EXTENDED REPORT

Salivary gland scintigraphy in Sjögren's syndrome and patients with sicca symptoms but without Sjögren's syndrome: the psychological profiles and predictors for salivary gland dysfunction

E-K Tensing, D C Nordström, S Solovieva, K-O Schauman, I Sippo-Tujunen, T Helve, S Natah, J Ma, T F Li, Y T Konttinen

Ann Rheum Dis 2003;62:964-968

See end of article for authors' affiliations

Correspondence to: Professor Y T Konttinen, Biomedicum, PO Box 700 (Haartmaninkatu 8), FIN-00029 HUS, Finland; yrjo.konttinen@helsinki.fi

Accepted 24 February 2003

Objective: To characterise the psychological profiles of Sjögren's syndrome (SS) and patients with sicca symptoms but without SS; to find predictors for salivary gland function; to evaluate salivary scintigraphy as a method to differentiate between SS and patients with sicca symptoms but without SS.**Patients and methods:** Psychological tests (Medical Outcomes Study Short Form General Health Survey (SF-36), Jenkins Activity Survey, Toronto Alexithymia Scale, and Maastricht Questionnaire for vital exhaustion) were performed and assessment of the function of the salivary glands made in 26 patients with primary SS, 8 with secondary SS, and 9 with sicca symptoms but without SS. Data were analysed with BMDP new system version 1.0 statistical program.**Results:** Psychological profiles were similar in all groups. Hb, RF, ANA, and SSA differentiated between the groups. Results of salivary scintigraphy were predicted to 51% by ANA, SSA, SSB, IgG, IgA, diagnosis, vitality, and role limitations due to emotional problems. No predictors were found for the resting salivary flow. Salivary scintigraphy was pathological in 21/26 (81%) and in 8/8 (100%) patients with secondary SS, but only in 2/9 (22%) patients with sicca symptoms without SS ($p=0.002$) (sensitivity 85.3%, specificity 77.8%).**Conclusions:** Patients with sicca symptoms but without SS have sickness behaviour similar to that of patients with SS. The results of salivary scintigraphy can be predicted by diagnosis and autoimmune findings; psychological characteristics added 20% to this predictive value. Distinction between SS and patients with sicca symptoms but without SS is difficult, but in addition to autoantibodies, salivary scintigraphy can be used for this purpose.

Focal sialadenitis in Sjögren's syndrome (SS) is associated with a decreased resting salivary flow of <0.1 ml/min and pathological salivary gland scintigraphy results.^{1,2} Salivary gland scintigraphy is a sensitive and valid method for evaluation of the function of the salivary glands. Scintigraphy results correlate with clinical³⁻⁶ and histopathological features of the salivary glands in patients with SS.⁶⁻⁹ Scintigraphy is relatively safe, well tolerated, and easy to perform, and enables an assessment of the function of all major salivary glands.

A significant discrepancy exists between the considerably decreased salivary flow and focal and often mild glandular involvement, with most of the glandular parenchyma being preserved.¹⁰⁻²¹ This suggests that the diminished salivary flow is in part functional and is not only caused by structural destruction of the secretory acinar cell.

The oral and ocular sites are considered to be part of a neuroendocrine immune loop that starts from the ocular/oral mucosal surface with afferent nerves and passes to lachrymatory and salivatory nuclei in the midbrain.²² These nuclei receive input also from higher cortical regions. This mechanism may lead to xerostomia in distressed and/or diseased patients who show no evidence of autoimmune inflammation in their exocrine glands. The net signal flow to and from the lachrymatory or salivatory nuclei is integrated and mediated to both the lachrymal and salivary glands through efferent cholinergic nerves. Vasoactive intestinal polypeptide (VIP) and acetylcholine (ACh) are released and stimulate VIPergic and muscarinic ACh receptors (mainly type M3) located on the glandular cells. The glands are also stimulated through effer-

ent adrenergic nerves releasing noradrenaline, which interacts with adrenergic receptors.

The aims of the study were (a) to evaluate the psychological profiles of patients with SS and patients with sicca symptoms but without SS. Depression/anxiety may lead to sicca symptoms owing to inhibitory interactions in the midbrain salivatory and lachrymatory nuclei; (b) to determine whether disease activity parameters and/or psychological profile might predict, at least to some extent, the sicca symptoms as measured by salivary scintigraphy; (c) to evaluate salivary scintigraphy as a method for differentiating between patients with SS and patients with sicca symptoms but without SS.

PATIENTS AND METHODS

Patients

Patients from the Sjögren's Syndrome Association in Helsinki were enrolled into the study by using advertisements in the journal of the patient organisation. Forty three patients (three men, 40 women) responded and were examined before the start of the study as part of a routine clinical examination. Twenty six patients had primary SS, eight patients had secondary SS, and nine patients did not fulfil the preliminary

Abbreviations: ACh, acetylcholine; ANA, antinuclear antibodies; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; JAS, Jenkins Activity Survey; RF, rheumatoid factor; SF-36, Short Form-36; SS, Sjögren's syndrome; TAS, Toronto Alexithymia Scale; VE, vital exhaustion

revised European criteria for SS; these last patients will be referred to as patients with sicca symptoms but without SS. Fourteen of the 26 patients with primary SS were SSA and/or SSB positive, 2/8 of the secondary SS were SSA positive, and none of the patients with sicca symptoms but without SS were SSA or SSB positive. None of the patients fulfilled the criteria for fibromyalgia. The mean age of the patients was 56.8 (11.5) years. The patients' drugs and drug dosage were recorded but did not seem to explain any of the findings.

Clinical and laboratory tests

A medical history of the patients was taken and a thorough physical examination was performed. The laboratory tests included haemoglobin (Hb), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF), anti-nuclear antibodies (ANA), Sjögren's syndrome autoantibodies (SSA, SSB), and serum immunoglobulins. The functional status of the lachrymal and salivary glands was analysed with the Schirmer-I and rose bengal tests and unstimulated and stimulated salivary flow measurements, respectively. These measurements were performed as recommended by the European Study Group of Sjögren's syndrome. Measurement time for the stimulated salivary gland flow was five minutes, for the unstimulated salivary flow 15 minutes, and for the unstimulated lachrymal flow five minutes. Salivary gland scintigraphy was performed in all patients, as described in detail below. Labial salivary gland biopsy and focus score counting were performed only when necessary for the diagnosis.²

Scintigraphic measurements

Patients were injected intravenously with 110 MBq technetium pertechnetate (^{99m}Tc) and images were obtained immediately after injection to follow the accumulation phase. Stimulation with citric acid was performed 25 minutes later, after which the secretory phase was followed for over 20 minutes.

Salivary gland scintigraphic data were gathered with a gammacamera with a low energy general purpose collimator. The patient lay supine and the camera was positioned frontally. A dynamic study of 20 minutes' duration with 30 seconds per frame and a zoom factor of 1.33 in a 64×64 pixel matrix was used. Immediately after the dynamic imaging, three static projection images (frontal, left lateral, and right lateral) with 300 000 counts each were obtained with a 128×128 pixel matrix and a zoom factor of 1.0. In the lateral projections the patient was asked to turn her head as much as possible, after which the camera head was aligned with the medial line of the head. Immediately after the static views, the same set of acquisition data was used again for another 20 minute dynamic acquisition. Five minutes after the start of the second dynamic acquisition 5% citric acid was given intraorally through a tube attached to a syringe. The patient was asked to swallow a few times during the same frame of 30 seconds and then to lie still. After the dynamic acquisition, another set of three static images with the same projections was taken again.

In the dynamic image sets the four major salivary glands (submandibular and parotid glands) were followed and the mouth and a background region on the brain were outlined to generate background curves for subtraction. The point of administration of the sialogogic citric acid was marked on the curves. An experienced specialist in nuclear medicine, who was unaware of the clinical diagnosis, analysed all curves. All curves were graded as normal, slightly pathological, or pathological.

Psychological tests

Short Form 36 (SF-36)

To evaluate fatigue and the physical and emotional status of the patients, the Medical Outcomes Study Short Form General Health Survey (MOS SF-36)²³⁻²⁴ was used. SF-36 is a questionnaire consisting of 36 items which measure eight health

concepts—namely, physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, vitality (the opposite of which is fatigue), mental health, social functioning, bodily pain, and general health. For each variable item scores are coded, summed, and transformed to a scale from 0 (the worst possible health state) to 100 (the best possible health state).

Jenkins Activity Survey (JAS)

The JAS scale consists of 84 items that are divided into four subscales. For this study we recorded the values of the actual A-B factor with 21 items which best reflect the stress behaviour of a person.²⁵ The instrument has been validated in the Finnish population in the Mini Finland Health Study.²⁶

Toronto Alexithymia Scale (TAS)

The TAS comprises 26 self descriptive statements measured on a five point Likert scale (ranging from "strongly disagree" to "strongly agree") and evaluates three intercorrelated dimensions of the alexithymia construct: difficulties identifying feelings, difficulties describing feelings, and externally oriented thinking. The TAS has been shown to have adequate internal consistency and test-retest reliability.²⁷⁻³⁰

Vital exhaustion (VE)

Vital exhaustion was assessed with form B of the Maastricht Questionnaire.³¹ The questionnaire consists of 21 questions answered "yes", "no", or "don't know", which are scored from 0 to 2. The maximum score is 42. Form B has a good internal consistency. Cronbach's α for VE is 0.85 and test-retest reliability 0.85.³² This questionnaire has been validated in the Finnish population in the Kuopio Ischemic Heart Disease Risk Factor Study.³³

Statistical analysis

The BMDP new system version 1.0 statistical program was used to analyse the data. When comparing the groups (primary SS/secondary SS/non-SS) Pearson's χ^2 and Kruskal-Wallis one-way analysis of variance were used. Values of $p < 0.05$ were considered significant. To evaluate the best possible predictors of scintigraphy and sialometry results, hierarchical linear regression analysis in a stepwise manner was applied. At the first step clinical data (factor 1: ANA, SSA, SSB, IgG, IgA; all with positive weights; factor 2: RF and IgM with positive weights and CRP with a negative weight; factor 3: Hb with a positive weight and ESR with a negative weight) were entered using a stepwise method. At the second step psychological data (VE, SF-36 subscales bodily pain, general health, vitality, and role limitations due to emotional problems) were entered into the regression equation also by a stepwise method.

Ethical aspects

The study was carried out according to the principles of the Declaration of Helsinki, and with the approval of the ethics committees of the institutions involved.

RESULTS

Laboratory tests and psychological profiles

Hb, CRP, and serum IgM were comparable in all study groups. Mean (SD) ESR (18.6 (12.1) mm/1st h), serum IgG (15.6 (5.1) g/l), and serum IgA (2.9 (1.2) g/l) were high in primary SS, followed by secondary SS, and controls, in this ranking order, but the differences between the groups were not statistically significant. RF was only found in primary SS (97.0 (108) IU/ml, range 0–387) and secondary SS (67.4 (56.8) IU/ml, range 0–154) ($p < 0.001$). Similarly, SSA was only found in primary and secondary SS (25.1 (41.0), range 0–128 and 2.3 (5.6), range 0–16, titres, respectively), but not in controls. Both patients with SS and patients with sicca symptoms but without SS had symptoms of xerostomia and diminished salivary

Table 1 Psychological profile in the three study groups (primary SS, secondary SS, and patients with sicca symptoms but without SS). Results are shown as mean (SD) [range]

Measurements	Primary SS (n=26)	Secondary SS (n=8)	Non-SS (n=9)	p Value
TAS (20–100)	49.7 (12.2) [32–78]	48.0 (14.9) [42–58]	47.3 (9.3) [30–58]	0.9
DIF scale (7–35)	18.7 (6.2) [7–31]	16.9 (7.1) [9–29]	17.9 (4.0) [10–23]	0.75
DDF scale (5–25)	11.9 (3.8) [5–18]	12.0 (5.0) [6–18]	13.1 (3.4) [9–19]	0.71
EOT scale (8–40)	19.1 (4.4) [8–30]	19.1 (5.3) [12–27]	16.3 (4.1) [9–24]	0.26
JAS (type A/B behaviour)	−0.8 (9.2) [−15–20]	−3.2 (4.4) [−7–6]	−1.2 (10.6) [−13–15]	0.84
Vital exhaustion (VE) (0–2)	1.2 (0.5) [0.2–2.0]	1.0 (0.5) [0.1–1.7]	1.2 (0.3) [0.8–1.7]	0.62
SF-36 (0–100)				
Physical functioning	67.1 (19.2) [10–100]	65.0 (19.8) [40–95]	61.1 (24.8) [20–90]	0.78
Role physical	27.9 (34.2) [0–100]	28.1 (38.8) [0–100]	11.1 (25.3) [0–75]	0.41
Bodily pain	44.8 (25.8) [0–100]	49.5 (19.7) [22–84]	34.7 (16.7) [10–62]	0.27
General health	33.3 (17.0) [5–77]	41.5 (19.0) [20–82]	30.0 (15.4) [5–60]	0.3
Vitality	38.8 (23.1) [5–100]	47.5 (12.0) [35–75]	41.1 (18.7) [5–65]	0.44
Role emotional	56.0 (43.8) [0–100]	45.8 (50.2) [0–100]	40.7 (43.4) [0–100]	<0.05
Mental health	57.1 (20.7) [20–100]	63.5 (12.2) [48–88]	64.3 (6.9) [56–76]	0.2
Social functioning	55.3 (27.2) [0–100]	57.8 (22.1) [37–100]	50.0 (24.2) [12–87]	0.74

DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking.

Table 2 Statistical characteristics of scintigraphy results. In this analysis both pathological and slightly pathological scintigraphy results were regarded as pathological

	Gl. submandibularis (%)	Gl. parotis (%)
Specificity	77.8	88.9
Sensitivity	85.3	47.1
Positive predictive value	93.5	94.1
Negative predictive value	58.3	30.8

flow rates. Unstimulated salivary flow was slightly lower in primary SS (0.9 (1.0) ml/15 min) and secondary SS (1.5 (1.8) ml/15 min) than in controls (2.1 (1.4) ml/15 min) ($p=0.05$). The stimulated salivary flow values were (7.2 (6.3), 10.5 (11.5) and 11.7 (5.4) ml/5 min, respectively; NS).

Table 1 shows the results of the tests reflecting the health status and psychological profile of the patients. The groups did not show statistically significant differences in most of these variables. The only exception was one subscale of SF-36—namely, the role limitations due to emotional problems. This was significantly lower ($p<0.05$) in non-SS and patients with secondary SS than in patients with primary SS.

Salivary gland scintigraphy

Submandibular gland scintigraphy was pathological in 18/26 (69%) patients with primary SS and, in addition, slightly pathological in three (12%) more cases and pathological in all eight patients with secondary SS, whereas patients with sicca symptoms but without SS showed normal results in 7/9 (78%) cases. Parotid gland scintigraphy was pathological in 4/26 (16%) patients with primary and in 5/8 (62%) patients with secondary SS, whereas patients with sicca symptoms but without SS had normal results in 8/9 (90%) cases. Subdivision of the scintigraphy data to the accumulation/uptake phase and to the secretory phase did not provide any additional value.

In both primary and patients with secondary SS, submandibular gland scintigraphies showed more pathological results than parotid gland scintigraphies. Compared to patients with primary SS, scintigraphies of patients with secondary SS had more severe pathology (in submandibular glands 100% v 69%, in parotid glands 62% v 16%).

The specificity and sensitivity of the scintigraphy were calculated so that the slightly pathological cases were classified as pathological, and table 2 shows these values together with the positive and negative predictive values. If, instead, the

Table 3 Results of regression analyses

	β Coefficient	p Value	Changes in R^2
Dependent: Subjective evaluation of submandibular gland scintigraphy			
$R=0.715$, $R^2=0.51$, $R^2_{adj}=0.45$, $F=8.356$, $df=4.32$; $p<0.0005$			
Factor 1	0.346	0.015	0.218
Diagnosis	−0.406	0.006	0.09
Vitality	0.506	0.001	0.117
Role emotional	−0.341	0.024	0.085
Dependent: Sialometry stimulated flow			
$R=0.364$, $R^2=0.133$, $R^2_{adj}=0.107$, $F=5.208$, $df=1.34$; $p=0.029$			
Factor 2	0.364	0.029	0.133

Factor 1 includes ANA, SSA, SSB, IgG, and IgA, all with positive weights.

Factor 2 includes IgM and RF, which have positive weights, and CRP, which has a negative weight.

slightly pathological cases were classified as normal, the specificity for the submandibular glands increased to 88.9% and the sensitivity declined to 76.5%, with the corresponding figures for parotid glands being 100% and 26.5%.

Multiple regression analysis

In the multiple regression analysis (table 3) the results of the scintigraphies of the submandibular glands were predicted to 51% by factor 1 (consisting of ANA, SSA, SSB, IgG, and IgA, all with positive weights), diagnosis, vitality, and role limitations due to emotional problems, with the last two of these representing subscales of SF-36. Stimulated salivary flow was explained to 13.3% by factor 2 (consisting of IgM and RF with positive weights and CRP with negative weight).

This study disclosed no significant predictors for parotid gland scintigraphies or for the unstimulated salivary flow rates.

DISCUSSION

Patients with SS and patients with sicca symptoms but without SS were similar for xerostomia and subnormal resting and stimulated salivary flow rate values. Furthermore, stimulated salivary flow values did not differ between the patients with SS and patients with sicca symptoms but without SS, and the difference in the unstimulated salivary flow was small. Despite this, the results of the present study show that scintigraphy, well recognised for its ability to differentiate between patients with SS and healthy controls, also differentiates reasonably well between patients with SS and patients with sicca symptoms but without SS.

The results of the study show that visual evaluation of scintigraphies is both sensitive and specific for the submandibular glands, with 85.3% sensitivity and 77.8% specificity. These results are similar to those described earlier by other groups using different evaluation methods.^{1 34–38} Submandibular glands were much more affected than the parotid glands. The difference in diagnostic potency of the parotid and submandibular glands seen in scintigraphy has also been described similarly with salivary secretion.³⁹ This might, at least in part, be because of differences in the structure and function of these two major salivary glands. This may also explain the poor discriminative potency of whole saliva in SS.

Both submandibular and parotid gland scintigraphy results showed more severe functional defects in patients with secondary SS than in patients with primary SS. As patients with secondary SS have worse scintigraphy results than patients with primary SS this may indicate that disease modifying antirheumatic drugs have little or no effect on the progression of salivary gland disease. Indeed, lack of clinically beneficial effects of hydroxychloroquine,⁴⁰ methotrexate,⁴¹ and azathioprine^{42 43} treatment has been reported, even though decreases in inflammatory parameters were achieved.

The original European classification criteria for SS¹ have been criticised, because their use may lead to overdiagnosis. If four of the six classification criteria are met, the specificity and sensitivity of the SS diagnosis should be quite high, about 95%. However, if these four items are subjective feelings of dry eyes and dry mouth associated with diminished lachrymal and salivary flow, then patients with neural dysregulation of the exocrine glands might become false positives.⁴⁴ This relates in particular to patients who have a diminished efferent neural outflow as a result of peripheral or central events—that is, anticholinergic drugs/blockade of the muscarinic receptors of the acinar cells or mood related inhibition of the central lachrymatory and salivatory nuclei. We believe that our patients with sicca symptoms but without SS belong to the last mentioned category. Therefore, in the modified European classification criteria, autoantibodies and/or focal sialadenitis are required for a diagnosis of SS.² However, particularly in elderly women, the presence of autoantibodies, like ANA, may be quite common. The present study suggests that in addition to various autoimmune features, scintigraphy also can be useful in the differentiation between patients with SS and patients with sicca symptoms but without SS.

No statistically significant differences were found in the psychological profiles between our patients with primary and secondary SS and patients with sicca symptoms but without SS. TAS values showed that our patients with SS and patients with sicca symptoms but without SS were not alexithymic. The mean TAS scores for the patients with primary and secondary SS and patients with sicca symptoms but without SS were 49.7 (12.2), 48.0 (14.9), and 47.3 (9.3), respectively. These scores are lower than in the Finnish primary healthcare patients in general (64.4 (11.7) for male and 63.5 (11.9) for female patients).⁴⁵ Only one patient had TAS score over the cut-off value of 74.²⁸ There was no difference between the groups in the VE scale—a mental state characterised by unusual tiredness and lack of energy, increased irritability, and feelings of demoralisation.³¹ However, when compared with the general population, all patients with SS and patients with sicca symptoms but without SS had lower values in all SF-36 subscales.⁴⁶ Clearly, patients with sicca symptoms but without SS, who lacked autoimmune findings and organ changes, felt that they were sick. This suggests that xerostomia and the diminished salivary flow values recorded in patients with sicca symptoms but without SS may indeed be due to inhibitory central signals paralysing the functions of the lachrymatory and salivatory nuclei and leading to diminished parasympathetic and adrenergic salagogic output. In addition to serological tests, scintigraphy was found to be useful in the differentiation between patients with sicca symptoms but without SS and patients with SS.

To analyse the abovementioned hypothesis of the psychological distress as an eventual cause of sicca symptoms in the absence of SS in more detail, multiple regression analysis was performed. Using this approach, it was possible to predict the results of the submandibular gland scintigraphy to 51% by the combined use of factor 1 (ANA, SSA, SSB, IgG, and IgA), diagnosis, vitality, and role limitations due to emotional problems. Our finding that it is possible to predict the results of scintigraphies with the use of laboratory data and results of psychological tests is a new one. This observation is consistent with the theory that the function of the major salivary glands may be affected, in addition to the autoimmune-inflammatory mechanisms, also by psychological mechanisms through the cortex of the brain and the salivatory nuclei in the midbrain. The integrating salivatory centres are subjected to control from the cerebral cortex, amygdala, and hypothalamus. Salivary secretion and subjective oral dryness have been shown to be associated with stress, depression, and anxiety.^{47–49} Depression has been found in 21.3% of subjects with a subjective dry mouth sensation and in only 3.2% of controls.⁵⁰ The explanatory value of the psychological distress, however, was quite limited, suggesting that it was more a confounding than causative factor, confounding in the sense that it makes the diagnosis of SS more difficult in the absence of hard data such as autoantibody tests and scintigraphy.

Interestingly, there were no statistically significant predictors for the subjective visual evaluation of parotid gland scintigraphy results or for the resting salivary flow. The resting salivary flow is considered to be more accurate than the stimulated salivary flow in the evaluation of salivary glands, and that was also why it was included in the diagnostic criteria for SS. However, none of the independent variables recorded in the present study could predict the resting salivary flow rates. This suggests that the independent variables recorded did not contain such measures that influence the resting salivary flow. One such variable might be autoantibodies to muscarinic ACh receptors. These autoantibodies have already been found to be associated with ocular symptoms.⁵¹ These muscarinic ACh receptor autoantibodies do not explain the sicca symptoms in the absence of SS. Another possible factor, which might affect the resting salivary flow and the immune status of the patient is cigarette smoking.^{52 53} Nicotine, which is one of the main constituents of cigarette smoke, suppresses the immune system but might have therapeutic potential as a neuroprotective and anti-inflammatory agent. Patients with sicca symptoms but without SS had dry eyes and dry mouth and they also had diminished resting lachrymal and salivary flow values. Despite this, their scintigraphy results were normal and found to be helpful in the differential diagnosis of SS in this situation, which is probably often found in rheumatology consultations. Future work may address the oral quality of life in patients with SS and in patients with sicca symptoms but without SS.^{54 55}

ACKNOWLEDGEMENTS

This study was supported by grants from Finska Läkaresällskapet, Wilhelm and Else Stockmann Foundation, HUS evo grant, and the Finnish Dental Society Apollonia.

Authors' affiliations

E-K Tensing, S Solovieva, S Natah, J Ma, T F Li, Y T Konttinen, Institute of Biomedicine/Anatomy, Biomedicum Helsinki, University of Helsinki
D C Nordström, T Helve, Y T Konttinen, Department of Medicine/Invärtes Medicin, Helsinki University Central Hospital, Helsinki
K-O Schaman, I Sipponen-Tuunonen, Clinical Laboratory Department, Malmi Hospital, Helsinki, Finland
Y T Konttinen, Orthopaedic Hospital of the Invalid Foundation, Helsinki

REFERENCES

- 1 Vitali C, Bombardieri S, and the European Study Group on Diagnostic Criteria for SS. The European classification criteria for Sjögren's

- syndrome (SS). Proposal for a modification of the rules for classification suggested by the analysis of the receiver operating characteristic (ROC) curve of the criteria performance. *J Rheumatol* 1997; 4:38.
- 2 **Kohn WG**, Ship JA, Atkinson JC, Patton LL, Fox PC. Salivary gland ^{99m}Tc -scintigraphy: a grading scale and correlations with major salivary gland flow rates. *J Oral Pathol Med* 1992;21:70-4.
 - 3 **Håkansson U**, Jacobsson L, Lilja B, Manthorpe R, Henriksson V. Salivary gland scintigraphy in subjects with and without symptoms of dry mouth and/or eyes, and patients with primary Sjögren's syndrome. *Scand J Rheumatol* 1994;23:326-33.
 - 4 **Vivino FB**, Hermann GA, Katz WA. Assessment of xerostomia in Sjögren's syndrome using two methods of salivary scintigraphy. *Clin Rheumatol* 1995;14:57.
 - 5 **Saito T**, Fukuda H, Horikawa M, Ohmori K, Shindoh M, Amemiya A. Salivary gland scintigraphy with ^{99m}Tc -pertechnetate in Sjögren's syndrome: relationship to clinicopathologic features of salivary and lacrimal glands. *J Oral Pathol Med* 1997;26:46-50.
 - 6 **Arrago JP**, Rain LD, Brocheriou DC, Rocher F. Scintigraphy of salivary glands in Sjögren's syndrome. *J Clin Pathol* 1987;40:1463-7.
 - 7 **Sugihara T**, Yoshimura Y. Scintigraphic evaluation of the salivary glands in patients with Sjögren's syndrome. *Int J Oral Maxillofac Surg* 1988;17:71-5.
 - 8 **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;40:64-9.
 - 9 **Jonsson R**, Kroneld U, Bäckman K, Magnusson B, Tarkowski A. Progression of sialadenitis in Sjögren's syndrome. *Br J Rheumatol* 1993;32:578-81.
 - 10 **Manganelli P**, Salaffi F, Nervetti A, Raffaini N, Olivetti G. Morphometric study of salivary glands in primary Sjögren's syndrome. *Clin Exp Rheumatol* 1989;7:273-6.
 - 11 **Cutolo M**, Sulli A, Villaggio B, Seriola B, Accardo S. Relations between steroid hormones and cytokines in rheumatoid arthritis and systemic lupus erythematosus. *Ann Rheum Dis* 1998;57:573-7.
 - 12 **Cutolo M**, Masi AT, Bijsma JW, Chikanza IC, Bradlow HL, Castanetta L. Neuroendocrine immune basis of the rheumatic diseases. *Ann NY Acad Sci* 1999;876:11-15.
 - 13 **Kontinen YT**, Hukkanen M, Kemppinen P, Segerberg M, Sorsa T, Malmström M, et al. Peptide-containing nerves in labial salivary glands in Sjögren's syndrome. *Arthritis Rheum* 1992;35:815-20.
 - 14 **Kontinen YT**, Platts IAM, Tuominen S, Eklund KK, Santavirta S, Törnwall J, et al. Role of nitric oxide in Sjögren's syndrome. *Arthritis Rheum* 1997;40:875-83.
 - 15 **Main C**, Blennerhassett P, Collins SM. Human recombinant interleukin 1 beta suppresses acetylcholine release from rat myenteric plexus. *Gastroenterology* 1993;104:1648-54.
 - 16 **Stern ME**, Beuremann RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea* 1998;17:584-99.
 - 17 **Kelles A**, Janssens J, Tack J. IL-1beta and IL-6 excite neurones and suppress cholinergic neurotransmission in the myenteric plexus of the guinea pig. *J Neurogastroenterol Motil* 2000;12:531-8.
 - 18 **Bacman S**, Sterin-Borda L, Camusso JJ, Arana R, Hubscher O, Borda E. Circulating antibodies against rat parotid gland M3 muscarinic receptors in primary Sjögren's syndrome. *Clin Exp Immunol* 1996;104:454-9.
 - 19 **Perez Leiros C**, Sterin-Borda L, Hubscher O, Arana R, Borda ES. Activation of nitric oxide signaling through muscarinic receptors in submandibular glands by primary Sjögren's syndrome antibodies. *Clin Immunol* 1999;90:190-5.
 - 20 **Törnwall J**, Kontinen YT, Tuominen RK, Törnwall M. Protein kinase C expression in salivary gland acinar epithelial cells in Sjögren's syndrome. *Lancet* 1997;349:1814-15.
 - 21 **Stern ME**, Beuremann RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. A unified theory of the role of the ocular surface in dry eye. *Adv Exp Med Biol* 1998;438:643-51.
 - 22 **Ware JE Jr**, Sherbourne CD. The MOS 36-item short form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
 - 23 **Jenkinson C**, Coulter A, Wright L. Short form 36 (SF-36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993;306:1437-40.
 - 24 **Jenkins CD**, Zyzanski SJ, Rosenman RH. Progress toward validation of a computer-scored test for the type A-coronary-prone behaviour pattern. *Psychosom Med* 1971;33:193-202.
 - 25 **Reunanen A**, Hanses O, Maatela J, Impivaara O, Aromaa A. Type A behaviour pattern in Finland. *Ann Clin Res* 1987;19:114-19.
 - 26 **Taylor GJ**, Ryan D, Bagby RM. Toward the development of a new self-report alexithymia scale. *Psychother Psychosom* 1985;44:191-9.
 - 27 **Taylor GJ**, Bagby RM, Ryan DP, Parker JD, Doody KF, Keefe P. Criterion validity of the Toronto alexithymia scale. *Psychosom Med* 1988;50:500-9.
 - 28 **Taylor GJ**, Bagby RM, Ryan DP, Parker JD. Validation of the alexithymia construct: a measurement-based approach. *Can J Psychiatry* 1990;35:290-7.
 - 29 **Bagby RM**, Taylor GJ, Parker JD, Loiselle C. Cross-validation of the factor structure of the Toronto alexithymia scale. *J Psychosom Res* 1990;34:47-51.
 - 30 **Appels A**. Loss of control, vital exhaustion and coronary heart disease. In: Steptoe A, Appels A, eds. *Stress, personal control and health*. Brussels: John Wiley and Sons Ltd; 1989:215-35.
 - 31 **Appels A**, Höppner P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol* 1987;17:15-24.
 - 32 **Julkunen J**, Salonen R, Kaplan GA, Chesney MA, Salonen JT. Hostility and progression of carotid atherosclerosis. *Psychosom Med* 1994;56:519-25.
 - 33 **Fossaluzza V**, De Vita S, Geatti O. Sequential salivary scintigraphy in Sjögren's syndrome: proposal for a new method of evaluation. *Clin Exp Rheumatol* 1990;8:469-74.
 - 34 **Markusse HM**, Pillay M, Cox PH. A quantitative index derived from ^{99m}Tc -pertechnetate scintigraphy to assist in the diagnosis of primary Sjögren's syndrome. *Nucl Med* 1992;31:3-6.
 - 35 **Markusse HM**, Pillay M, Breedveld FC. The diagnostic value of salivary gland scintigraphy in patients suspected of primary Sjögren's syndrome. *Br J Rheumatol* 1993;32:231-5.
 - 36 **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* 1993;30:161-70.
 - 37 **Hermann GA**, Vivino FB, Shnier D, Krumm RP, Mayrin V. Diagnostic accuracy of salivary scintigraphy indices in xerostomic populations. *Clin Nucl Med* 1999;24:167-72.
 - 38 **Kruize AA**, Hene RJ, Kallenberg CG, van Bijsterveld OP, van der Heijde, Kater L, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. *Ann Rheum Dis* 1993;52:360-4.
 - 39 **Kalk WW**, Vissink A, Spijkervet FK, Bootsma H, Kallenberg CG, Nieuw Amerongen AV. Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. *Ann Rheum Dis* 2001;60:1110-16.
 - 40 **Tishler M**, Yaron I, Shirazi I, Yaron M. Hydroxychloroquine treatment for primary Sjögren's syndrome: its effect on salivary and serum inflammatory markers. *Ann Rheum Dis* 1999;58:253-6.
 - 41 **Skopouli FN**, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjögren's syndrome. *Clin Exp Rheumatol* 1996;14:555-8.
 - 42 **Price EJ**, Rigby SP, Clancy U, Venables PJ. A double blind placebo controlled trial of azathioprine in the treatment of primary Sjögren's syndrome. *J Rheumatol* 1998;25:896-9.
 - 43 **Fox RI**, Kontinen Y, Fisher A. Use of muscarinic agonists in the treatment of Sjögren's syndrome. *Clin Immunol* 2001;101:249-63.
 - 44 **Joukamaa M**, Sohlman B, Lehtinen V. Alexithymia in primary health care patients. *J Psychosom Res* 1995;39:833-42.
 - 45 **Tensing EK**, Solovieva SA, Tervahartala T, Nordstrom DC, Laine M, Niissalo S, et al. Fatigue and health profile in sicca syndrome of Sjögren's and non-Sjögren's syndrome origin. *Clin Exp Rheumatol* 2001;19:313-6.
 - 46 **Aung W**, Yamada I, Umehara I, Ohbayashi N, Yoshino N, Shibuya H. Sjögren's syndrome: comparison of assessments with quantitative salivary gland scintigraphy and contrast sialography. *J Nucl Med* 2000;41:257-62.
 - 47 **Moret S**, Coudert JL, Bejat C, Robin O, Lissac M. The influence of basal anxiety on unstimulated parotid and submandibular saliva. *Arch Oral Biol* 1993;38:751-4.
 - 48 **Bergdahl M**, Bergdahl J. Low unstimulated salivary flow and subjective oral dryness: association with medication, anxiety, depression, and stress. *J Dent Res* 2000;79:1652-6.
 - 49 **Pedersen A**, Reibel J, Nauntofte B. Primary Sjögren's syndrome: subjective symptoms and salivary findings. *J Oral Med* 1999;28:303-11.
 - 50 **Bergdahl M**, Bergdahl J, Johansson I. Depressive symptoms in individuals with idiopathic subjective dry mouth. *Oral Pathol Med* 1997;26:448-50.
 - 51 **Bacman S**, Berra A, Sterin-Borda L, Borda E. Muscarinic acetylcholine receptor antibodies as a new marker of dry eye Sjögren syndrome. *Invest Ophthalmol Vis Sci* 2001;42:321-7.
 - 52 **Sopori M**. Effects of cigarette smoke on the immune system. *Nature Rev Immunol* 2002;2:372-7.
 - 53 **Manthorpe R**, Benoni C, Jacobsson L, Kirtava Z, Larsson A, Liedholm R, et al. Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjögren's syndrome? *Ann Rheum Dis* 2000;59:54-60.
 - 54 **Slade GD**, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. *Community Dent Health* 1994;11:3-11.
 - 55 **Thomson WN**, Chalmers JM, Spencer AJ, Williams SM. The xerostomia inventory: a multi-item approach to measuring dry mouth. *Community Dent Health* 1999;16:12-17.