10-year follow-up of patients with rheumatoid arthritis and secondary Sjögren's syndrome or sicca symptoms in daily clinical practice

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ABSTRACT

Objective. *To evaluate the presence of sicca symptoms and secondary Sjögren's syndrome (SS) and the association with clinical characteristics, functional tests and patient-reported outcomes in patients with rheumatoid arthritis (RA) at baseline and after 10 years of follow-up.*

Methods. *A cohort of RA patients was evaluated in 2008 and re-evaluated in 2018 with respect to sicca symptoms, presence of secondary SS according to AECG classification criteria, disease activity of RA and patient-reported outcomes. Patient characteristics were compared between the RA-non-sicca, RA-sicca and RA-SS groups.*

Results. *Of the original 2008 cohort of 96 RA patients, 32 (33%) had sicca symptoms and 6 (6.3%) secondary SS. Of the 36 patients who agreed to be re-evaluated in 2018, 6 (17%) had sicca symptoms and 2 (6%) developed secondary SS. In the majority of patients, sicca symptoms were reversible while the functional tests of salivary and lacrimal glands significantly decreased. 67% of RA-sicca patients had no sicca complaints at the second screening, while only two RA-sicca patients developed secondary SS. RA-SS patients and, to a slightly lesser extent, RA-sicca patients had significantly higher RA disease activity (DAS-28), lower lacrimal (Schirmer's test) and salivary gland function, more limitations in daily activities (HAQ), worse health-related quality of life (RAND-36), more fatigue (MFI) and more patient symptoms (ESSPRI) compared to RA-non-sicca patients.*

Conclusion. *Secondary SS was found in a minor subset of the RA patients. Sicca symptoms of the eyes or mouth were more frequent, but their presence varied over time. Higher RA disease activity was associated with SS and sicca symptoms. These patients had lower gland function and worse patient-reported outcomes.*

Introduction

Sicca symptoms of eyes and mouth are rather common in patients with rheumatoid arthritis (RA) (1-6). These sicca symptoms can be due to a variety of diseases that are associated with RA and/or the use of xerogenic medication that patients take because of these diseases (7). More specifically, RA patients with sicca symptoms as main complaint can suffer from secondary Sjögren's syndrome (SS) (8-11).

SS is a chronic autoimmune inflammatory disease characterised by progressive focal lymphocytic cell infiltration of the salivary and lacrimal glands giving rise to focal sialoadenitis with, amongst others, the sensation of a dry mouth (xerostomia) and dry eyes (keratoconjunctivitis) as a result. Moreover, extra glandular manifestations can occur in the course of SS (12). Sicca symptoms and rheumatic nodules are the most common extra-articular manifestations in RA patients (2). Therefore, RA patients with sicca symptoms should be evaluated for secondary SS because of the risks of excessive fatigue, early dental loss, damage of the cornea, desiccation of the oral mucosa, oral infections, increased risk of developing mucosa associated lymphoid tissue (MALT) lymphomas, and increased mortality (13-16). Additionally, treatment choice of RA should be carefully evaluated if SS is present, as some treatment modalities, like methotrexate, can predispose to lymphoma, in particular the development of MALT lymphoma (17).

Several clinical characteristics of RA have been reported to be associated with SS: RA patients with longstanding disease, female gender, high disease activity, high titers of rheumatoid factor, ero-

sions and extra-articular manifestations are at risk of developing sicca symptoms and SS (10, 11, 18-22). Most studies evaluated either sicca complaints among the RA patients or secondary SS in RA patients. We are not aware of the studies that compared sicca complaints and secondary SS simultaneously and prospectively. Furthermore, little is known whether sicca symptoms change over time and if RA patients with sicca symptoms will develop secondary SS over time. In the present study, we assessed the prevalence and progression of sicca symptoms and secondary SS over time and the association with clinical characteristics, functional tests and patient-reported outcomes in a cohort of RA outpatients.

Methods

In 2008, established RA patients were randomly selected from eligible RA patients attending our outpatient clinic. Patients were selected by appointment time: RA patients who had an appointment at 9.00, 10.00 and 11.00 o'clock were asked to participate. Patients were included if they were 18 years or older and have been diagnosed with RA according to American College of Rheumatology 1987 criteria (23). All patients were on a routine six month recall schedule by their rheumatologist or had, due to their disease activity, more frequent visits. As the development of sicca complaints made RA patients suspect to have developed secondary SS, these RA patients with sicca complaints were subjected to a routine diagnostic Sjögren's work-up according to normal clinical practice. Patients with a history of HIV, hepatitis C, head and neck radiotherapy, pre-existing lymphoma, sarcoidosis, graft versus host disease and diabetes mellitus were excluded from the study. Disease activity of RA was measured by a rheumatologist using Disease Activity Score of 28 joints (DAS-28 score) (24). Age of onset of RA, duration of RA, presence of erosions and extra-articular manifestations, and current medication were recorded. Laboratory parameters, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibodies (anti-CCP), antinuclear antibodies (ANA), anti-SSA/SSB antibodies, and immunoglobulin's (IgG, IgA, IgM) were measured.

Table I. Patient questionnaire for the assessment of xerostomia and ocular dryness based on sicca questionnaire from the AECG 2002 classification criteria (27).

1.	Did you have daily, persistent, troublesome dry eyes for more than 3 months?
2.	Do you have a recurrent sensation of sand or gravel in the eyes?
3.	Do you use tear substitutes more than 3 times a day?
4.	Did you have daily feeling of dry mouth for more than 3 months?
5.	Did you have recurrently or persistently swollen salivary glands as an adult?
6.	Do you frequently drink liquids to aid in swallowing dry food?

To assess sicca symptoms, a sicca-questionnaire was applied (Table I). Patients reporting at least one sicca symptom of the eyes or mouth were classified into the RA-sicca group. All patients from the sicca group underwent a diagnostic work-up for the presence of secondary SS according to the American-European Consensus Group (AECG) classification criteria as applied in daily clinical practice (25, 26). In addition to whole saliva, submandibular/sublingual (SM/SL) and parotid (PAR) saliva were collected to assess salivary gland function. Glandular saliva was collected in pre-weighed plastic tubes from each parotid gland and simultaneously from the submandibular/sublingual (SM/SL) glands by syringe aspiration. The first five minutes unstimulated salivary secretions was collected, followed by citric acid stimulated secretions over 10 minutes (27, 28). Schirmer's test was performed to assess lacrimal function (29). Patients were asked to complete the Health Assessment Questionnaire (HAQ) to assess functional status, RAND-36 questionnaire to asses health-related quality of life and Multidimensional Fatigue Inventory (MFI) to assess fatigue (30-32).

In 2018, all RA patients who participated in the screening in 2008 were asked to participate again. The identical screening protocol as in 2008 was applied in 2018. In addition, patients were asked to complete the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) to assess patient symptoms of dryness, fatigue and pain (33).

The Medical Ethical Committee of the University Medical Centre Groningen, the Netherlands, assessed the study proposal and concluded that formal approval was not required as we looked to the patients from the standard of care point.

Statistical analysis

Results are presented as number of patients (%) for categorical data and mean±SD (median) for continuous data. Three groups were distinguished: RA-non-sicca group, RA-sicca group and RA-SS group. Because the sample size of RA-SS group was small, non-parametric statistics were used to compare clinical characteristics, functional tests and patient-reported outcomes. Continuous parameters were overall compared between these three groups with Kruskal-Wallis test. Only parameters with a p value ≤ 0.05 were further tested between each two groups with Mann-Whitney test. For categorical parameters, Chi-Square test was used, followed by Chi-Square or Fisher's exact test. Additionally, univariable and multivariable logistic regression analyses were used to assess the associations between sicca symptoms or secondary SS and disease activity parameters corrected for potential confounders (age, sex, and RA duration) at baseline.

To explore if there was potential bias in the selection of patients, Independent Samples t-test or Mann Whitney U-test and Chi-Square or Fisher's Exact test were used as appropriate to compare baseline characteristics of the patients from 2008 who did and did not take part in the screening in 2018.

Clinical characteristics, functional tests and patient-reported outcome of RA patients who participated in the screening in 2018 were compared over time (2008 *vs*. 2018) with Paired Samples t-test or Wilcoxon Signed Rank test for continuous parameters and McNemar test for categorical parameters.

Finally, clinical characteristics, func-

Table II. Clinical characteristics of RA patients with SS, with sicca symptoms but no SS, and without sicca symptoms in 2008.

	RA-Non-Sicca (n=58)	RA-Sicca (n=32)	RA-SS (n=6)	*p*-value (overall)
Demographics				
Female gender	42 (72%)	28 (88%)	5 (83%)	0.241
Age (years)	54 ± 12 (56)	54 ± 8 (55)	58 ± 7 (60)	0.655
Disease variables				
Time since RA diagnosis (years)	10 ± 8 (10)	14 ± 9 (11)	15 ± 9 (13)	0.175
RF positive	48 (83%)	28 (88%)	6 (100%)	0.481
Anti-CCP positive	48 (83%)	27 (84%)	5 (83%)	0.584
Anti-SSA positive	4 (7%)	2 (6%)	1 (17%)	0.661
ANA positive	40 (53%)	21 (66%)	5 (83%)	0.461
IgG level	12.9 ± 2.8 (12.7)	12.7 ± 2.7 (12.7)	14.9 ± 2.6 (15.2)	0.191
Xerogenic drug use	29 (50%)	26 (81%)*	4 (67%)	**0.014**
Presence of erosions	39 (67%)	27 (84%)	6 (100%)	0.068
Presence of EAMs	25 (43%)	17 (53%)	4 (67%)	0.421
DAS-28(ESR)	2.7 ± 1.1 (2.6)	3,2 ± 1.1 (3.1)*	5.1 ± 1.4 (5.9)*†	**0.001**
DAS-28(CRP)	2.4 ± 0.8 (2.2)	2.9 ± 0.9 (3.0)*	4.1 ± 1.5 (4.2)*	**0.001**
Dryness				
Schirmer's test (mm/5min)	16.7 ± 10.5 (14.0)	15.4 ± 11.4 (13.8)	3.9 ± 1.8 (3.0)*†	**0.001**
Whole rest saliva (ml/min)	0.35 ± 0.27 (0.23)	0.18 ± 0.12 (0.15)	0.05 ± 0.04 0.06)*†	**0.001**
SM/SL, at rest (ml/min)	0.27 ± 0.24 (0.18)	0.15 ± 0.10 (0.11)*	0.05 ± 0.04 (0.05)*†	**0.001**
SM/SL, stimulated (ml/min)	0.55 ± 0.32 (0.50)	0.38 ± 0.33 (0.34)*	0.11 ± 0.11 (0.07)*†	**0.000**
PAR, at rest (ml/min)	0.07 ± 0.06 (0.07)	0.04 ± 0.04 (0.03)*	0.01 ± 0.02 (0.01)*	**0.000**
PAR, stimulated (ml/min)	0.18 ± 0.12 (0.16)	0.14 ± 0.11 (0.10)	0.06 ± 0.04 (0.05)*	**0.013**
Patient-related outcomes				
HAQ	0.5 ± 0.6 (0.4)	1.0 ± 0.6 (1.0)*	1.4 ± 1.0 (1.4)*	**0.001**
RAND-36				
Physical functioning	69 ± 25 (75)	48 ± 24 (50)*	38 ± 29 (40)*	**0.000**
Role physical	64 ± 42 (100)	35 ± 41 (25)*	17 ± 41 (0)*	**0.002**
Bodily pain	70 ± 19 (67)	57 ± 21 (57)*	37 ± 24 (38)*	**0.001**
General health	54 ± 22 (55)	42 ± 21 (35)*	33 ± 14 (35)*	**0.012**
Vitality	66 ± 18 (70)	54 ± 22 (50)*	31 ± 12 (33)*†	**0.000**
Social functioning	81 ± 19 (88)	67 ± 25 (63)*	50 ± 18 (44)*	**0.001**
Role emotional	81 ± 35 (100)	73 ± 42 (100)	56 ± 50 (67)	0.434
Mental health	80 ± 15 (84)	76 ± 20 (80)	56 ± 18 (52)*†	**0.020**
MFI				
General fatigue	9 ± 4 (10)	12 ± 4 (12)*	14 ± 2 (14)*	**0.001**
Physical fatigue	9 ± 4 (10)	12 ± 4 (13)*	15 ± 3 (16)*	**0.000**
Reduced activity	9 ± 4 (8)	11 ± 5 (12)*	14 ± 4 (16)*	**0.004**
Reduced motivation	9 ± 4 (8)	10 ± 4 (10)	15 ± 4 (16)*†	**0.003**
Mental fatigue	7 ± 3 (6)	9 ± 5 (9)*	12 ± 3 (12)*	**0.006**

Values are presented as number of patients (percentage) or mean ±SD (median).
*$p<0.05$ compared to non-sicca group.
†$p<0.05$ compared to only sicca group.

tional tests and patient-reported outcome parameters were compared between three groups based on their screening in 2018: RA-non-sicca group, RA-sicca group and RA-SS group. Continuous variables were overall compared between three groups with Kruskal-Wallis test. Only parameters with a *p*-value ≤0.05 were further tested between two groups with Mann-Whitney U-test. For categorical parameters, Chi-Square test was performed, followed by Fisher's exact test.

Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS). *p*-values ≤0.05 were considered statistically significant.

Results

Screening 2008

From the 116 eligible RA patients invited to participate in the study in 2008, 20 (17%) patients were unwilling to participate due to lack of time (n=12) or lack of interest (n=8) in the diagnostic SS work-up. As a result, 96 RA patients accepted to join the study, of whom 75 (78%) were female with a mean age of 54±10 years and a median disease duration of 10 years (IQR 5–17). 32 of the 96 (33%) included patients reported to have at least one sicca symptom of the eyes or mouth (RA-sicca group). Six (6.3%) patients were classified as suffering from secondary SS according to AECG classification criteria (RA-SS group). Most patients were using methotrexate as conventional DMARD and anti-TNF as biological DMARD. A minority of patients was using rituximab, abatacept or tocilizumab therapy.

No significant differences were found in age, gender, disease duration and the proportion of patients with RF, anti-CCP, ANA or anti-SSA/SSB antibody positivity between the three groups. RA-sicca patients used significantly more xerogenic drugs compared to RA-non-sicca and RA-SS patients. RA disease activity assessed with DAS-28 (including CRP and ESR) was significantly higher in RA-SS patients than in

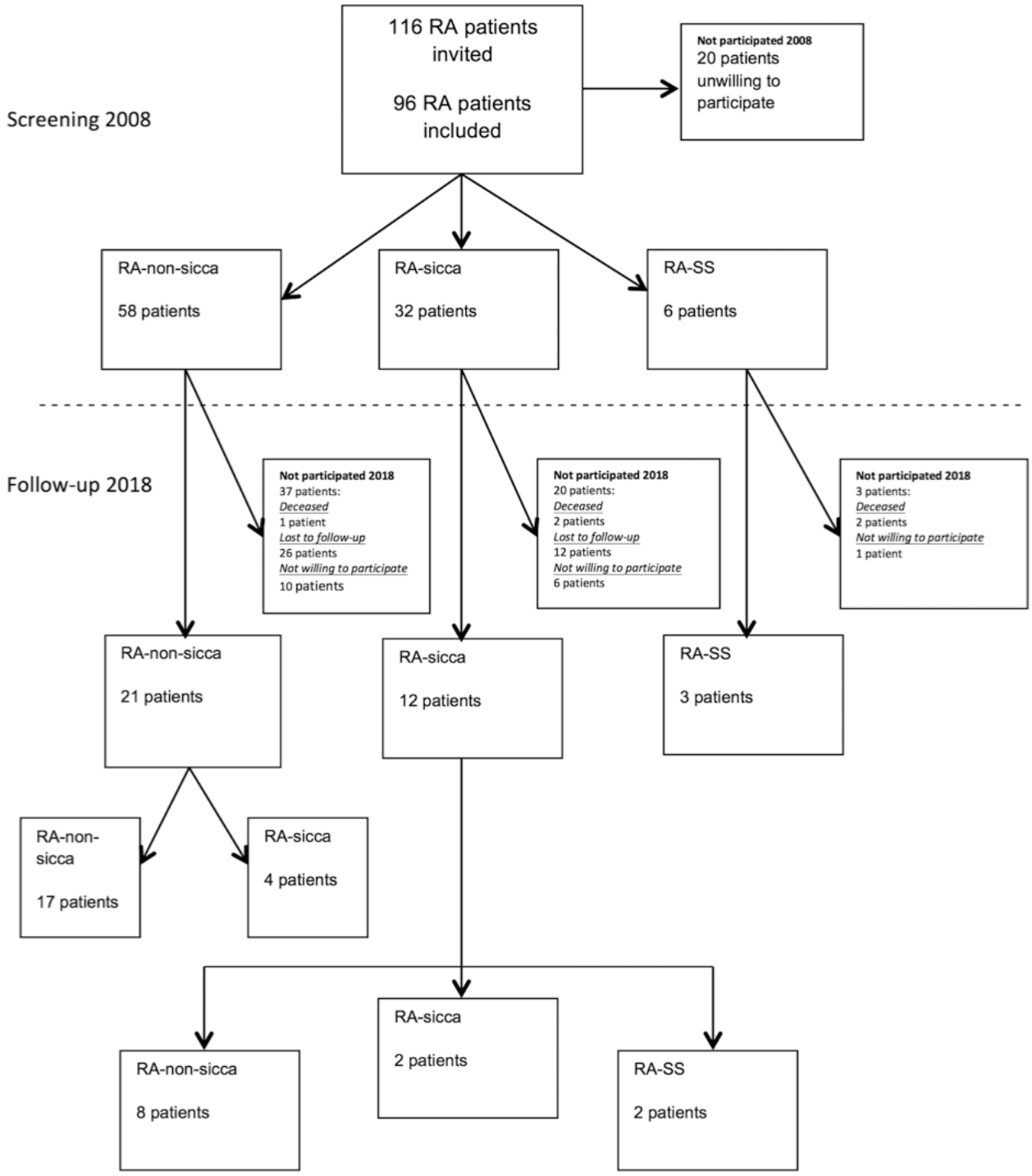

Fig. 1. Flowchart of inclusion screening in 2008 and follow-up in 2018.

RA-sicca and RA-non-sicca patients. RA-sicca patients had also higher disease activity than RA-non-sicca patients (Table II).

Functional tests of lacrimal (Schirmer's test) and salivary glands (whole and glandular saliva) were significantly impaired in RA-SS patients compared to RA-non-sicca and RA-sicca patients (Table II). RA-sicca patients showed lower saliva production of submandibular and sublingual glands both at rest and after stimulation and also lower parotid gland secretion at rest compared to RA-non-sicca patients.

Both groups of RA patients with sicca complaints and SS had more limitations in daily activities (HAQ), experienced worse health-related quality of life (RAND-36), and reported more fatigue (MFI) than RA-non-sicca patients (Table II).

Follow-up 2018

From the 96 RA patients included in the study in 2008, 36 (38%) were able and willing to participate in the follow-up screening in 2018 (Fig. 1). From the 60 patients without follow-up data, 5 patients were deceased (one patient be-

cause of a pulmonary embolism after surgery, 4 other patients because of a malignancy (lung, oesophagus, breast and cholangiocarcinoma)), 38 patients were lost to follow-up and 17 patients were not willing to participate.

To check for a potential selection bias on inclusion in 2018, we compared baseline parameters of patients who took part in the screening in 2018 (N=36) to those of patients who did not participate in 2018 (N=60, Table III). We did not find any significant differences in clinical characteristics, functional tests and patient-reported outcome between these two groups.

In most patients, sicca symptoms were not constantly present over time. We screened 21 patients in 2018 who were originally in RA-non-sicca group in 2008. Of these 21 patients, 17 patients had still no sicca complaints and 4 patients reported to have developed at least one sicca symptom of the eyes or mouth. Furthermore, we screened 12 patients in 2018 from the RA-sicca group in 2008. Of these 12 patients, 2 patients had developed secondary SS, 2 patients still had sicca symptoms and 8 patients did not experience sicca complaints anymore after 10 years of follow-up.

Furthermore, we compared the clinical characteristics of the 36 RA-patients who participated in the screening in 2018 with their clinical characteristics from 2008. We found that except for IgG levels, all serological parameters like RF, anti-CCP, anti-SSA and ANA positivity did not change over time. RA disease activity did not change significantly over time, whereas lacrimal flow, whole rest saliva and submandibular/sublingual saliva both at rest and after stimulation were significantly lower in 2018. Furthermore, RA patients experienced more limitations in daily activities, lower general health and more mental fatigue in 2018 (Table IV).

RA-sicca and RA-SS patients showed in 2018 significant impairment in the secretion of whole rest salivary flow and submandibular/sublingual salivary flow both at rest and after stimulation. The domains Role Emotional and Mental Health of RAND-36 were impaired in both RA-sicca and RA-SS patients and these patients also reported more fatigue. In addition, patient-reported symptoms assessed with total ESSPRI score and the subscales dryness and pain were significantly higher compared to RA-non-sicca patients (Table V).

Table III. Comparison of clinical characteristics of RA patients from 2008 who took part in the follow-up screening in 2018 *vs*. those who did not take part in the follow-up in 2018.

	RA-follow-up 2018+ (n=36)	RA-follow-up 2018- (n=60)	*p*-value
Demographics			
Female gender	27 (75%)	48 (80%)	0.615
Age (years)	54 ± 10 (55)	55 ± 11(56)	0.628
Disease variables			
Time since RA diagnosis (years)	13 ± 9 (10)	11 ± 8 (10)	0.542
RF positive	27 (75%)	54 (90%)	0.136
Anti-CCP positive	30 (83%)	50 (83%)	1
Anti-SSA positive	3 (8%)	4 (7%)	1
ANA positive	21 (58%)	39 (65%)	0.523
IgG level	13 ± 3 (12.5)	13 ± 3 (12.9)	0.851
Xerogenic drug use	21 (58%)	38 (63%)	0.669
Presence of erosions	24 (67%)	48 (80%)	0.154
Presence of EAMs	19 (53%)	27 (45%)	0.529
DAS-28(ESR)	3.0 ± 1.2 (3.0)	2.9 ± 1.1 (2.6)	0.696
DAS-28(CRP)	2.8 ± 1.0 (2.6)	2.6 ± 1.0 (2.4)	0.403
Dryness			
Schirmer's test (mm/5min)	16.3 ± 11 (14.5)	14.5 ± 10.7 (12.50)	0.552
Whole saliva (ml/min)	0.27 ± 0.21 (0.20)	0.28 ± 0.26 (0.20)	0.994
SM/SL, at rest (ml/min)	0.22 ± 0.17 (0.16)	0.22 ± 0.23 (0.14)	0.881
SM/SL, stimulated (ml/min)	0.49 ± 0.36 (0.45)	0.46 ± 0.31 (0.38)	0.984
PAR, at rest (ml/min)	0.05 ± 0.05 (0.04)	0.06 ± 0.06 (0.04)	0.584
Patient-related outcomes			
HAQ	0.8 ± 0.7 (0.7)	0.7 ± 0.6 (0.6)	0.287
RAND-36			
Physical functioning	57 ± 28 (0.60)	61 ± 26 (0.61)	0.613
Role physical	49 ± 42 (0.50)	52 ± 45 (0.50)	0.634
Bodily pain	61 ± 21 (0.67)	64 ± 22 (0.67)	0.338
General health	49 ± 19 (0.47)	48 ± 25 (0.45)	0.674
Vitality	59 ± 21 (0.60)	60 ± 21 (0.60)	0.994
Social functioning	73 ± 21 (0.75)	75 ± 24 (0.75)	0.371
Role emotional	76 ± 37 (100)	77 ± 40 (100)	0.640
Mental health	80 ± 14 (0.84)	76 ± 19 (82)	0.560
MFI			
General fatigue	11 ± 4 (12)	11 ± 5 (10)	0.693
Physical fatigue	10 ± 4 (11)	11 ± 5 (10)	0.923
Reduced activity	10 ± 4 (10)	10 ± 5 (11)	0.936
Reduced motivation	9 ± 4 (9)	10 ± 4 (9)	0.571
Mental fatigue	8 ± 4 (6)	8 ± 4 (8)	0.557

Discussion

To our knowledge, this is the first study evaluating as well sicca symptoms as SS in patient with RA over a period of 10 years. In this study we showed that RA patients with higher disease activity more often have sicca symptoms and more often are diagnosed with secondary SS than RA patients with lower disease activity. Furthermore, RA patients with sicca complaints and SS experienced more limitations in daily activities, had lower general health status and more fatigue. Furthermore, they had more SS-related symptoms measured by the ESSPRI total score and the subscales dryness and pain.

The prevalence of SS in RA in our study was 6.3% and the prevalence of sicca symptoms was 33%. These findings are in line with reported prevalence's in the literature (10, 11, 20, 34-36). A Danish study reported a prevalence of 3.8% of SS in patients with RA, whereas a Brazilian study reported a prevalence of 24.3% in a similar group. These differences in the prevalence of SS in RA can be possibly explained by the definition of SS and application of different classification criteria, geographical differences and perhaps differences in the treatment modalities of RA, assuming that the disease activity may be a

Table IV. Comparison of clinical characteristics of 36 RA patients from screening in 2008 and the same 36 RA patients from follow-up in 2018.

	RA-screening 2008 (n=36)	RA-follow-up 2018 (n=36)	*p*-value
Disease variables			
RF positive	27 (75%)	27 (79%)	1
Anti-CCP positive	30 (83%)	27 (75%)	0.375
Anti-SSA positive	3 (8%)	3 (8%)	1
ANA positive	21 (58%)	21 (46%)	0.727
IgG level	13 ± 3 (12.5)	11 ± 3 (11)	0.000*
Xerogenic drug use	21 (58%)	25 (69%)	0.289
Presence of erosions	24 (67%)	30 (83%)	0.109
Presence of EAMs	19 (53%)	19 (53%)	1
DAS-28(ESR)	3.0 ± 1.2 (3.0)	2.8 ± 1.1 (2.6)	0.251
DAS-28(CRP)	2.8 ± 1.0 (2.6)	2.2 ± 1.0 (2.0)	0.499
Dryness			
Schirmer's test (mm/5min)	16.3 ± 11 (14.5)	10 ± 9 (6.7)	0.000*
Whole rest saliva (ml/min)	0.27 ± 0.21 (0.20)	0.17 ± 0.21 (0.8)	0.003*
SM/SL, at rest (ml/min)	0.22 ± 0.17 (0.16)	0.12 ± 0.15 (0.06)	0.001*
SM/SL, stimulated (ml/min)	0.49 ± 0.36 (0.45)	0.19 ± 0.20 (0.09)	0.000*
PAR, at rest (ml/min)	0.05 ± 0.05 (0.04)	0.05ì ± 0.07 (0.02)	0.742
PAR, stimulated (ml/min)	0.17 ± 0.11 (0.16)	0.12 ± 0.12 (0.08)	0.056
Patient-related outcomes			
HAQ	0.8 ± 0.7 (0.7)	1.08 ± 0.9 (1.0)	0.006*
RAND-36			
Physical functioning	57 ± 28 (0.60)	56 ± 29 (52)	0.828
Role physical	49 ± 42 (0.50)	47 ± 44 (50)	0.652
Bodily pain	61 ± 21 (0.67)	63 ± 24 (66)	0.858
General health	49 ± 19 (0.47)	56 ± 22 (55)	0.031*
Vitality	59 ± 21 (0.60)	60 ± 21 (60)	0.770
Social functioning	73 ± 21 (0.75)	74 ± 25 (81)	0.705
Role emotional	76 ± 37 (100)	79 ± 38 (100)	0.752
Mental health	80 ± 14 (0.84)	80 ± 16 (84)	0.748
MFI			
General fatigue	11 ± 4 (12)	15 ± 5 (12)	0.135
Physical fatigue	10 ± 4 (11)	12 ± 5 (12)	0.059
Reduced activity	10 ± 4 (10)	10 ± 4 (9)	0.772
Reduced motivation	9 ± 4 (9)	9 ± 3 (9)	0.097
Mental fatigue	8 ± 4 (6)	9 ± 4 (8)	0.008*

predicting factor for developing of SS. The prevalence of SS in our study might be underestimated due to lack of a full diagnostic work-out in all included RA patients, *i.e.* salivary gland biopsy and full ophthalmologic investigation was not done in all patients. We did not add a salivary gland biopsy or a full ophthalmologic examination to the RA patients suspected for having developed secondary SS when adding these examinations would not result in a patient to be classified as secondary SS according to the AECG criteria. Furthermore, three anti-SSA positive patients from the RA-non-sicca (n=2) and RA-sicca (n=1) groups in 2008 were lost to follow-up.

The reported prevalence of sicca symptoms in RA is higher than the prevalence of SS, but is very variable as well. In a Turkish study 11.4% of RA patients had sicca symptoms (2), whereas in a Brazilian study 57.3% of RA patients had sicca symptoms (36). In a population of RA patients from Egypt with high disease activity (mean DAS-28 of 5.3±1.2) and duration of RA of 4.7±4.2 years, 71% of the patients had sicca symptoms, but no patients were diagnosed with SS (22). This scattered prevalence may be caused by various concomitant diseases and/or xerogenic medication use (7, 13). Age-related alterations of salivary and lacrimal glands, irradiation and infections, such as hepatitis C and HIV, amyloidosis, diabetes mellitus (DM) IgG4 disease and sarcoidosis are all associated with sicca syndrome.

Associations between sicca symptoms and/or the presence of SS in RA patients, and poorer health status measures are frequently reported. However, there are conflicting results in the literature concerning the association between disease activity and the presence of sicca symptoms and SS.

Some studies did not report an association between disease activity, sicca and SS, while other studies found this association as well (10, 11, 20, 36, 37). It is still not clear if secondary SS should be considered as an extra-articular manifestation of RA or as a concomitant auto-immune disease. It is known that patients with RA have more extra-articular manifestations if their disease activity is high (18). Therefore, RA treatment should be aggressive, especially at the start of the disease, using the window of opportunity. In 2008, our RA population already had a long disease duration of at least 10 years. It will be interesting to investigate the prevalence of SS in early RA patients in the new era of biological therapies. Treatment modalities of RA can possibly be of influence on the development of SS in RA as we observed that patients with high disease activity of RA more often suffered from sicca complaints and/or SS.

We consider SS not as an extra-articular manifestation of RA, but as a distinct disease entity. SS occurs concomitantly in other diseases like SLE, scleroderma or myositis etc. Furthermore, SS can be the first auto-immune disease detected in a patient, while RA or SLE or scleroderma can be diagnosed in the same patient thereafter. Salivary gland biopsies in patients with secondary SS showed comparable abnormalities between primary SS patients, SS-RA, SS-SLE and SS-scleroderma patients, as reported by Hérnandez-Molina *et al*. (26). Important shortcoming of the term 'secondary' SS is that this disease always comes to the second place and too little research is provided on this field. Moreover, probably most patients with secondary SS are not well recognised by clinicians as their attention goes to the primary disease, like RA or SLE or scleroderma (38, 39). In our study, we found that 2 patients (6%) had developed SS during the 10 years of follow-up. Both patients had sicca complaints in 2008. This indicates that the minority of established RA-sicca patients will develop SS in the later course of RA. Both patients were anti-

Table V. Clinical characteristics of RA patients with SS, with sicca symptoms but no SS, and without sicca symptoms in 2018.

	RA-Non-sicca (n=25)	RA-sicca (n=6)	RA-SS (n=5)	*p*-value (overall)
Disease variables				
RF positive	19 (76%)	5 (83%)	3 (60%)	0.843
Anti-CCP positive	18 (72%)	5 (83%)	4 (80%)	0.482
Anti-SSA positive	2 (8%)	1 (17%)	1 (20%)	0.841
ANA positive	15 (60%)	4 (67%)	4 (80%	0.502)
IgG titer	12 ± 3 (12)	9 ± 2 (9)	8.8 ± 1.6 (9.2)	0.168
Xerogenic drug use	16 (64%)	4 (67%)	5 (100%)	0.358
Presence of erosions	21 (84%)	5 (83%)	4 (80%)	0.710
Presence of EAMs	10 (40%)	4 (67%)	5 (100%)	0.097
DAS-28(ESR)	2.8 ± 1.2 (2.6)	3.1 ± 0.8 (2.7)	2.0 ± 0.8 (1.7)	0.461
DAS-28(CRP)	2.2 ± 1.1 (2.0)	2.8 ± 0.6 (2.7)	1.8 ± 0.3 (1.7)	0.579
Dryness				
Schirmer's test (mm/5min)	10.6 ± 9.5 (7)	18 ± 11 (22)	1.4 ± 2.3 (0.5)	0.051
Whole rest saliva (ml/min)	0.21 ± 0.22 (0.10)	0.17 ± 0.15 (0.13)*	0.01 ± 0.01 (0.00)†	**0.010**
SM/SL, at rest (ml/min)	0.15 ± 0.17 (0.09)	0.10 ± 0.11 (0.04)*	0.01±0.01 (0.00)†	**0.005**
SM/SL, stimulated (ml/min)	0.23 ± 0.22 (0.11)	0.25 ± 0.19 (0.24)*	0.01±0.01 (0.01)†	**0.019**
PAR, at rest (ml/min)	0.05 ± 0.07 (0.04)	0.08 ± 0.05 (0.09)	0	0.092
PAR, stimulated (ml/min)	0.14 ± 0.12 (0.09)	0.14 ± 0.11 (0.16)	0.01 ± 0.01 (0.00)	**0.054**
Patient-related outcomes				
HAQ	0.8 ± 0.7 (0.6)	1.6 ± 0.9 (1.4)	1.9 ± 0.9 (1.9)	0.274
RAND-36				
Physical functioning	65 ± 26 (65)	43 ± 26 (45)	28 ± 29 (25)	0.136
Role physical	62 ± 43 (75)	8 ± 20 (0)	15 ± 22 (0)	0.224
Bodily pain	71 ± 23 (67)	45 ± 14 (45)	47 ± 20 (47)	0.648
General health	59 ± 23 (60)	48 ± 17 (52)	49 ± 17 (50)	0.391
Vitality	68 ± 18 (70)	45 ± 21 (52)	40 ± 13 (50)	0.084
Social functioning	82 ± 21 (88)	65 ± 28 (69)	48 ± 42 (50)	0.125
Role emotional	88 ± 30 (100)	67 ± 52 (100)*	47 ± 45 (67)†‡	**0.013**
Mental health	84 ± 16 (88)	77 ± 9 (76)*	30 ± 11 (25)†‡	**0.021**
MFI				
General fatigue	10 ± 4 (9)	15 ± 3 (14)*	16 ± 4 (16)†‡	**0.044**
Physical fatigue	11 ± 5 (10)	15 ± 4 (15)	13 ± 4 (13)	0.232
Reduced activity	9 ± 4 (8)	11 ± 2 (12)*	14 ± 4 (15)†‡	**0.040**
Reduced motivation	9 ± 3 (9)	11 ± 1 (11)	12 ± 4 (11)	0.398
Mental fatigue	8±4 (8)	9 ± 3 (9)*	13 ± 4 (16)†‡	**0.033**
ESSPRI				
Dryness	0.3 ± 0.7 (0)	4.0 ± 2.7 (4.5)*	8.7 ± 1.5 (9)†‡	**0.037**
Fatigue	3.1 ± 2.0 (3.0)	6.3 ± 1.6 (6.5)	8.0 ± 1.7 (7)	0.079
Pain	3.2 ± 2.5 (2.5)	5.7 ± 1.9 (5.5)*	7.0 ± 2.6 (6)†	**0.024**
Total ESSPRI	2.2 ± 1.3 (1.8)	5.3 ± 1.2 (5.2)*	7.8 ± 1.9 (7.3)†‡	**0.021**

*$p<0.05$ RA-non-sicca *vs*. RA-sicca; † $p<0.05$ RA-non-sicca *vs*. RA-SS; ‡ $p<0.05$ RA-sicca *vs*. RA-SS.

SSA/SSB negative, but they still met the classification criteria for secondary SS. Nowadays, 2016 ACR/EULAR classification criteria are developed for SS (40). These criteria do not differentiate between primary or secondary SS. In these criteria, anti-SSA/SSB antibodies have a prominent weight in the diagnosis. The reported prevalence of these antibodies in secondary SS in RA is 7.3–40% (11, 36, 41). In our study only one secondary SS patient was positive for anti-SSA/SSB antibodies. In a recent study with 300 patients with systemic lupus erythematosus, rheumatoid arthritis and scleroderma the performance of ACR/EULAR classification criteria of SS using clinical diagnosis as a gold standard was assessed. The 2016 ACR/EULAR criteria showed the best AUCs results (0.87 definitive/probable diagnosis, 0.90 definitive diagnosis) compared to AECG and ACR criteria. It was concluded that ACR/EULAR classification criteria are applicable in the setting of secondary SS (42). The consequence of the 2016 ACR/EULAR criteria fordaily clinical practice is that patients with RA suspected to have SS should undergo salivary gland biopsy in the majority of cases (43).

In our study over a period of 10 years we found that 2 of 6 RA-SS patients deceased and in RA-non-sicca and RA-sicca group 3 of 90 patients deceased. Although our numbers are small, previous studies also reported that SS is significantly associated with an increased morbidity and mortality (44, 45). The prevalence of joint damage, pulmonary, neurologic, nephrologic and cutaneous organ involvement is increased in RA-SS patients compared to RA patients without SS. RA patients with SS also have an increased risk of developing non-Hodgkin lymphoma as well as other haematologic malignancies (8, 11, 46, 47).

An important finding in our study is that sicca symptoms are not constant over time. We expected that once hav-

ing sicca complaints, patients will stay in sicca group for the next years and that the number of patients in the sicca group will constantly increase. In contrary, we found that 8 out of 12 examined patients had no sicca complaints after 10 years of follow-up. These results could be a result of the use of xerogenic drugs, but we found no differences in xerogenic drug use between screening in 2008 and follow-up in 2018. In contrast, the objective measurements of functional tests decreased significantly over time, especially the submandibular and sublingual salivary flow, as well at rest as stimulated. These results indicate that there is no strong correlation between the objective and subjective sicca symptoms. The overall decrease of salivary and lacrimal flow is related to the physiological changes in the salivary and lacrimal glands with age. The size of submandibular glands and lacrimal glands decreases with age due to decline in acinar volume while the volume of adipose and fibrose tissue increases (48-51).

We did not find any association between serological parameters like RF, anti-CCP, ANA and anti-SSA/SSB and the presence of sicca symptoms and SS in RA patients. Such associations have been investigated by others too and in most studies the serological profile of RA patients with SS were not different from those without SS (11, 37, 52, 53). In our study we did not find a relationship between the prevalence of anti-SSA/SSB antibodies and the presence of SS. IgG titer decreased after 10 years of follow-up, probably due to the B-cell depletion therapy, like rituximab (54).

A limitation of our study is the small sample size at the 2018 follow-up, but in spite of the small sample size, we found no selection bias in our second screening group and even with this small sample size we found clear differences between the groups.

In conclusion, high disease activity of RA is associated with sicca symptoms and SS. Patients with sicca symptoms and SS had more limitations in daily activities, had lower general health status, more fatigue and patients with SS were at higher risk of mortality. Sicca complaints are not constantly present and vary over time within patients, while functional tests significantly decrease over time in all patients. During 10 years of follow-up, 2 out of 36 patients developed SS. Based on these results we suggest that RA patients with high disease activity should be monitored for development of sicca symptoms and SS.

Take home messages

- In rheumatoid arthritis, high disease activity is associated with the presence of sicca symptoms and secondary Sjögren's syndrome.
- Sicca symptoms are not constantly present over time within rheumatoid arthritis patients, while functional capacity of salivary and lacrimal glands significantly decreases.
- Patients with sicca symptoms and secondary Sjögren's syndrome have more limitations in daily activities, worse health-related quality of life and more fatigue and pain.

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