in the salivary glands in successive scans have been used objectively and reproducibly to follow changes, thus indicating progression or improvement of the pathologic condition [13, 18].

SGS is a well-standardised procedure, and results are reported in a qualitative way. The use of computer-assisted time–activity curves allows quantification of salivary gland radioactivity turnover in a defined time period during SGS [11, 12]. In this study, the decrease in EF values in both parotid and submandibular glands help to evaluate SS patients according to histopathological groups. Although semiquantitative SGS data have been studied before, this is one of the few studies using absolute measures for isotope uptake and excretion. The degree of reduction in secretion in our study agrees with the data presented in other studies of paired time–activity curves for submandibular and parotid glands in primary SS patients [3, 13, 14].

Reduced uptake in the submandibular glands more than parotids in SS patients was noted in other studies [9]; however, in this study, we were unable to show this. This discrepancy could be because of the methodological aspects. The present SS cohort had shorter duration (12 to 36 months) of dry mouth symptoms in our study compared to long-standing disease symptoms (mean 11 years) in the mentioned study. Variable sensitivities of the parotid and submandibular glands to the insult over time could be another explanation [15–17]. Besides, as shown by Gerli et al., the onset of the disease is more important than the duration [18], which might be the reason for the discordance between the studies.

Delayed tracer uptake and secretion in SS patients are thought to be due to a progressive reduction in exocrine function of the major salivary glands resulting from morphological changes induced by chronic immune-mediated inflammation [1, 3, 4, 19]. This thought is mainly based on indirect evidence from minor labial gland biopsy findings in SS. However, normal acinar cells are commonly observed in biopsy materials indicating that dryness cannot be solely explained by glandular destruction. Autoantibodies against muscarinic M3 receptors that inhibit parasympathetic neurotransmission by acetylcholine may also contribute to impaired glandular function through the disruption of autonomic function without mediating inflammation [6, 7]. High concentrations of cholinesterase, produced by local T lymphocytes, in the resting and stimulated salivas of SS patients has been found [20]. Besides anticholinergic receptor antibodies have also

been tentatively described [20]. Although we lack the necessary expertise to measure muscarinic receptor autoantibodies, studying the influence of this new class of autoantibodies on salivation may also profit from quantitative SGS testing.

## Conclusion

Semiquantitative analysis of salivary gland scintigraphy provides further information on the decreased secretion velocity in the submandibular and parotid glands. EF value seems to be a sensitive and valuable parameter for the differentiation of patients with pathological secretion function in the salivary glands.

**Disclosures** None.

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