Evaluation of diagnostic parameters from parotid and submandibular dynamic salivary glands scintigraphy and unstimulated sialometry in Sjögren's syndrome

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Abstract

Our aim was to validate eight scintigraphic salivary gland (SG) parameters, as diagnostic parameters in patients with Sjörgen's syndrome (SS). *We used the standardized stimulated dynamic salivary gland scintigraphy* (DSGS) protocol and correlated this with the unstimulated whole sialometry (UWS) functions. The DSGS and UWS tests meeting the European and the USA diagnostic classification criteria for SS were applied in twenty patients and in ten normal controls. The DSGS tests were performed 60min after the intravenous (i.v.) injection of 370MBq of technetium-99m-pertechnetate ($^{99m}TcO^-_4$) and after per os stimulation with a 0.5g tablet of ascorbic acid administered 40min after the injection. Using time-activity curves, eight different parameters were calculated for each parotid gland (PG) and each submandibular salivary gland (SMG): a) time at maximum counts (*Tmax*), b) time at minimum counts (*Tmin*), c) maximum accumulation (*MA*), d) accumulation velocity (*AV*), e) maximum secretion (MS), f) maximum stimulated secretion (*MSS*), g) stimulated secretion velocity (*SSV*), and h) uptake ratio (*UR*). Values of UWS below 2.5mL/15min were considered abnormal. *All these parameters, as for the PG, showed* significant abnormality in SS patients ($P<0.001$), especially of the secretion function. All SMG parameters also showed a significant abnormality ($P<0.001$), but especially of the accumulation function. There was a greater impairment of the above parameters in SMG than in PG in the SS patients. Sensitivity of the standardized DSGS was 100%, specificity 80%, negative prognostic value 100%, and positive prognostic value 91%. Sensitivity of UWS was 75%. *In conclusion*, this paper suggested that the best diagnostic parameters for the SS patients were those of: a) the maximum secretion, b) the maximum stimulated secretion for both the parotid and the submandibular glands, c) maximum accumulation and d) accumulation velocity of submandibular glands. The times at maximum and at minimum counts were non diagnostic.

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by sicca complex, that is: dry eyes (conjunctivitis sicca) and dry mouth (xerostomia) due to lymphocytic infiltration of the exocrine glands, particularly the salivary and lacrimal. Having in mind the clinical, immunogenetic and immunoserologic heterogeneity of SS patients [1] it has been recently suggested that the disease should be divided into a primary (pSS) and a secondary (sSS) type. The pSS is characterized by sicca complex, but can also have systemic manifestations and is described as a connective tissue disease. The sSS, besides the sicca symptoms is associated with another well-defined autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, or biliary cirrhosis [1-3].

The uniform specific classification criteria for both types of SS are still missing. Although the ophthalmic component of the SS is well defined, criteria for classifying the oral component of this syndrome remain controversial [3-6]. The average time from the first onset of symptoms to the establishment of the diagnosis of the syndrome is more than six years [7]. The diagnosis of SS cannot be based on the sicca complex symptoms alone [6-8]. The classification criteria for the SS currently used by clinicians and researchers around the world are the American-European Consensus Classification Criteria (US-EU-CCC). Physicians usually diagnose the SS for clinical purposes on a more individual, medically intuitive and broader basis. The US-EU-CCC revised in 2002 include six items [9-14]: a) Ocular symptoms b) Oral symptoms c) Ocular signs d) Histopathology, e) Oral signs including at least one unstimulated whole gland salivary flow (≤1.5mL in 15min), abnormal parotid sialography or abnormal salivary scintigraphy and f) Autoantibodies. For the diagnosis of pSS any 4 of these 6 criteria can be used, provided

that histopathology or autoantibodies are included or any 3 of the above criteria provided that histopathology, autoantibodies, salivary flow, salivary gland scintigram (SGS) or sialography are included. For the diagnosis of the sSS the presence of one symptom from the first two out of the above 6, plus 2 of the 3 objective criteria, including histopathology, salivary glands flow and sialography must be included. Exclusion criteria for the diagnosis of the SS are: the past head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency syndrome (AIDS), preexisting lymphoma, sarcoidosis, graft versus host disease, and current use of anticholinergic drugs [14]. From the above is obvious that salivary glands flow and other nuclear medicine tests are necessary for the diagnosis of all stimulated, dynamic salivary glands scintigraphy (DSGS).

Dynamic SGS (DSGS) can provide valuable information on the function and morphology of salivary glands and has been used for more than 40 years, for SS and various other salivary glands pathologies [15-18]. In numerous studies, DSGS protocols and parameters of saliva accumulation and secretion have been analysed aiming for better determination of the salivary glands function and damage in SS patients [19, 20]. Similar studies are still under discussion [19-22] or under investigation [23-31].

The aim of this study was to perform the DSGS protocol and the unstimulated whole sialometry (UWS) tests in order to evaluate which test is more sensitive for early diagnosis of SS. We have proposed and used a standardized DSGS protocol of eight scintigraphic salivary gland parameters and correlated them with the UWS values.

Subjects, materials and methods

Patients

In a period of 4 years and 10 months, between September 2004 and June 2009, DSGS and UWS parameters were studied in 68 patients with xerostomia suspicious for SS. All patients were first seen by a rheumatologist in our Reumatology Clinic. Twenty of these patients were diagnosed by the US-EU-CCC as having both DSGS and UWS parameters of parotid glands (PG) and of submandibular glands (SMG) positive for SS. Fifteen of these patients had pSS and 5 sSS. They were 17 female and 3 male with a mean age of 47.6y (range: 24-72y). Ocular symptoms were obvious in 17/20 patients and oral symptoms in all 20 patients. Nineteen patients had the feeling of dry mouth without swollen salivary glands, and only one sSS patient had the feeling of dry mouth and had parotid glands swelling. The feeling of dry mouth lasted from 11m to 5y prior to the diagnosis of SS. Labial biopsy was performed on 15/20 patients of which 10 had positive histopathology for focal lymphocytic sialoadenitis.

Control group

The control group consisted of 10 persons who met the US-EU-CCC exclusion criteria for xerostomia and SS. They were 7 female and 3 male with mean age 44.3y and range of 22-75y. Approval for performing this study was obtained by the local Ethics Committee. All subjects studied gave their informed written consent prior to the study.

Scintigraphy

Scintigraphy was performed with a gamma-camera and data analysis system (PDP-11 Philips, USA), using low energy, and general purpose, parallel-hole collimator, with a 20% energy window and 64x64 pixel matrix. The camera was adjusted to record background (bg) activity at box shaped regions of interest (ROI) at sites: a) above the left temporal region of PG, b) the mean value of the region above and the region left to the thyroid gland were taken as bg for the SMG (Fig. 1) and c) above the oral cavity (OC), following the intravenous (i.v.) injection of the radiopharmaceutical. Dynamic salivary gland scintigraphy started immediately after the i.v. injection of 370MBq $^{99m}TcO^{-}_{4}$ and lasted for 60min, with one frame per minute. Per os saliva secretion was stimulated with a 0.5g tablet of ascorbic acid given 40min after the injection.

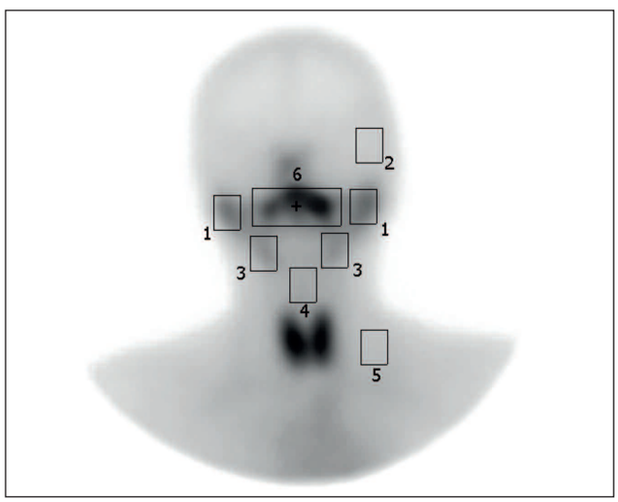

Figure 1. Regions of interest: 1-over the right and left parotid glands; 2- at the left temporal region, as bg of the PG, 3- over the right and left SMG; 4- above the thyroid gland and 5- left to the thyroid gland (the mean value of the last two regions was taken for bg of the SMG); 6-above the oral cavity.

The static scintigram of the OC started 90min after the i.v. injection of $^{99m}TcO^{-}_{4}$ and lasted for 3min.

Analysis of the time activity curves

Time-activity curves (TAC) were generated over the PG and SMG ROI, after bg subtraction and five-points smoothing. The following points were designated on the schematic presentation of the glandular TAC (Fig. 2): Point a: at the end of the initial up-slope vascular perfusion, or if the end of vascular perfusion is unclear, at the 4th min; Point b: at the maximum activity point prior to stimulation; Point c: points the number of counts at the stimulation point; Point d: points the minimum activity point after stimulation; Ta: marks the time at point a; Tb: the time of reaching maximum activity; Tc: the time of per os stimulation; Td: the time of reaching the minimum activity.

Using defined points as above, eight different semi-quantitative parameters were calculated for each salivary gland: Time at maximum counts (Tmax), Time at minimum counts (Tmin), The maximum accumulation (MA)=(b-a)/bx100%, Accumulation velocity (AV)=(b-a)/(Tb-Ta), in imp/min, The maximum secretion (MS)=(b-d)/bx100%, The maximum

stimulated secretion (MSS)=(c-d)/cx100%, Stimulated secretion velocity (SSV)=(c-d)/(Tc-Td), in imp/min and Uptake ratio (UR): gland to bg ratio at maximum counts.

The MA and UR parameters refer to the quantity of accumulation, AV to the velocity of accumulation, Tmax both to

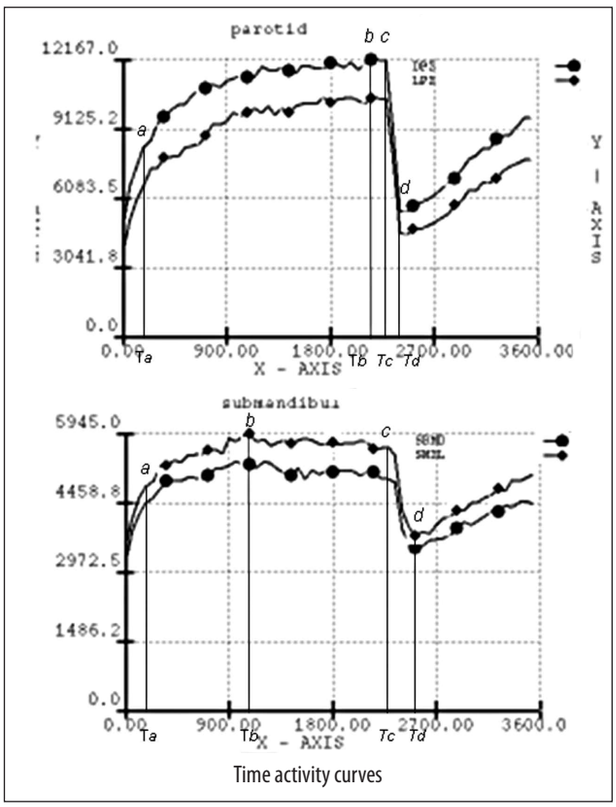

Figure 2. The TAC of the PG and SMG showing points a, b, c and d, representing the number of counts-impulses on the y axis, and points Ta, Tb, Tc and Td, representing the time in minutes, on the x axis.

velocity of accumulation and to spontaneous secretion. MS to spontaneous secretion, MSS and Tmin to stimulated secretion and SSV refers to the velocity of stimulated secretion.

Unstimulated whole sialometry

Unstimulated whole sialometry lasting for 15min was performed 2h after breakfast using the standardized collection procedure. Collection of saliva in a graduated tube via funnel occurred every 2min. Volumes amounting up to ≤1.5mL/15min were marked as abnormal; volumes between 1.5 and 2.5mL/15min were marked as intermediate and volumes amounting to ≥2.5mL/15min as normal. Volumes of <2.5mL/min were considered abnormal and used for estimation of sensitivity for correlation with all scintigraphic parameters.

Statistical methods

Sensitivity, specificity, negative prognostic value (NPV) and positive prognostic value (PPV) were calculated using decision matrix. Software program SPSS was used for statistical analysis. All results in figures and tables of this study are presented as mean values and standard deviations. With regard to the parametric data, the Student's t-test was used for determination of the statistical significance between SS patients parameters and those of the control group. X^2 test was applied for comparison of frequencies. Pearson correlation analysis was used for correlation between scintigraphic parameters and UWS values. P values<0.05 were considered statistically significant.

Results

Sensitivity for DSGS was 100%, specificity 80%, NPV 100%, and PPV 91%.

Accumulation parameters of the PG: MA, AV and UR, were significantly different in SS patients showing lesser and slower accumulation of $^{99m}TcO^{-}_{4}$ than in the control group. Time of PG maximum and minimum activity, as the accumulation and spontaneous secretion parameters did not differ significantly between the SS and the control examined groups (Table 1).

There was also a significant difference among all secretion parameters of the PG: MS, MSS and SSV, showing lesser and slower secretion in SS patients in relation to the control group (Table 1).

The PG secretion parameters were more impaired than the accumulation parameters showing a greater degree of secretion than accumulation function damage of the PG in SS patients as compared to the control group (shown in Table 1 and Fig. 3).

All parameters of the SMG in SS patients disclosed significant abnormality in relation to the control group, indicating accumulation and secretion damage but greater impairment of the accumulation than the secretion function (shown in Table 2 and Fig. 3).

Comparison of parameter values of the PG and the SMG in SS patients and in the control group revealed a greater SMG than PG impairment (Fig. 3).

Fifteen patients had UWS under 2.5mL/15min (4 of them had UWS≤1.5mL/15min and 11 had UWS between 2.5mL

***Table 1**. Mean parametric values of the parotid gland in the 10 subjects of the control group (20 glands) and in the 20 SS patients (40 glands) with the corresponding P values*

	Control group		Patients		t test	P
Parameters	Mean value	SD	Mean value	SD		
Tmax	33.75	7.72	31.72	8.29	.91139	.3658
Tmin	44.05	1.66	46.02	3.59	2.3293	.0233
MA	54.91	11.17	32.40	15.55	5.7591	.001
AV	225.97	116.22	69.65	42.18	7.6122	.001
MS	65.49	8.33	32.30	19.74	7.1782	.001
MSS	63.57	10.13	30.34	20.20	6.9110	.001
SSV	-1338.07	976.31	-252.82	254.20	6.6443	.001
UR	2.70	.88	1.82	.43	5.2205	.001

Tmax: time at maximum count, in min, Tmin: time at minimum count, in min, MA: maximum accumulation %, AV: accumulation velocity, in imp/min, MS: maximum secretion %, MSS: maximum stimulated secretion, in %, SSV: stimulated secretion velocity, in imp/min, UR: uptake ratio, gland to background ratio at maximum count.

Table 2. *Mean parametric values of the submandibular glands in the 10 subjects of the control group (20 glands) and in the 20 SS patients (40 glands) with the corresponding P values*

Para-meters	Control group Mean value	SD	Patients Mean value	SD	t test	P
Tmax	20.80	8.83	28.50	9.82	2.9554	.0045
Tmin	42.75	9.41	48.70	5.38	3.1190	.0028
MA	30.01	10.61	18.37	11.94	3.6870	.001
AV	203.74	66.72	61.58	52.53	9.0165	.001
MS	52.12	9.53	28.75	16.31	5.9042	.001
MSS	45.44	6.86	27.30	16.07	4.8135	.001
SSV	-646.42	199.48	-283.59	288.31	5.0 461	.001
UR	1.83	.28	1.51	.30	3.9417	.001

Tmax: time at maximum count, in min, Tmin: time at minimum count, in min, MA: maximum accumulation %, AV: accumulation velocity, in imp/min, MS: maximum secretion %, MSS: maximum stimulated secretion %, SSV: stimulated secretion velocity, in imp/min, UR: uptake ratio, gland to background ratio at maximum count.

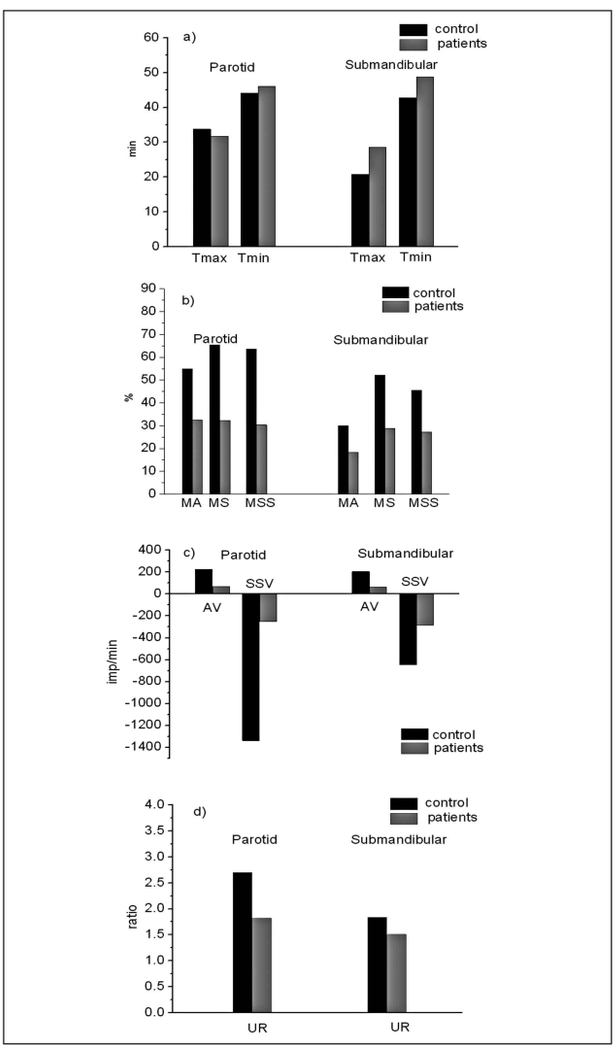

Figure 3. The DSGS parameters of PG and SMG in the control and the patients group: a) Tmax and Tmin, in minutes. b) MA: maximum accumulation, MS: maximum secretion and MSS: maximum stimulated secretion, presented %. c) AV: accumulation velocity and SSV: stimulated secretion velocity, presented in imp/min, d) UR: uptake ratio.

and 1.5mL/15min). Five patients had UWS≥2.5mL/15min. Estimated sensitivity of UWS was 75%.

From all DSGS values of both glands, only the MS values of SMG correlated strongly with UWS values with P<0.0001 (Tables 3 and 4).

Table 3. *Correlation of Tmax and MS of parotid glands with UWS values*

Parotid glands				
Tmax	↑	UWS	↓	P<0.05
MS	↓	UWS	↓	P<0.05

Tmax: time at maximum count, in min, MS: maximum secretion %, UWS: unstimulated whole sialometry in mL/15min.

Table 4. *Correlation of DSGS parameters of submandibular glands with UWS values*

Submandibular salivary glands				
Tmax	↑	UWS	↓	P<0.05
Tmin	↑	UWS	↓	P<0.05
MA	↓	UWS	↓	P<0.05
AV	↓	UWS	↓	P<0.05
SSV	↓	UWS	↓	P<0.05
MS	↓	UWS	↓	P<0.001

Tmax: time at maximum count, in min, Tmin: time at minimum count, in min, MA: maximum accumulation %, AV: accumulation velocity, in imp/min, SSV: stimulated secretion velocity, in imp/min, MS: maximum secretion %, UWS: unstimulated whole sialometry in mL/15min.

Discussion

Scintigraphic patterns in SS patients are similar as in chronic sialoadenitis of any origin. They vary and depend on the stage of the inflammatory process of SS. As the inflammatory process progresses, flattening of the TAC along with progressive decrease of scintigraphic outline of the involved glands appears [16-21]. It has been shown that DSGS is a very sensitive method to detect early salivary dysfunction in SS patients even if they still don't have the dry mouth feeling. There is experimental evidence that DSGS can detect functional damage when histological abnormalities of the glands are just above 25% [26] and that the dry mouth feeling occurs when more than 60% of the gland tissue is damaged [22, 32, 33].

The protocol for DSGS is still not standardized. Duration of this dynamic study and the variety of its parameters differ in different studies [23, 24]. Some authors (1998) [22] had used the 60min DSGS lemon stimulation study in the 45thmin of the study with a 64x64 matrix and 15sec temporal resolution and found a wide scatter of semi-quantitative scintigraphic indices in healthy individuals. They concluded that the choice of scintigraphic conditions and the physiological characteristics of the salivary glands could affect the above values and proposed the adoption of a broadened physiological model including both spontaneous and stimulated salivary secretion parameters [22].

In our study, the 60min DSGS study with ascorbic acid stimulation at 40min allowed spontaneous secretion in the normal glands and emphasized their secretion abnormali-

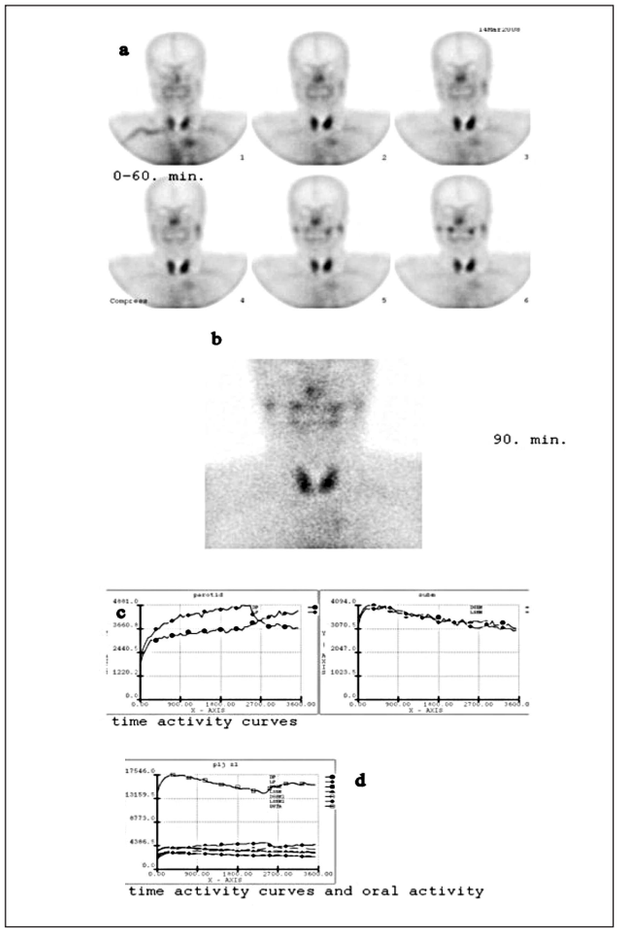

Figure 4. Findings of DSGS in one of our pSS patient with severe salivary functional damage: a) compressed dynamic scintigrams 0-60min after the i.v. injection of $^{99m}TcO^{-}_{4}$; b) static scintigram 90min after the i.v. injection of $^{99m}TcO^{-}_{4}$; c) TAC of both parotid (left-c) and both submandibular (right-c) glands; d) TAC of all salivary glands and the oral cavity.

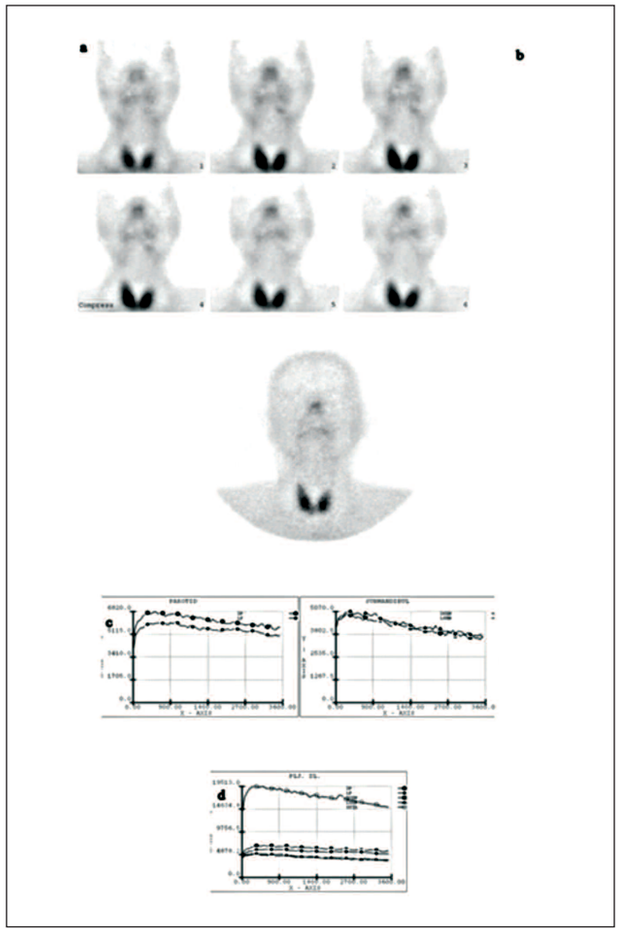

Figure 5. Findings of DSGS in one of our pSS patients with complete salivary functional damage: a) compressed dynamic scintigrams 0-60min after the i.v. injection of ^{99m}Tc; b) static scintigram 90min after the i.v. injection of $^{99m}TcO^{-}_{4}$; c) TAC of both parotid (left-c) and both submandibular (right-c) glands; d) TAC of all salivary glands and the oral cavity.

ties in the SS patients (Fig. 4, 5). Temporal resolution at 60sec in our study was sensitive enough to record changes of the glandular function and to enable a smooth slope for TAC and good estimation of the parameters studied.

In many other studies, a DSGS graded from 1-4 [18], showed a good correlation with the stage of the SS disease, the UWS, and SWS values, the histopathologic grade and the contrast sialography results [25-28]. More recent studies introduced scintigraphic parameters deriving from the glandular TAC, discussed their value and correlated them with other oral tests [25, 26, 29-31]. Other studies [25] found that scintigrapic variables showed severe abnormalities in patients with pSS as compared to the control group while other researchers [26] found a good correlation between certain scintigraphic parameters and contrast sialography. It has been recently reported that DSGS parameters reflected the degree of salivary gland involvement in pSS, and were in good correlation with histopathologic grades and labial focused biopsy scores [34, 35].

Validity of different TAC parameters is still under discussion. Some researchers (1999) [36] had found substantial inter-individual variability in frequency and in magnitude of salivary glands secretion in normal individuals. Other researchers (1994) [25] had found significant differences in parametric values between normal and SS patients, and also found great individual variations of MA of the PG in SS patients, which could not be explained either by the duration of symptoms or the age of the patients. Some other papers discussed the limited discriminatory value of scintigraphic parameters for the diagnosis of SS [22, 37]. Previous reports found a greater impairment of parameters which reflected secretion deterioration of the PG, accumulation deterioration of the SMG [25-27, 30], and in general, greater dysfunction of the SMG as compared with the PG [20, 25]. More recent studies gave ranges of normal values of parameters in order to better discriminate normal from damaged salivary glands in SS patients and in some other diseases [38-41]. The value of the accumulation parameters and of the stimulated secretion parameters for the detection of salivary glands dysfunction has also been discussed [36, 42].

In this study, large individual variations of all parameters were found in the group of SS patients. Significant standard deviation was found for SSV of both pairs of glands. At the same time, in the control group, only the values of AV and SSV showed large individual variations while other parameter values were consistent in the control group. Furthermore,

in our study, there was a significant difference in almost all parameters of both pairs of the salivary glands, except for Tmax and Tmin of PG, between the SS patients and the control group, which can partly be explained by the fact that half of normal PG in healthy population don't have episodes of spontaneous secretion and that secretion of saliva appeared after gustatory stimulation [22]. Absolute value of MA for PG as compared to SMG was 3:2 in both investigated groups, which is in agreement with previous results [31]. Our results are in agreement with many studies emphasizing validity of both, accumulation and secretion parameters [20, 26, 27, 29]. Parameters of PG manifested a greater impairment of the secretion function, while SG parameters manifested greater impairment of the accumulation function, as in other studies [25-27, 30]. Individual variations of parameter values, in our and other studies, can partly be explained by individual differences in the size, mass and secretion capacity and differences in the composition of the serous and mucous structure of the salivary glands in both, healthy individuals and SS patients. On the other hand, to reduce variations of calculated parameters of salivary glands function, a standardized protocol like this one for dynamic salivary glands scintigraphy is needed. Salivary scintigraphy's clinical utility might be extended by standardization of its test protocol and uniformity in its interpretative algorithms [43].

In conclusion, for a fast and specific diagnosis of the procedure of xerostomia of SS patients, we suggest as the best parameters the MS and MSS of both PG and SMG and the MA and AV of the SMG. Further scintigraphic studies with a larger patient population will confirm the validity of these proposed scintigraphic parameters for the evaluation of salivary glands function in SS patients.

The authors declare that they have no conflicts of interest.

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A: Inscription in ancient Greek at the entrance of Yale University. "Having the knowledge, must distribute it one to the other". B: Inscription in ancient Greek outside the administration building at the University of Edinburgh. "Those who have knowledge, can talk and understand".