Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis

Till Uhlig, Tore Kristian Kvien, Janicke Liaaen Jensen, Tony Axéll

Abstract

***Objectives*—(1) To estimate the prevalence of ocular and oral sicca symptoms (SISY) or reduced saliva and tear production; (2) to relate SISY and sicca signs to measures of disease activity, damage, and health status; and (3) to examine the relation between symptoms and objective signs of tear and saliva production in a large sample of representative patients with rheumatoid arthritis (RA).**

***Methods*—From an unselective county RA register 636 patients (age 20–70 years) were examined with Schirmer-I test (ST), unstimulated whole saliva (UWS), questions on SISY and measures of disease activity, damage and health status.**

***Results*—Ocular sicca symptoms were reported in 38%, oral sicca symptoms in 50%, and a combination of both in 27%. Reduced tear production was present in 29%, and reduced saliva production in 17%. The minimum frequency of secondary Sjögren's syndrome was 7%. Measurements of exocrine disease manifestations were to variable extents bivariately correlated to disease activity measures, physical disability, pain, fatigue, and use of xerogenic drugs, but were not related to deformed joint count. Multivariate analyses revealed significant associations between disease activity and reduced saliva production. Only weak associations between SISY and tear or saliva production were observed.**

***Conclusion*—SISY, reduced tear and saliva production were frequent extra-articular manifestations in RA, but were only weakly intercorrelated. High disease activity and at least two SISY were independent predictors of reduced saliva production, but ocular and oral dryness did not seem to be closely related to disease duration, disease activity, damage or health status.**

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Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
T Uhlig
T K Kvien

Factulty of Dentistry, University of Oslo, Oslo, Norway
J L Jensen
T Axéll

Correspondence to:
Dr T Uhlig, Department of Rheumatology, Diakonhjemmet Hospital, Box 23 Vinderen, N-0319 Oslo, Norway.

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Rheumatoid arthritis (RA) is a chronic inflammatory musculoskeletal disease with considerable morbidity and mortality,[1] and may present with extra-articular manifestations including involvement of exocrine lacrimal and salivary glands.[2] The relation between RA and secondary Sjögren's syndrome (SS) has been unclear, partly because classification criteria are still controversial.[3] Henrik Sjögren originally encountered RA as the most frequent of all connective tissue diseases among patients with the sicca complex.[4] Other connective tissue diseases besides RA, such as systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis or dermatomyositis are also considered when classifying sicca symptoms or secondary SS.[5] A high prevalence of secondary SS has previously been reported in a patient sample with heterogeneous inflammatory rheumatic diseases.[6]

Oral and ocular exocrine gland involvement have received limited attention in RA compared with primary SS. Ocular or oral sicca symptoms (SISY) in RA patients have previously been reported in 18–25%[7 8] and 6–53%[2 9 10] of the patients, respectively. In a recently published pilot study[11] we found a high prevalence of SISY in RA patients, but also an association with xerogenic medication—that is, medication with the capacity to induce dryness, for example xerostomia.

At the recent OMERACT IV meeting in Cancun, Mexico[12] it was decided on a core set of domains to be included in all longitudinal observational studies. Furthermore, a variety of demographic and possible risk factors should be included as covariates. Extra-articular manifestations of RA represent a domain in between outcome and process end points, as they may be considered either as an indicator of damage or as a marker reflecting disease activity. This concerns also disease manifestations from exocrine glands, but little is known about the relation between signs of glandular dysfunction and process or outcome measures.

The unselective, county based register of RA in the city of Oslo, Norway, provides the opportunity to explore exocrine gland function in a large sample of patients, applying measurement tools from published criteria for SS.[13] Our first aim with this study was to estimate the prevalence of SISY and reduced saliva and tear production in a representative and large sample of RA patients. Secondly, we wanted to explore possible differences between patients with and without SISY and reduced saliva and tear production regarding demographic variables, comedication, clinical and self reported measures of disease activity, health status, and damage. The third objective was to examine the relation between SISY and quantitative measures of saliva and tear production. Our hypothesis was to find a significant correlation between SISY and exocrine gland function. SISY as well as objective signs of lacrimal and salivary gland involvement were considered to be an extra-articular complication of RA. We expected,

Table 1 Comparison of demographic features between examined and not examined RA patients from the Oslo RA register (mean(SD) or %)

	Examined (n=636)	*Not examined (n=258)*	*p value*
Age (y)	53.6 (12.2)	54.7 (12.8)	0.25
Female	80.2	78.7	0.61
Disease duration (y)	12.2 (9.3)	13.0 (9.3)	0.25
RF positive*	51.5	47.3	0.27

*Waaler-Rose IgM titre ⩾64.

therefore, to find a relation to disease duration and markers of disease activity and severity.

Methods

PATIENTS

Patients in this study were recruited from the Oslo Rheumatoid Arthritis Register (ORAR). The ORAR has earlier been described in detail[14–16] and is estimated to be complete for about 85% of all RA patients aged 20–79 years in the county of Oslo.[14] Over an 18 month period in 1996 and 1997 all patients from ORAR with RA[17] aged 70 years or younger (born 1926 or later, n=894) were contacted by mail and invited to participate in a clinical examination at the department of rheumatology. Of the 894 patients invited to participate, 636 (71.1%) attended. Non-participants (n=258) comprised patients not willing to attend (n=147), failing to respond at all after a reminder (n=95), and those deceased after 1 January 1996 (n=16). Demographic variables and presence of rheumatoid factor were similar between examined patients and non-attendants from the ORAR (table 1). Of the patients examined, 43% were currently using non-steroidal anti-inflammatory drugs, 40% used prednisolone and 48% were current users of disease modifying anti-rheumatic drugs.

CLINICAL EXAMINATION

The clinical examination by a rheumatologist (TU, n=135) or by two specially trained research nurses (n=501) included 28 swollen joint count, 28 tender joint count, 18 deformed joint count, Schirmer-I test (ST), test of unstimulated whole saliva (UWS), and investigator's global assessment of disease activity. Blood tests, including laboratory markers of inflammation were part of the clinical examination. The two research nurses were specially trained to reliably administer both the joint counts, ST and UWS, and they were under continuous supervision of a rheumatologist (TU or TKK). A test of inter-examiner agreement[18] between physician and research nurse in 10 RA patients showed a good result for the strength of agreement on swollen joints (κ value 0.64) and moderate value for tender joints (κ value 0.48).

SCHIRMER-I TEST

The test was performed according to published guidelines.[19–21] Patients had not used tear substitutes for at least one hour before examination. Patients dried their eyes carefully with a soft paper tissue; then the test strips—always starting with the right eye—were placed between the medial and lateral parts of the lower eyelid, and removed after five minutes. Anaesthesia was not used. A positive result for reduced tear production was recorded if the strips were wetted 5 mm or less in one or both eyes, starting from the notch of the test strip corresponding to the inferior lid margin.

UNSTIMULATED WHOLE SALIVA

The test was usually most commonly performed, as recommended, during morning hours before noon.[21] Patients had not eaten, smoked, swallowed liquids or rinsed their mouths for at least one hour before the test. They were seated on a chair and protected from gustatory or other stimulation. After swallowing, saliva was collected over 15 minutes by passive spitting into preweighed containers. Flow rate was expressed as ml/min (1 g=1 ml). The upper limit for reduced saliva production was 1.5 ml/15 min.

QUESTIONNAIRE

The questions on oral and ocular dryness were identical with those from the European classification criteria for SS (three questions on eyes and mouth each).[13] The questionnaire also comprised RA history (medication, complications), and a list of co-morbidities. The investigator recorded medication taken during the past 10 days. Self reported health status was evaluated by the Modified Health Assessment Questionnaire (MHAQ) (physical disability),[22] and by 100 mm visual analogue scales (VAS) (pain and fatigue).

DATA ANALYSES AND STATISTICS

Cases with at least one SISY from mouth and eyes were classified into the group "moderate SISY", and those with at least two symptoms from mouth and eyes into the group "severe SISY". These groups were compared with the "non-sicca group" consisting of patients reporting no SISY at all. Thereby, the moderate sicca group also comprised cases from the severe sicca group, as well as, for example, patients with two mouth and one eye symptoms. Thus, patients with intermediate findings (for example, one sicca symptom) were not eligible for comparable analyses of sicca and non-sicca groups. The cases with pathologically reduced ST were classified as the "reduced tears group", and those with reduced UWS as the "reduced saliva group".

The number of positive sicca questions was computed into a sum score of total SISY (range 0–6). The modified disease activity score (DAS) was computed from the 28 tender and swollen joint counts, the erythrocyte sedimentation rate (ESR) and patient global assessment (range 0–4).[23 24] Medication taken during the past 10 days coded as xerogenic (that is, a capacity of inducing dryness) comprised β blockers, diuretics, anti-depressants, neuroleptics, anti-histamines, adrenergic agents, atropine, opioids or other agents with dryness as a well known side effect.[25 26]

The data were analysed using the SPSS/PC software version 8.0. Comparisons were made using a two sample *t* test for continuous

*Table 2 Number and frequency of positive answers to sicca questions and for combinations in RA patients (n=631)**

Questions[13]	*Number**	*%*
Dry eyes daily for more than 3 months?	126	20.3
Sensation of sand or gravel?	218	34.7
Use of tear substitutes more than three times a day?	19	3.1
Dry mouth daily for more than 3 months?	204	32.6
Experienced swollen salivary glands?	28	4.6
Drink liquids to swallow dry food?	259	41.7
Combinations		
at least one sicca symptom	383	60.7
at least one eye symptom	237	37.6
at least one mouth symptom	318	50.4
at least one symptom from eyes and mouth	172	27.3
at least two symptoms from eyes and mouth	60	9.5

*Number varies because of missing data.

variables and Pearson's χ^2 test for categorical variables. Pearson's test was used to examine bivariate correlations. For all analyses a 5% level of significance was chosen.

In multivariate analyses the relative risk of reduced tear or saliva production by potential predictive risk factors was estimated as odds ratios (OR) with 95% confidence intervals (CI). Reduced tear or saliva production were chosen as dependent variables from a clinical point of view so that the independent predictive value of other clinical conditions could be determined. Using multiple logistic regression analyses, the estimated effect of each individual variable was statistically adjusted for differences in the distributions of and associations among the other independent variables. The following potential confounding and interacting factors were entered into the multifactorial model: age, sex, disease duration, xerogenic drugs, total SISY, rheumatoid factor, DAS. The variables were categorised. Age was categorised into decades and during the statistical analyses condensed into four categories: up to 40 years, 41–50 years, 51–60 years, and 61–70 years. There were two categories for sex (male/female), rheumatoid factor (positive/not positive), and xerogenic medication (yes/no). Four response categories were created for the other variables. SISY categories were 0, 1, 2–3, and 4–6 symptoms. The DAS was categorised into quartiles. Contrasts in the categorical variables were analysed with a method equivalent to the traditional group of "dummy variables" (indicator contrasts), keeping the category with the lowest risk as reference category. Potential interaction terms were during the analyses included in the model. We then removed the variable with the smallest contribution to the model (or the largest p value) as long as that p value was greater than the level chosen ($p>0.05$). Nevertheless, demographic variables of interest (age, sex, disease duration, and xerogenic medication) were kept in the model. In subsequent explanatory analyses DAS was—one at a time—substituted with other markers of disease activity or severity: ESR, C reactive protein (CRP), number of tender joints, swollen joints or deformed joints, MHAQ, pain, fatigue, patient global assessment, or investigator's global assessment.

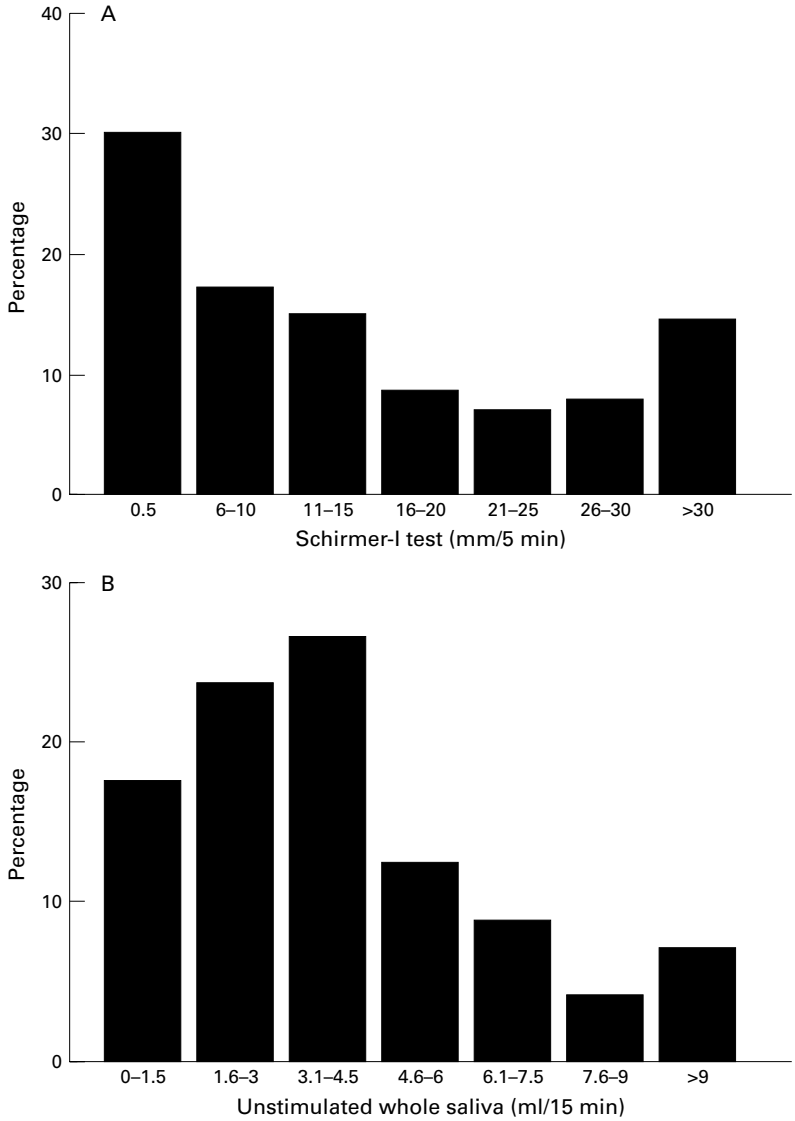

Figure 1 (A) Distribution of tear production (Schirmer I-test) in patients with rheumatoid arthritis. (B) Distribution of saliva production (unstimulated whole saliva) in patients with rheumatoid arthritis.

Results

SICCA SYMPTOMS, SALIVA, AND TEAR PRODUCTION

The mean number of reported SISY was 1.35 (SD 1.44). The upper part of table 2 shows the distribution of positive responses to the six questions on dryness as used in the European classification criteria for SS. Of 631 patients, 383 (60.7%) reported at least one of six SISY, 172 (27.3%) at least one symptom from eyes and from mouth, and 60 (9.5%) reported at least two symptoms from eyes and from mouth (lower part of table 2).

The mean value for ST—considering the worst eye—was 14.7 (SD 11.7) mm; for the right eye 16.1 (SD 12.2) and for the left eye 18.5 (SD 12.2). The correlation coefficient between both eyes was r=0.80. The mean value of UWS was 4.1 (SD 2.9) ml.

The distributions of values for ST and UWS are presented in figure 1A and 1B. Of 614 patients examined with ST, 178 (29.0%) had reduced tear production in at least one eye (fig 1A), and 107 (17.4%) in both eyes (data not shown). Reduced saliva production was found in 104 (16.6%) of 626 patients examined with UWS (fig 1B). Reduced tear and saliva production were found in 46 (7.6%) of 609

*Table 3 Comparison of demographic characteristics and markers of disease activity and severity between non-sicca and sicca groups (n=631)**

	Non-sicca group (no symptoms)	*Moderate sicca group (≥ one symptom from eyes and mouth)*		*Severe sicca group (≥ two symptoms from eyes and mouth)*	
	(n=248)	*(n=172)*	*p value‡*	*(n=60)*	*p value‡*
Dryness					
Unstimulated whole saliva (ml)	4.85 (3.03)	3.49 (2.84)	<0.001	2.55 (2.48)	<0.001
Schirmer-I test (mm)	16.2 (12.0)	12.0 (11.3)	<0.01	10.6 (10.7)	0.01
Demographic features					
Age (y)	50.8 (12.7)	55.9 (11.1)	<0.001	56.5 (12.1)	<0.01
Female %	78.6	84.9	0.11	86.7	0.16
Disease duration (y)	11.4 (9.0)	13.8 (10.0)	0.01	15.0 (10.1)	0.01
Rheumatoid factor positive	51.3	50.6	0.89	50.0	0.86
Xerogenic drugs (used %)†	13.7	27.3	<0.001	33.3	<0.001
Disease activity					
ESR (mm 1st h)	20.4 (16.5)	20.4 (18.3)	0.96	21.1 (16.3)	0.76
C-reactive protein (mg/dl)	12.8 (13.3)	12.7 (13.3)	0.07	11.8 (9.2)	0.50
Swollen joint count (0–28)	7.2 (6.3)	7.5 (5.7)	0.56	7.7 (6.3)	0.55
Tender joint count (0–28)	4.9 (5.9)	8.4 (6.8)	<0.001	11.2 (7.4)	<0.001
Patient's global assessment (range 1–5)	2.34 (0.90)	2.84 (0.83)	<0.001	3.07 (0.83)	<0.001
Investigator's global (100 mm VAS)	27.0 (25.9)	31.8 (24.0)	0.06	34.4 (26.9)	0.06
Disease activity score	3.97 (1.59)	4.69 (1.25)	<0.001	5.04 (1.33)	<0.001
Damage					
Deformed joint count (0–18)	1.8 (3.5)	1.9 (3.5)	0.91	1.6 (3.2)	0.64
Health status					
MHAQ (1–4)	1.44 (0.44)	1.77 (0.52)	<0.001	1.92 (0.55)	<0.001
Pain (100 mm VAS)	28.5 (22.4)	41.0 (21.6)	<0.001	46.1 (23.7)	<0.001
Fatigue (100 mm VAS)	32.9 (27.6)	53.3 (26.5)	<0.001	59.1 (24.8)	<0.001

*Mean (SD) for continuous or % for categorical variables. †Drugs with potential to induce sicca complaints in eyes or mouth (β blockers, diuretics, antidepressants, neuroleptics, antihistamines, adrenergic agents, atropine, opioids or other specific drugs). ‡p value compared with non-sicca group.

patients examined with both ST and UWS, while 377 (61.8%) had normal values for both tear and saliva production.

Of these 46 patients with reduced saliva and tear production, 42 fulfilled at least three criteria (at least one mouth or eye symptom, positive ST, and positive test for UWS) from the European criteria for secondary SS.[13] Thus, the minimum prevalence of secondary SS was 7% without performed lip biopsies, rose bengal tests, parotid sialographies, and salivary scintigraphies.

GROUP COMPARISONS OF DEMOGRAPHIC FEATURES

Demographic features were compared between sicca and non-sicca groups (table 3) and the patient groups defined according to tear and saliva production (table 4). Patients in the sicca groups were older and had longer disease duration than those in the non-sicca group, while the proportions of women or presence of rheumatoid factor were similar (table 3). Mean values of UWS and ST were lower in the highest age group (fig 2A and 2B). A higher mean

*Table 4 Comparison between patient groups according to tear (Schirmer-I test) and saliva (unstimulated whole saliva) production (n=610)**

	Normal tears and saliva	*Reduced tears*		*Reduced saliva*		*Reduced tears and saliva*	
	ST and UWS normal(n=377)	*ST ≤5 mm (n=178)*	*p value‡*	*UWS ≤1.5 ml (n=104)*	*p value‡*	*ST ≤5 mm, UWS <1.5 ml (n=46)*	*p value‡*
Measures of dryness							
Positive sicca questions (0–6)	1.17 (1.34)	1.66 (1.55)	<0.001	2.19 (1.53)	<0.001	2.76 (1.38)	<0.001
Demographic features							
Age (y)	52.9 (12.0)	54.4 (12.1)	0.18	58.0 (11.3)	<0.001	58.3 (10.8)	<0.01
Female %	79.0	79.2	0.96	83.7	0.30	78.3	0.90
Disease duration (y)	11.8 (8.8)	12.5 (9.6)	0.42	13.2 (9.5)	0.20	12.8 (9.5)	0.50
Rheumatoid factor positive %	48.2	59.6	0.01	52.6	0.44	62.2	0.08
Xerogenic drugs (used %)†	20.2	19.7	0.89	29.8	0.04	32.6	0.05
Disease activity							
ESR (mm 1st h)	18.6 (15.0)	24.2 (19.1)	0.001	27.5 (20.1)	<0.001	26.8 (18.2)	<0.01
C reactive protein (mg/dl)	11.9 (11.5)	14.9 (14.7)	0.02	14.1 (13.0)	0.13	13.8 (12.1)	0.33
Swollen joint count (0–28)	7.0 (5.7)	7.5 (6.4)	0.41	8.3 (6.2)	0.06	8.5 (6.7)	0.17
Tender joint count (0–28)	6.1 (6.2)	6.5 (6.7)	0.51	9.0 (7.5)	<0.001	9.6 (8.0)	<0.01
Patient's global assessment (range 1–5)	2.55 (0.87)	2.67 (0.93)	0.15	2.87 (0.95)	<0.01	2.91 (0.98)	0.02
Investigator's global (100 mm VAS)	26.6 (23.8)	30.5 (25.2)	0.09	35.0 (25.7)	<0.01	35.6 (26.6)	0.04
Disease activity score	4.20 (1.42)	4.46 (1.52)	0.06	5.02 (1.37)	<0.001	5.08 (1.41)	<0.001
Damage							
Deformed joints (0–18)	1.8 (3.5)	1.8 (3.3)	0.99	2.1 (3.7)	0.49	1.8 (3.4)	0.99
Health status							
MHAQ (1–4)	1.55 (0.47)	1.60 (0.53)	0.30	1.72 (0.47)	<0.01	1.75 (0.64)	0.04
Pain (100 mm VAS)	32.9 (22.0)	37.0 (22.6)	0.04	43.1 (22.8)	<0.001	43.1 (22.0)	<0.01
Fatigue (100 mm VAS)	39.7 (27.9)	44.0 (28.4)	0.10	53.5 (27.5)	<0.001	49.8 (27.5)	0.03

*Mean (SD) for continuous and % for categorical variables. †Drugs with capacity to induce sicca symptoms (β blockers, diuretics, antidepressants, neuroleptics, antihistamines, adrenergic agents, atropine, or other specific drugs). ‡p value compared with normal tears and saliva group.

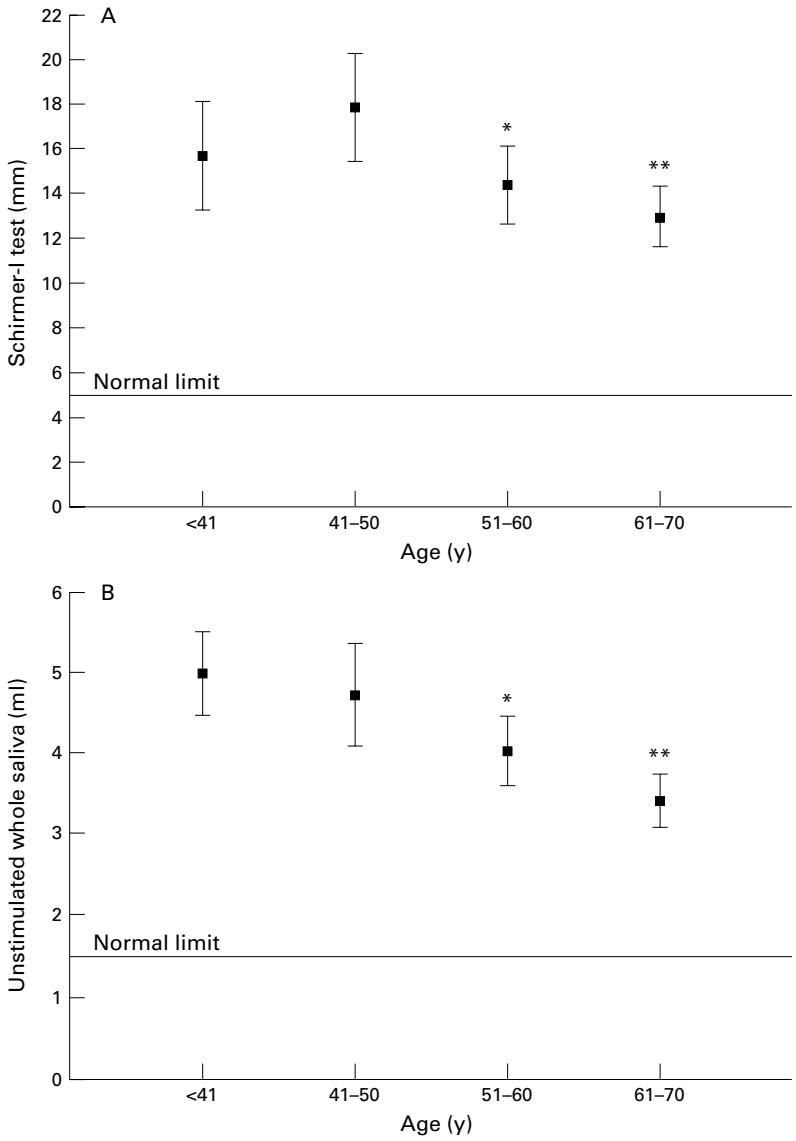

*Figure 2 (A) Variation of tear production (Schirmer I-test) in various age groups. Mean values and 95% confidence intervals (*p<0.05 v 41–50 years, **p=0.056 v <41 years, p<0.001 v 41–50 years). (B) Variation of saliva production (unstimulated whole saliva) with age. Mean values and 95% confidence intervals (*p<0.01 v <41 years, **p<0.001 v <41 years, p<0.001 v 41–50 years, p<0.05 v 51–60 years).*

age was also found in the reduced saliva group, but not in the reduced tears group (table 4). The use of xerogenic medication was about twice as frequent in the moderate sicca group compared with the non-sicca group (table 3), and more prevalent in the reduced saliva group compared with the group with normal tears and saliva (table 4).

GROUP COMPARISONS OF DISEASE ACTIVITY, DAMAGE, AND HEALTH STATUS

The 28 tender joint count, patient's global assessment, and the DAS had higher scores in the moderate sicca group, with even more pronounced findings in the severe sicca groups, while no statistically significant differences were demonstrated for other parameters (table 3). More distinct differences for disease activity measures were found when comparing patients with reduced and normal saliva production (table 4). All seven disease activity measures indicated higher disease activity in the reduced saliva group with significant findings for ESR, 28 tender joint count, patient's as well as investigator's global assessment, and DAS. In the reduced tears group only the two laboratory markers of inflammation indicated increased disease activity (table 4). As for the domain of damage, the 18 deformed joint count did not discriminate between the patient groups defined according to SISY, saliva production, and tear production (table 3 and 4).

Both the moderate sicca and the severe sicca group had worse health status scores (physical disability (MHAQ), pain and fatigue) than the non-sicca group (table 3). Similar, but less evident differences were seen between the reduced saliva/reduced tears and saliva group compared with the normal tears and saliva group (table 4).

RELATION BETWEEN SISY, SALIVA, AND TEAR PRODUCTION

As expected, reported SISY were related to saliva and tear production. The severe sicca group (at least two SISY from both eyes and mouth) had lower mean values for ST and for UWS than the non-sicca group. The mean values (table 3) exceeded though by far the limits for positive test results, and neither did the lower bounds of their 95% confidence intervals (data not shown) include these limits. More SISY were seen in the groups with reduced tears, reduced saliva or both, compared with that with normal tear and saliva secretion (table 4). The sum score of SISY correlated only very weakly with ST (r=0.14) and UWS (r=0.24). The correlation coefficient between ST and UWS was r=0.14 (all p<0.001).

PREDICTION OF REDUCED SALIVA OR TEAR PRODUCTION BY CLINICAL VARIABLES

As shown in tables 3 and 4, patients with reduced tear and saliva production differed from patients with normal production with respect to both demographic and disease related variables. Therefore, multivariate analyses were performed to explore predictors of reduced saliva or reduced tear production (table 5). Possible risk factors were categorised and entered into a multiple logistic regression model, and final results were adjusted for age, sex, disease duration, xerogenic drugs, rheumatoid factor, total SISY, and DAS. The risk of reduced tear production as well as reduced saliva production was increased when at least two SISY were present, compared with the reference group with no SISY. As shown in table 5, patients with the highest disease activity were at increased risk of reduced saliva production but not of reduced tear production. No increased risk of reduced tear or saliva production was present for patients in the highest age group, with female sex, or long disease duration. Presence of several SISY remained the strongest predictor for reduced tear and saliva production. Substituting DAS with separate other markers of disease activity or severity in additional analyses revealed an increased risk of reduced tears or reduced saliva in patients with high ESR, and a risk of reduced saliva production with increasing number of tender joints (data not shown).

Table 5 Risk (odds ratios (OR) and 95% confidence intervals (CI)) of reduced tear or saliva production for demographic characteristics and measures of disease activity and severity†

	Reduced tears (ST ⩽5 mm)		*Reduced saliva (UWS ⩽5 ml)*	
	OR	*95% CI*	*OR*	*95% CI*
Age (y)				
⩽40	1.0		1.0	
41–50	0.88	0.47, 1.65	0.99	0.40, 2.44
51–60	0.88	0.49, 1.57	1.19	0.52, 2.71
61–70	0.86	0.48, 1.53	1.82	0.83, 3.96
Sex				
Male	1.0		1.0	
Female	1.18	0.74, 1.87	1.35	0.39, 2.41
Drug with dryness potential	0.78	0.48, 1.30	1.35	0.79, 2.30
Rheumatoid factor	1.53*	1.04, 2.24	0.90	0.55, 1.47
Number of sicca symptoms				
0	1.0		1.0	
1	0.98	0.54, 1.66	1.08	0.49, 2.39
2–3	1.78*	1.11, 2.85	3.11**	1.66, 5.81
4–6	2.25*	1.18, 4.28	5.59***	2.63, 11.89
Disease activity score				
Lowest quartile	1.0		1.0	
2.quartile	0.61	0.35, 1.08	1.08	0.48, 2.46
3.quartile	0.88	0.51, 1.54	1.61	0.74, 3.48
Highest quartile	1.08	0.62, 1.89	2.45*	1.15, 5.24

†OR adjusted for age, sex, disease duration, drugs with capacity to induce sicca symptoms, rheumatoid factor, number of sicca symptoms, and disease activity score. *p<0.05, **p<0.001, ***p<0.0001.

Discussion

This study demonstrated a high prevalence of ocular and oral SISY and sicca signs in RA patients. Twenty seven per cent of all patients had SISY from eyes and mouth; and a similar proportion had reduced tear production, while saliva was reduced in 17%. We had expected to detect positive associations between SISY and the objective measures of tear and saliva production, but only weak associations were found, even in patients with the most severe symptoms. Mean values for measures of saliva and tear production were far from the pathological limits (table 3), and a considerable overlap of the measured values between patient groups with varying SISY was found. This weak association between symptoms and signs was also observed in two population-based studies of individuals without RA.[27 28]

Previous studies, examining SISY or exocrine signs from eyes and mouth in RA patients, are sparse. Andonopoulos *et al*[2] examined 111 RA patients and found SISY from eyes in 38% and from mouth in 6%, while objective ocular or oral signs of dryness were observed in 45% and 23%. In another minor study[29] ST was reduced in 30% of RA patients. The prevalence of oral SISY was 6% when spontaneously reported by RA patients,[2] 32% when recorded as responses to questions,[9] and 53% in a study considering frequent and periodical symptoms together.[10] Such different results may be partly explained by different approaches in the assessment of SISY.

Some community-based surveys on dryness from eyes and mouth have been performed, applying various questions for SISY.[27 30–33] In a population-based study from the United Kingdom,[27] applying identical questions on SISY as in the present study, at least one ocular symptom was reported in 24%, and at least one oral symptom in 29%. A combination of both was seen in 14%, compared with 27% in the present study. Identical questions were also used in a study from Greece[31] where 14% of women without RA reported at least one of six symptoms. Persistent symptoms of dry mouth are common in about one of six people in the elderly population.[32] Thus, in these population-based studies SISY were frequent but not as common as in our RA patients. In contrast, reduced tear production was nearly as prevalent in the population-based study from the UK[27] as in our investigation (23% *v* 29%), and reduced saliva production was even more prevalent in that population than among the RA patients (29% *v* 17%). One possible explanation for this unexpected difference is the short collection time of five minutes used in the British study, which may give less accurate results.[27]

The patients with reduced saliva had a more active disease than those with normal tears and saliva, as shown by the group differences in most disease activity and all health status measures (table 4). The reduced tears group differed in two disease activity measures and only one health status measure from the group with normal tears and saliva. The moderate sicca and the severe sicca groups had consistently worse self reported health status measures than the non-sicca group, whereas disease activity measures differed only for 28 tender joint count, patient's global assessment and DAS. Thus, disease activity and health status measures seemed to discriminate between the groups with and without reduced saliva production, but not consistently between those with and without reduced tear production. The associations between self reported symptoms and self reported health status may indicate a trait phenomenon of patients' tendency to respond positively to questions about health problems.

Some of the extra-articular manifestation of RA reflect the disease activity process, for example, manifestations of serositis, whereas others mainly reflect damage, as for example renal failure. We considered exocrine gland dysfunction as an extra-articular manifestation, possibly related to either disease activity or damage. Other studies have not examined such a relation. Some associations between disease activity measures and glandular dysfunction were seen in bivariate comparisons, but they were limited to reduced saliva production in multivariate comparisons. No relation was seen to disease duration or the number of deformed joints as a marker for damage. Salivary gland dysfunction therefore seemed to be more closely related to markers of disease activity than to damage. However, all relations were rather weak, and the 18 deformed joint count may be less sensitive as a marker of disease severity than radiographic damage. Unfortunately no reliable scores of radiographic damage were available in this study. Time integrated measures of disease activity would be expected to produce a better picture of the relation between disease activity and gland dysfunction. Our cross sectional approach does not allow conclusions regarding the causal

relation between disease activity and gland dysfunction.

Our findings are of interest in relation to the classification of SS in the older age groups. Vitali *et al*[34] have suggested that UWS and ST should not be considered for the classification of patients over 60 years, as high age and medication might reduce tear and saliva production.[5] Other studies report conflicting evidence whether increasing age reduces tear or saliva secretion[35–39] or not.[27 40–44] We found that objective measures of both tear and saliva production gradually and slightly decreased until the age of 70 years (fig 2A and fig 2B), with a more pronounced reduction for saliva than for tears. The risk of reduced saliva or tear production was not increased in the highest age group (table 5) when controlling for disease duration and disease variables. Thus, our and other studies indicate that ST and UWS are valid measures for the classification of SS until the age of 70 years.

Medication is a covariate for potential dryness.[25] An association of SISY and slightly reduced saliva but not tear production has been reported.[11] The use of xerogenic drugs in our patients was twice as frequent in the moderate sicca group as in the non-sicca group (27.3% *v* 13.7%, $p<0.001$). There was an association with reduced saliva production (29.8% *v* 20.2%, $p<0.05$), but not reduced tear production (19.7 *v* 20.2, non-significant). Surprisingly, in multivariate analyses the use of xerogenic medication did not turn out as an independent predictor of reduced tear or saliva production (OR 1.35, 95% CI 0.79, 2.30) (table 5). Confounding influence of age or disease activity may have contributed to the negative finding.

The number of patients (n=42) fulfilling at least three criteria of the European classification criteria for secondary SS indicates a minimum prevalence of 7%. Assessment of the patients with the complete set of criteria including performance of lip biopsies as well as rose bengal staining, parotid sialography, and salivary scintigraphy would further have increased the prevalence. Other studies estimated a clearly higher prevalence of secondary SS among RA patients, being 31%[7 45] and 55–62%,[29 46] partly depending on classification criteria applied. The European criteria for primary SS have been estimated to classify six times more patients than the more restrictive criteria favoured by American investigators.[3]

Differences in the prevalence of secondary SS may also be explained by differences in the patient materials. A major strength of this study is its size in a setting of a county-based register,[14 16] applying recommended measures for assessment of disease activity and health status.[12 47–49] Selection bias is a possible concern, but the participant rate of 71% was very satisfying, and the examined patients had representative demographic features (table 1). Only a minority of patients could or would not perform ST (n=22) or UWS (n=9), mainly because of intolerance for test strips. Findings in our study are limited to patients until the age of 70 years. That excluded a great number of RA patients,[15] but we expected findings in the highest age group to be confounded by co-morbidities, co-medication, participation bias, and a less reliable diagnosis of RA.[50]

One limitation of the present and previous studies has been that SISY and signs were not adequately compared with age and sex matched healthy controls. Some research data from our department indicate, however, that SISY—applying the same questions—are clearly less frequent in healthy controls (unpublished observations) than in RA patients.

Exocrine gland dysfunction was in this study assessed by measuring tear production with ST and saliva production with UWS. ST has shown to have a good balance between sensitivity and specificity,[5 13] though it contains weakness as a diagnostic test.[20 51–54] ST was in other epidemiological studies preferred[27 30] rather than the van Bijsterveld score or the tear break up time. Collection of unstimulated rather than stimulated saliva as test for oral dryness is part of the criteria for SS,[13 34] and is supposed to be the best test for salivary flow.[55] However, a considerable overlap has been found for salivary flow rates in patients with SS and normal subjects,[27 28 56] in line with the present findings. We have in our patients been aware of the problem with stimulation of secretory glands by passive chewing and aimed at preventing false positive results.

How may the present results help the clinician to suspect and identify manifestations of secondary SS in patients with RA? From a clinical point of view it is of interest to identify predictors of reduced tear and saliva production. A high DAS as well as the presence of at least two SISY were independent predictors of reduced saliva production (table 5), whereas reduced tear production was only predicted by a high number of SISY. Rheumatologists should be vigilant for SISY in patients with RA, particularly given that hyposalivation is known to be a major contributor to poor oral health. Dryness complaints are frequent in RA and should be further examined by measuring tear and saliva production.

In summary, this article highlights that SISY as well as reduced tear or saliva production are frequent extra-articular manifestations in RA patients. They are generally related to disease activity and health status, but not to disease duration and number of deformed joints. Clinicians should be aware of problems with reduced tear or saliva secretion, especially in patients with high disease activity or when several SISY are present.

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