# Longitudinal evaluation of major salivary gland functioning in Sjögren's disease patients in a prospective standard-of-care cohort

N.R.F. Sluijpers[1], K. Delli[1], L. De Wolff[2], A.J. Stel[2], F.K.L. Spijkervet[1], F.G.M. Kroese[2], H. Bootsma[2], S. Arends[2], A. Vissink[1]

*[1]Department of Oral and Maxillofacial Surgery, [2]Department of Rheumatology and Clinical Immunology University of Groningen, University Medical Center Groningen, The Netherlands.*

## Abstract

### Objective

*To evaluate changes in major salivary gland functioning over time using salivary gland ultrasonography (SGUS), salivary flow measurements (sialometry), and patient-reported outcome measures (PROMs) in patients diagnosed with primary Sjögren's disease (SjD).*

### Methods

*Consecutive outpatients from the ongoing prospective REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort, all fulfilling the ACR-EULAR classification criteria for SjD, were included. SGUS images assessed with the Hocevar and OMERACT scoring system, unstimulated and stimulated whole saliva (UWS/SWS), unstimulated and stimulated submandibular/sublingual saliva (uSMSLS/sSMSLS) and parotid saliva, EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) general dryness, oral dryness, and Xerostomia Inventory were assessed at baseline (BL), 2-year (Y2) and 5-year (Y5) follow-up.*

### Results

*In total, BL and Y2 data were available for 253 patients and 75 patients had already reached Y5. At group level, SGUS Hocevar (i.e. mean±SD: 22±10 at BL, 22±10 at Y2 and 23±10 at Y5), OMERACT scores, UWS, SWS and PROMs remained stable over time (all p>0.05). Slightly decreased uSMSLS (p=0.025) and sSMSLS (p=0.004) were observed at Y5. At individual patient level, a similar proportion showed an increase or decrease of ≥25% for Hocevar, UWS and SWS. At baseline, poor associations were observed between SGUS and PROMs and fair associations between sialometry and PROMs. Over time, changes in objective assessments did not correlate with changes in PROMs.*

### Conclusion

*Overall, major salivary gland functioning assessed with SGUS, sialometry and PROMs did not change significantly up to 5 years of follow-up in a standard-of-care cohort of SjD patients from daily clinical practice.*

**Key words**

Sjögren's syndrome, Sjögren's disease, major salivary glands, salivary gland ultrasonography, sialometry, patient-reported outcome measures, prospective cohort

*Niels R.F. Sluijpers, MD*
*Konstantina Delli, DDS, Dr Med Dent, PhD*
*Liseth De Wolff, MD*
*Alja J. Stel, MD, PhD*
*Frederik K.L. Spijkervet, DDS, PhD*
*Frans G.M. Kroese, PhD*
*Hendrika Bootsma, MD, PhD*
*Suzanne Arends, PhD*
*Arjan Vissink, DDS, MD, PhD*

*Please address correspondence to:*
*Niels Sluijpers*
*Department of Oral and Maxillofacial Surgery,*
*University of Groningen,*
*University Medical Center Groningen,*
*Hanzeplein 1, HPC BB70, Postbus 30001, 9700 RB, Groningen, The Netherlands.*
*E-mail: n.r.f.sluijpers@umcg.nl*

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## Introduction

Primary Sjögren's disease (SjD) is a common systemic auto-immune disease characterised by lymphocytic infiltration of the exocrine glands (1). In particular the lacrimal and salivary glands are affected, which can result in pain, swelling of the glands, glandular hypofunction, and a sensation of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) (2). To assess salivary gland-related changes in SjD patients, histopathology of the salivary glands, measurement of salivary flow (sialometry), and salivary gland ultrasound (SGUS) are widely used (3-5).

With regard to the salivary gland parameters, SGUS and sialometry are easily performed, non-invasive and well-tolerated, making them ideal instruments to use in follow-up visits (4, 5). However, little is known regarding the longitudinal changes in and natural variation of sialometry and SGUS over time (6). Moreover, only a few studies have examined the progression of salivary gland dysfunction over time using sialometry in SjD patients (7, 8). Pijpe *et al*. described a significant decrease in stimulated salivary flow rates over time in patients with very early SjD (7), while Gannot *et al*. showed relatively stable salivary flow rates after 5 years of follow-up. However, in the latter study the duration of symptoms at baseline was not mentioned (8). Thus, there is a paucity of longitudinal sialometric and SGUS data in SjD patients.

Salivary gland dysfunction has a large impact on life of SjD patients (9). While salivary gland dysfunction, as measured with sialometry, often is associated with xerostomia, a reduction in salivary flow does not necessarily correspond with increased xerostomia (10). Thus, patient-reported outcome measurements (PROMs) assessing dryness symptoms should be analysed in addition to SGUS and sialometry. Our standard-of-care REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort provides a unique opportunity to assess the major salivary glands of established SjD patients using repeated measurements of SGUS, sialometry and PROMs (11). Therefore, the objective of this study was to assess changes in major salivary glands over time using SGUS, sialometry and PROMs in SjD patients from daily clinical practice up to five years of follow-up. Secondly, we aimed to explore the associations between baseline scores and changes in objective assessments and PROMs.

## Materials and methods

### *Patient cohort*

All patients included in this study participated in the RESULT cohort (11). The RESULT cohort is an ongoing prospective observational standard-of-care cohort, in which patients with SjD or incomplete SjD are included and followed up for 10 years. Patients visit the expertise centre for SjD at the University Medical Centre Groningen yearly, or on clinical indication more often. At follow-up visits patients are evaluated at the rheumatology, ophthalmology, and oral and maxillofacial surgery outpatient clinics by medical specialists of each specialty. For the present study, the inclusion criteria were as follows: fulfilment of the 2016 American College of Rheumatology and European League against Rheumatology (ACR/EULAR) criteria for SjD and available data of at least 2-year follow-up (12). SGUS and sialometry measurements were performed according to the RESULT cohort protocol at baseline (BL), year 2 (Y2) and year 5 (Y5) follow-up visits. In addition, questionnaires were administered at these visits.

This study was performed in accordance with the Declaration of Helsinki. Approval of the research protocol by the Medical Ethics Committee of the UMCG (METC 2014/491) was obtained. All patients provided informed consent.

### *Salivary gland ultrasound*

Salivary gland grey-scale ultrasound was performed by trained operators using an ultrasound machine (Esaote, MyLabSeven, Genova, Italy) with a high-resolution linear probe (4–13 MHz). Ultrasound images were scored during the visits using the Hocevar scoring system (scale 0–48) (13). In this scoring system, parenchymal echogenicity, parenchymal homogeneity,

hypoechogenic areas, hyperechogenic reflections and clarity of the salivary gland border are assessed. In case it was not possible to score a gland, for example due to previous removal of the gland, the Hocevar score from the other gland was used to calculate the total score. From 2021 onwards, images were additionally scored using the Outcome Measures in Rheumatology Clinical Trials (OMERACT) ultrasound scoring system (14, 15). The OMERACT ultrasound scoring system is a semi-quantitative four-graded scoring system (scale 0-3). Grade 0 represents normal parenchyma, grade 1 is mild inhomogeneity without anechoic or hypoechogenic areas, grade 2 is moderate inhomogeneity with focal anechoic or hypoechogenic areas, and grade 3 corresponds to severe inhomogeneity with diffuse an- or hypoechogenic areas occupying the entire gland. For SGUS data prior to 2021, the OMERACT score was calculated from the Hocevar score using conversion tables (Supplementary Tables S1 and S2).

*Sialometry*

To assess secretory function, unstimulated whole saliva (UWS) and stimulated whole saliva (SWS) and gland-specific saliva, *i.e.* unstimulated parotid saliva (UPS), unstimulated submandibular/sublingual saliva (uSMSLS), stimulated parotid saliva (SPS) and stimulated submandibular/sublingual saliva (sSMSLS), was collected by trained dental hygienists according to a standardised protocol (4, 7). In short, patients were instructed not to drink, eat, and smoke 90 minutes before saliva collection. All saliva samples were collected in pre-weighed plastic tubes. First, unstimulated whole saliva was collected during 15 minutes, followed by glandular saliva from both the right and left parotid glands, which was collected using Lashley cups for ten minutes. These cups were placed over the orifices of the Stenson's ducts. Simultaneously, syringe aspiration from the orifices of the Wharton's duct was used to collect saliva from the submandibular/sublingual glands. Next, stimulated saliva was collected during 10 minutes. SWS after stimulation with paraffin wax, gland-specific saliva after stimulation at 30 second intervals with a citric acid solution (2%wt/vol) applied with a cotton swab to the lateral borders of the tongue (4, 7). Flow rates were calculated after weighing the tubes, with the assumption that the specific gravity of saliva is 1.0 g/cm$^3$. In case a patient did not have any saliva production after repeated measurements, saliva production was imputed as 0 ml/min.

*Patient-reported outcome measurements*

Patient-reported dryness symptoms were assessed using the following questionnaires: the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) general dryness component, the Numeric Rating Scale (NRS) for oral dryness and the Xerostomia Inventory (XI). The ESSPRI general dryness component and NRS for oral dryness assess general and oral dryness on a 0-10 scale in the last two weeks (16). The XI is a questionnaire consisting of 11 items, scored on an ordinal scale of 1–5, which are combined into a total score (11-55). The following items are included in the XI: use of liquids for swallowing food, oral dryness during food consumption, drinking during the night, general feeling of oral dryness, difficulty eating dry food, usage of lollypops/sweets to stimulate saliva production, difficulty swallowing food, feeling of a dry skin, feeling of dry eyes, feeling of dry lips, and lastly feeling of a dry nose (17).

**Table I.** Baseline characteristics of included SjD patients of the RESULT cohort (n=253).

| | |
|---|---|
| Age (years) | 55 (45-65) |
| Sex (female) | 224 (89%) |
| Time since diagnosis (years) | 5 (2-10) |
| Symptom duration (years)[b] | 11 (6-19) |
| Total ESSDAI score[a] | 4 (2-7) |
| ESSDAI glandular domain score >0[a] | 60 (24%) |
| Oral symptoms; daily feeling of dry mouth for more than 3 months[a] | 209 (84%) |
| Oral symptoms; recurrent or persistent swelling of the major salivary glands[a] | 124 (50%) |
| Oral symptoms; patient requires regular intake of liquids to swallow dry food[a] | 189 (77%) |
| Use of DMARDs at baseline | 52 (21%) |
| History of MALT lymphoma at baseline | 39 (15%) |

Values are presented as numbers (%) or median + interquartile range (IQR).
[a]<5% missing data.
[b]10-15% missing data.
ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; MALT: mucosa-associated lymphoid tissue; DMARDs: disease modifying anti-rheumatic drugs.

*Statistical analysis*

All statistical analyses were performed using IBM SPSS Statistics 28. Mean (±SD), median (IQR) or n (%) was used for descriptive statistics of normally distributed data, non-normally distributed data and categorical data, respectively. To assess measurements over time at individual patient level, a change of ≥25% was defined as a clinically relevant change for Hocevar score, UWS and SWS (18). Linear Generalized Estimating Equations (GEE) analysis was performed to assess changes over time in SGUS, sialometry and PROM data. Residuals were checked for normality. In case of non-normally distributed residuals, transformations were performed on the dependent variables. If residuals remained non-normally distributed, Wilcoxon signed ranks test was performed. Three different correlation structures (exchangeable, M-dependent and unstructured) were tested. The model with the lowest corrected quasi likelihood under independence model criterion (QICC) was used, which was the exchangeable correlation structure in all cases. The association between objective assessments and PROMs was analysed using Spearman's rank correlation coefficient (ϱ), and interpreted as poor (0.0–0.2), fair (0.2–0.4), moderate (0.4–0.6), good (0.6–0.8), or excellent (0.8–1.0) association.

## Results

Between January 2016 and October 2022, 346 consecutive patients diag-

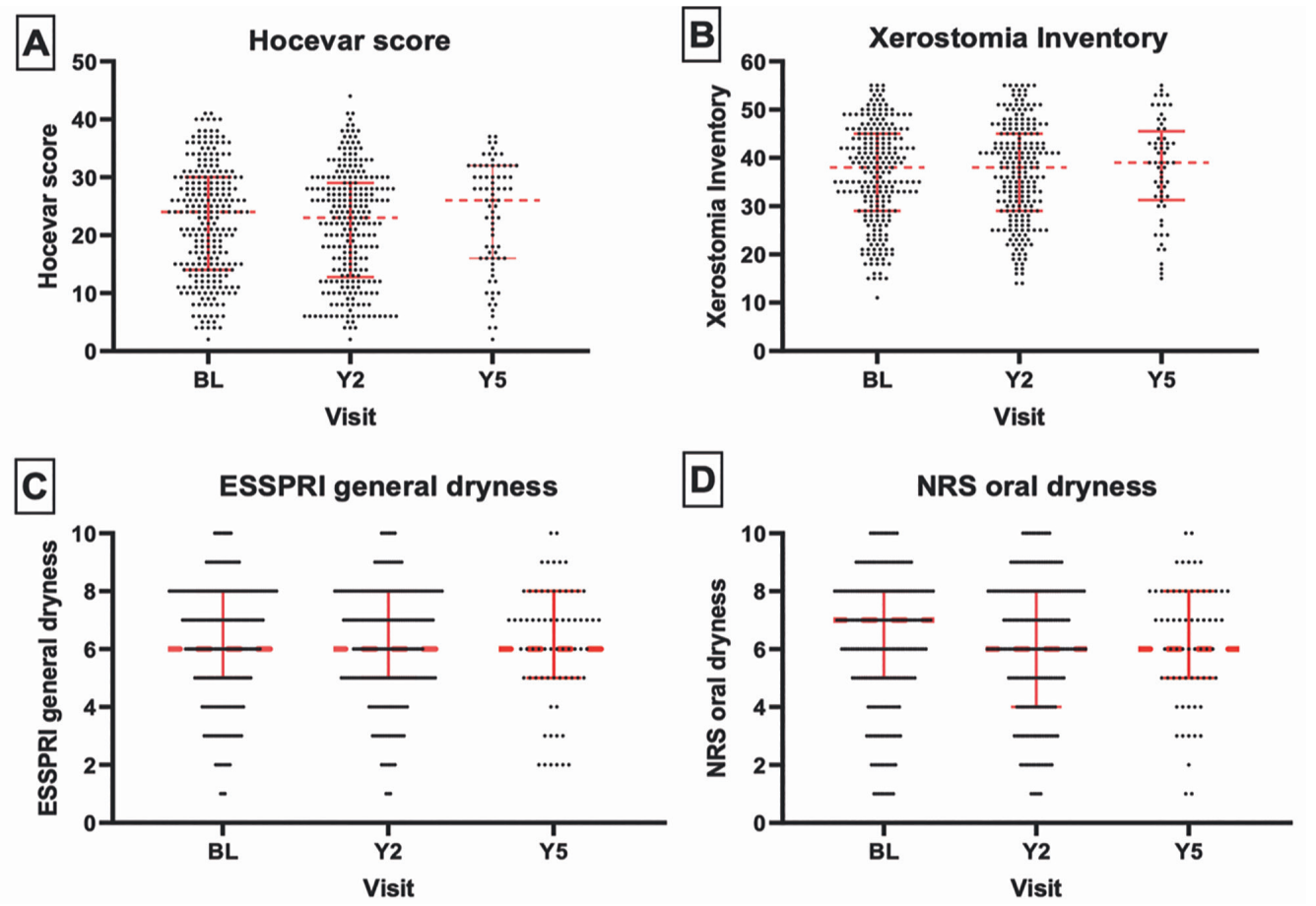


**Fig. 1.** SGUS and PROMs over time. **A)** Total Hocevar score. **B)** Xerostomia inventory. **C)** ESSPRI general dryness. **D)** NRS oral dryness. Displayed in red are the median + interquartile range. BL: baseline; Y2: year 2; Y5: year.

nosed with SjD were included in the RESULT cohort. For this analysis, 27 patients were excluded because they did not fulfil the ACR-EULAR criteria. A further 66 patients were excluded because no Y2 follow-up data was present. This resulted in a total of 253 patients for inclusion in this study. Of the 253 patients, 75 patients had reached Y5. The median age at the baseline visit was 55 years (range 20-78) and 89% of the patients were female. Median symptom duration was 11 years (IQR 6-19) and median time since diagnosis was 5 years (IQR 2-10). Fifty-two patients (21%) were treated with a DMARD, *i.e.* abatacept, azathioprine, cyclophosphamide, cyclosporin, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, prednisone and rituximab, at baseline and 107 patients (42%) at any point during follow-up. Of the patients who completed Y2 and Y5, 2 patients (2.7%) developed a MALT lymphoma during follow-up. Baseline characteristics are presented in Table I.

*Salivary gland ultrasound (SGUS)*

Mean Hocevar score was 22 (SD±10) at BL, 22 (±10) at Y2 and 23 (±10) at Y5. Overall, no change in total Hocevar score between visits was observed at group level (BL *vs.* Y2, $p$=0.095, BL *vs.* Y5, $p$=0.095, Y2 *vs.* Y5, $p$=0.440) (Fig. 1, Table II). Similarly, the specific SGUS characteristics, *i.e.* parenchymal echogenicity, homogeneity, hypoechoic areas, hyperechogenic reflections, and clarity of the posterior border remained constant over time (Table II). In addition, OMERACT scores of all individual four major salivary glands were stable during follow-up. Patients with recurrent and/or persistent swelling of the major salivary glands at BL had higher mean total Hocevar scores at BL compared to patients without swelling (24±9 *vs.* 20±10, $p$=0.002). In addition, at Y2 and Y5 no statistically significance differences were found in total Hocevar score between patients with and without recurrent and/or persistent swelling of the major salivary glands at BL.

At individual patient level, Hocevar scores were stable (within 25% change over time) in 53% and 60% of patients at Y2 and Y5, respectively. Furthermore, a similar proportion of patients, showed either an increase (23% and 19% respectively) or decrease (24% and 21% respectively) in scores of ≥25% at Y2 and Y5 compared to BL (Table III). Patients who presented with a decreased total Hocevar score at Y2 had at BL statistically significant higher UWS compared to patients with a stable or increased total Hocevar score ($p$=0.006). Specifically, at Y2 baseline median UWS was 0.09 (IQR 0.02-0.16) ml/min for patients with a decreased total Hocevar score, 0.02 (IQR 0–0.12) ml/min for patients with a stable total Hocevar total score and 0.05 (IQR 0.02–0.14)

**Table II.** SGUS assessments at baseline, 2 years and 5 years of follow-up in included SjD patients.

| Parameter | Gland | Baseline (n=253)[a] | Year 2 (n=253)[c] | Year 5 (n=75)[b] |
|---|---|---|---|---|
| **OMERACT** | Left SM | 2 (1-2) | 2 (1-2) | 2 (1-3) |
| | Right SM | 2 (1-3) | 2 (1-3) | 2.5 (1-3) |
| | Left PAR | 2 (1-2) | 2 (1-2) | 2 (1-3) |
| | Right PAR | 2 (1-3) | 2 (1-3) | 2 (1-3) |
| **Total Hocevar score:** | - | 22 (±10) | 22 (±10)[a] | 23 (±10) |
| **echogenicity** | Left SM | 1 (0-1) | 1 (0-1) | 1 (1-1) |
| | Right SM | 0 (0-1) | 1 (0-1) | 0 (0-1) |
| | Left PAR | 1 (0-1) | 1 (0-1) | 1 (1-1) |
| | Right PAR | 1 (0-1) | 1 (0-1) | 1 (0-1) |
| **homogeneity** | Left SM | 2 (1-2) | 2 (1-2) | 2 (1-2) |
| | Right SM | 2 (1-2) | 2 (1-2) | 2 (1-3) |
| | Left PAR | 2 (1-2) | 2 (1-2) | 2 (1-2) |
| | Right PAR | 2 (1-2) | 2 (1-2) | 2 (1-3) |
| **hypoechogenic areas** | Left SM | 2 (1-2) | 2 (1-2) | 2 (1-2) |
| | Right SM | 2 (1-3) | 2 (1-3) | 2 (1-3) |
| | Left PAR | 2 (1-2) | 2 (1-2) | 2 (1-2) |
| | Right PAR | 2 (1-3) | 2 (1-3) | 2 (1-3) |
| **hyperechogenic reflections** | Left SM | 1 (0-1) | 1 (0-1) | 1 (0-1) |
| | Right SM | 1 (1-1) | 1 (1-1) | 1 (1-1) |
| | Left PAR | 1 (0-1) | 1 (0-1) | 1 (0-1) |
| | Right PAR | 1 (1-1) | 1 (1-1) | 1 (1-1) |
| **posterior gland border** | Left SM | 0 (0-1) | 0 (0-1) | 0 (0-1) |
| | Right SM | 1 (0-1) | 1 (0-1) | 1 (0-1) |
| | Left PAR | 0 (0-1) | 0 (0-1) | 0 (0-1) |
| | Right PAR | 1 (0-1) | 1 (0-1) | 1 (0-1) |

Values are presented as mean ± standard deviation (SD) or median + interquartile range (IQR).
[a]<5% data missing. [b]5-10% data missing. [c]10-15% data missing.
There were no statistically significant changes between baseline, year 2, and year 5.
SM: submandibular; PAR: parotid.

**Table III.** Changes over time in UWS, SWS and Hocevar score from baseline to year 2 and year 5 at individual patient level.

| Parameter | Change | Year 2 | Year 5 |
|---|---|---|---|
| **Hocevar** | Increase of ≥25% compared to baseline | 57/248 (23%) | 14/73 (19%) |
| | Stable (within 25% change) | 131/248 (53%) | 44/73 (60%) |
| | Decrease of ≥25% compared to baseline | 60/248 (24%) | 15/73 (21%) |
| **UWS** | Increase of ≥25% compared to baseline | 47/209 (23%) | 11/61 (18%) |
| | Any increase if baseline is 0 | 13/209 (6%) | 7/61 (12%) |
| | Stable (within 25% change) | 75/209 (36%) | 20/61 (33%) |
| | Decrease of ≥25% compared to baseline | 74/209 (35%) | 23/61 (38%) |
| **SWS** | Increase of ≥25% compared to baseline | 72/215 (36%) | 14/63 (22%) |
| | Any increase if baseline is 0 | 9/215 (4%) | 9/63 (14%) |
| | Stable (within 25% change) | 90/215 (42%) | 26/63 (41%) |
| | Decrease of ≥25% compared to baseline | 44/215 (21%) | 14/63 (22%) |

Values are presented as numbers (%).
UWS: unstimulated whole saliva; SWS: stimulated whole saliva.

ml/min for patients with an increased total Hocevar score. In contrast, SWS at baseline was not statistically significant different between the three subgroups, *i.e.*, patients with increased, decreased or stable total Hocevar score. Regarding possible clinical predictors: age, gender, time since diagnosis, symptom duration, total ESSDAI score, and use of (b)DMARDS were not statistically significant. Patients with an increased total Hocevar score at Y2 did not differ significantly in any of the previously mentioned parameters compared to patients with a stable or decreased total Hocevar score.

*Sialometry*

Median UWS was 0.05 (IQR 0.01–0.15) ml/min at BL, 0.05 (0-0.15) ml/min at Y2 and 0.03 (0-0.09) ml/min at Y5. Median SWS was 0.54 (0.16–0.96) ml/min at BL, 0.52 (0.20–1.00) ml/min at Y2 and 0.36 (0.08–0.73) ml/min at Y5. GEE analysis of sialometry could not be performed due to no Gaussian distribution of the residuals. Alternatively, Wilcoxon signed rank tests were performed. All sialometry values, *i.e.* UWS, uSMSLS, UPS, SWS, sSMSLS and SPS remained stable between BL and Y2 (Fig. 2, Table IV) at group level. At Y5, lower values were observed for all sialometry parameters, but additional analyses showed that lower values of patients having completed Y5 were already present at BL and Y2 (Table IV). A slight, but statistically significant ($p$=0.025), reduction in uSMSLS at Y5 was found compared to BL. Similarly, lower sSMSLS values at Y5 were found compared to BL ($p$=0.004). Of interest, there was no statistically significant difference in UWS and SWS at BL between patients with and without recurrent or persistent swelling of the major salivary glands. In addition, no statistically significant differences were found in UWS and SWS at Y2 and Y5 between patients with and without swelling of the major salivary glands at BL.

At individual patient level, changes in sialometry over time were found in both directions (Table III). A decrease in UWS of ≥25% at Y2 compared to BL was present in 35% of patients. For SWS, only 21% of patients had a decrease of ≥25% at Y2 compared to BL. At Y5, similar percentages were observed. Patients who presented with improved UWS at Y2 had at BL statistically significant lower total Hocevar scores ($p$<0.001) and less hypoechogenic areas in the left submandibular ($p$=0.011), left parotid ($p$=0.003), right submandibular ($p$<0.001) and right parotid gland ($p$=0.009) compared to patients with stable UWS. Mean total Hocevar score was 17 (±9) for patients with 25% improvement of UWS at Y2, 24 (±9) for patients with stable UWS, 21 (±10) for patients with ≥25% decrease of UWS and 24 (±10) for patients

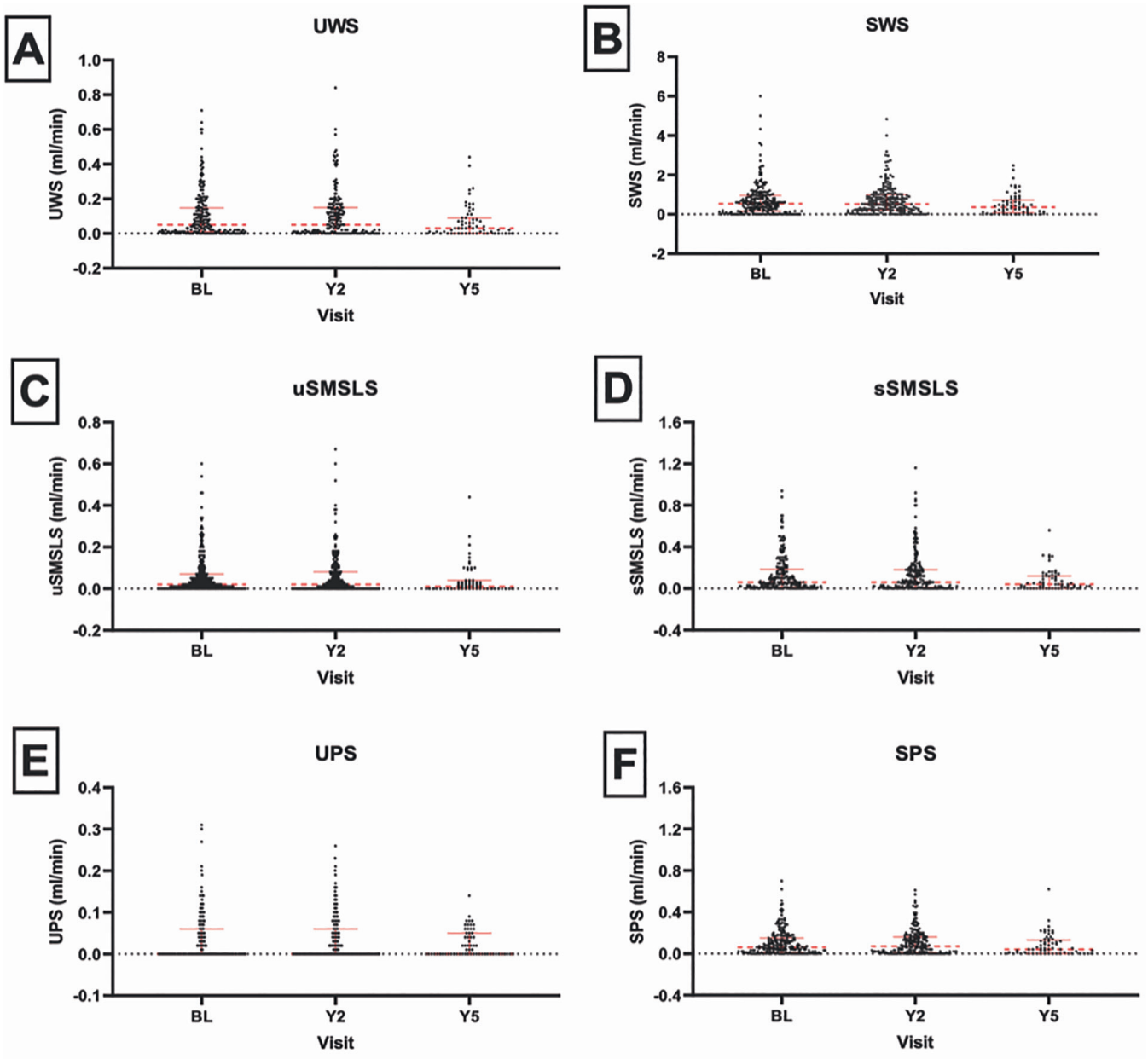


**Fig. 2.** Sialometry over time **A)** Unstimulated whole saliva (UWS). **B)** Stimulated whole saliva (SWS). **C)** Unstimulated submandibular/sublingual saliva (uSMSLS). **D)** Stimulated submandibular/sublingual saliva (sSMSLS). **E)** unstimulated Parotid saliva (UPS). **F)** Stimulated parotid saliva (SPS). Displayed in red are the median + Interquartile range. BL: baseline; Y2: year 2; Y5: year 5.

with any improvement of UWS when UWS was 0 ml/min at BL. Regarding possible clinical predictors: age, gender, time since diagnosis, symptom duration, total ESSDAI score, and use of (b)DMARDS were not statistically significant. Patients with decreased UWS at Y2 did not differ significantly in any of the previously mentioned parameters compared to patients with stable UWS. Lastly, in the patient group with improved, stable, and decreased SWS at Y2 we could not detect any statistically significant predictive parameters.

*Patient-reported outcome measurements*

At group level, the scores of all three questionnaires, *i.e.* ESSPRI general dryness, NRS oral dryness, and XI, remained rather stable during follow-up (Fig. 1, Table V). There were no statistically significant changes in scores over time.

*Correlations*

Moderate associations were found between UWS and the Hocevar score for BL ($p$=-0.48), Y2 ($p$=-0.52) and Y5 ($p$=-0.59). Likewise, moderate associations were found between SWS and the Hocevar score for BL ($p$=-0.48), Y2 ($p$=-0.47) and Y5 ($p$=-0.61). A similar pattern was observed for associations between the OMERACT scores, UWS and SWS at all timepoints, although the correlations were generally lower between $p$=-0.43 and $p$=-0.64 than the correlations between sialometry and the Hocevar score. At BL, poor associations were observed between the Hocevar score and general dryness ($p$=0.18) or oral dryness ($p$=0.17) (Table VII).

**Table IV.** Sialometry data at baseline, 2 years and 5 years of follow-up in included SjD patients.

| Parameter | Baseline (n=253)[a] | Year 2 (n=253) | Year 5 (n=75) |
|---|---|---|---|
| UWS (ml/min) | 0.05 (0.01-0.15) | 0.05 (0.00-0.15)[d] | 0.03 (0.00-0.09)[c] |
| uSMSLS (ml/min) | 0.02 (0.01-0.07) | 0.02 (0.00-0.08)[c] | 0.01 (0.00-0.04)[d] |
| UPS (ml/min) | 0.00 (0.00-0.06) | 0.00 (0.00-0.06)[c] | 0.00 (0.00-0.05)[d] |
| SWS (ml/min) | 0.54 (0.16-0.96) | 0.52 (0.20-1.00)[c] | 0.36 (0.08-0.73)[c] |
| sSMSLS (ml/min) | 0.06 (0.01-0.19) | 0.06 (0.01-0.18)[c] | 0.04 (0.00-0.12)[c] |
| SPS (ml/min) | 0.06 (0.01-0.15) | 0.07 (0.01-0.16)[c] | 0.04 (0.00-0.13)[d] |

Values are presented as median + interquartile range (IQR).
UWS: unstimulated whole saliva; uSMSLS: unstimulated submandibular/sublingual saliva; UPS: unstimulated parotid saliva; SWS: stimulated whole saliva; sSMSLS: stimulated submandibular/sublingual saliva; SPS: stimulated parotid saliva.
[a]<5% data missing. [b]5-10% data missing. [c]10-15% data missing. [d]15-20% data missing.
There were no statistically significant changes between baseline and year 2. uSMSLS did differ statistically significant between baseline and year 5 ($p$=0.025), as did sSMSLS ($p$=0.004). For the other sialometry measurements there was no statistically significant difference between baseline and year 5.

**Table V.** Sialometry data at baseline, 2 years and 5 years of follow-up in the subgroup of SjD patients who completed all 3 visits (n=75).

| Parameter | Baseline[a] | Year 2 | Year 5 |
|---|---|---|---|
| UWS (ml/min) | 0.02 (0.00-0.09) | 0.01 (0-0.12)[c] | 0.03 (0.00-0.09)[c] |
| uSMSLS (ml/min) | 0.02 (0.00-0.05) | 0.01 (0-0.07)[b] | 0.01 (0.00-0.04)[d] |
| UPS (ml/min) | 0.00 (0.00-0.02) | 0.00 (0.00-0.02)[b] | 0.00 (0.00-0.05)[d] |
| SWS (ml/min) | 0.33 (0.00-0.80) | 0.29 (0.12-0.78)[b] | 0.36 (0.08-0.73)[c] |
| sSMSLS (ml/min) | 0.04 (0.01-0.15) | 0.05 (0.00-0.18)[b] | 0.04 (0.00-0.12)[c] |
| SPS (ml/min) | 0.05 (0.01-0.12) | 0.04 (0.00-0.12)[c] | 0.04 (0.00-0.13)[d] |

Values are presented as median + interquartile range (IQR).
UWS: unstimulated whole saliva; uSMSLS: unstimulated submandibular/sublingual saliva; UPS: unstimulated parotid saliva; SWS: stimulated whole saliva; sSMSLS: stimulated submandibular/sublingual saliva; SPS: stimulated parotid saliva.
[a]<5% data missing. [b]5-10% data missing. [c]10-15% data missing. [d]15-20% data missing.
There were no statistically significant changes between baseline and year 2. uSMSLS did differ statistically significant between baseline and year 5 ($p$=0.025), as did sSMSLS ($p$=0.004). For the other sialometry measurements there was no statistically significant difference between baseline and year 5.

**Table VI.** PROMs related to dryness at baseline, 2 years and 5 years of follow-up in included SjD patients.

| Parameter | Baseline (n=253)[b] | Year 2 (n=253) | Year 5 (n=75) |
|---|---|---|---|
| ESSPRI general dryness | 6 (5-8) | 6 (5-8)[b] | 6 (5-8)[b] |
| NRS oral dryness | 7 (5-8) | 6 (4-8)[b] | 6 (5-8)[c] |
| XI total score | 37 (±10) | 37 (±10)[c] | 38 (±11)[d] |

ùValues are presented as mean ± standard deviation (SD) or as median + interquartile range (IQR).
ESSPRI: EULAR Sjögren Syndrome Patient Reported Index; NRS: numeric rating scale; XI: xerostomia inventory.
[a]<5% data missing. [b]5-10% data missing. [c]10-15% data missing. [d]15-20% data missing.
There were no statistically significant changes between baseline, year 2, and year 5.

Fair associations were found between UWS and general dryness ($p$=-0.34), oral dryness ($p$=-0.37) or XI ($p$=-0.29). Similarly, fair associations were found between SWS and general dryness ($p$=-0.29), oral dryness ($p$=-0.35) or XI ($p$=-0.32). However, changes over time in Hocevar score, UWS and SWS did not correlate at all with changes in PROMs.

*DMARD vs. non-DMARD users*

A subgroup analysis on patients using DMARDs during follow-up was performed (Suppl. Table S3). No statistically significant differences were found between the non-DMARD and the DMARD group, except of a higher median SWS in the non-DMARD group compared to the DMARD group compared at Y2 follow-up (0.66 *vs.* 0.41; $p$=0.038).

## Discussion

In this study, we showed that major salivary gland functioning assessed with SGUS, sialometry and PROMs remained stable at group level during a follow-up period of 5 years in established SjD patients. At individual patient level, a similar proportion of patients showed an increase or decrease in scores. To the best of our knowledge, this is the first study to evaluate SGUS together with sialometry and PROMs in a prospective long-term follow-up setting of SjD patients from daily clinical practice.

The finding that overall SGUS remained stable over time in our standard-of-care cohort is very relevant, since SGUS is already being used in clinical trials to monitor changes and effect of treatment (18-21). Until now, it was not clear if observed changes in clinical trials were due to the medication tested, or if the natural course of the disease also contributed to the changes observed. Our findings indicate that overall, SGUS scores, assessed with the Hocevar and OMERACT score, remain stable over 2 to 5 years in patients with SjD. Thus, a significant change in SGUS scores in clinical trials, usually with a follow-up period of 6 months to 1 year, may be attributed to pharmacological intervention, under the condition that ultrasonographers are well-trained and calibrated (22).

In addition to the SGUS results, we showed that overall sialometry measurements remained stable between BL and Y2. At Y5, both lower uSMSL and sSMSL salivary flow rates were observed. The absolute decrease of SMSL saliva production over time was minimal. This, and the fact that other sialometry parameters did not change significantly, implies that the clinical impact of this decrease is limited. In the study of Pijpe *et al*. it was shown that very early after start of symptoms a change in salivary glandular function can be seen (7). In the latter study, patients included were further classified as having symptoms for <1 year, 1-4 years and >4 years. In our study in es-

**Table VII.** Associations between baseline scores and changes in objective measurements and PROMs.

| **Baseline** | | **Total Hocevar score** | **UWS** | **SWS** | **ESSPRI General dryness** | **NRS oral dryness** | **XI total score** |
|---|---|---|---|---|---|---|---|
| **Total Hocevar score** | | - | -0,48* | -0.48* | 0.180* | 0.17* | 0.10 |
| **OMERACT** | Left SM | 0.80* | -0.41* | -0.39* | 0.17* | 0.14* | 0.09 |
| | Right SM | 0.81* | -0.40* | -0.36* | 0.17* | 0.07 | 0.05 |
| | Left PAR | 0.84* | -0.45* | -0.43* | 0.15* | 0.17* | 0.07 |
| | Right PAR | 0.85* | -0.41* | -0.39* | 0.14* | 0.13* | 0.04 |
| **UWS** | | -0.48* | - | 0.64* | -0.34* | -0.37* | -0.29* |
| **SWS** | | -0.48* | 0.64* | - | -0.29* | -0.35* | -0.32* |
| **Δ0-2 years** | | **ΔTotal Hocevar score** | **ΔUWS** | **ΔSWS** | **ΔESSPRI general dryness** | **ΔNRS oral dryness** | **ΔXI total score** |
| **ΔTotal Hocevar score** | | - | 0.19* | -0.05 | 0.036 | 0.028 | 0.013 |
| **ΔOMERACT** | Left SM | 0.58* | 0.05 | -0.04 | 0.00 | -0.03 | -0.08 |
| | Right SM | 0.55* | -0.04 | -0.06 | -0.02 | -0.12 | -0.16* |
| | Left PAR | 0.52* | 0.00 | 0.01 | -0.03 | 0.02 | -0.04 |
| | Right PAR | 0.56* | 0.08 | 0.06 | 0.01 | 0.02 | -0.08 |
| **ΔUWS** | | 0.19* | - | 0.22* | -0.03 | -0.04 | 0.03 |
| **ΔSWS** | | -0.05 | 0.22* | - | 0.01 | 0.03 | -0.07 |
| **Δ0-5 years** | | **ΔTotal Hocevar score** | **ΔUWS** | **ΔSWS** | **ΔESSPRI general dryness** | **ΔNRS oral dryness** | **ΔXI total score** |
| **ΔTotal Hocevar score** | | - | 0.00 | 0.05 | 0.03 | 0.13 | 0.11 |
| **ΔOMERACT** | Left SM | 0.66* | 0.15 | 0.05 | -0.26* | -0.01 | -0.05 |
| | Right SM | 0.51* | -0.10 | -0.05 | -0.19 | 0.08 | 0.09 |
| | Left PAR | 0.71* | -0.14 | 0.07 | 0.06 | 0.10 | 0.09 |
| | Right PAR | 0.71* | -0.20 | -0.12 | 0.09 | 0.16 | 0.09 |
| **ΔUWS** | | 0.00 | - | 0.39* | -0.21 | -0.27 | -0.05 |
| **ΔSWS** | | 0.05 | 0.39* | - | -0.11 | -0.22 | -0.01 |

Values are presented as Speaman's rank correlation coefficients (ϱ). **Δ** represents the difference in values between follow-up and baseline visit.
ESSPRI: EULAR Sjögren Syndrome Patient Reported Index; NRS: numeric rating scale; XI: xerostomia inventory; UWS: unstimulated whole saliva; SWS: stimulated whole saliva; SM: submandibular; PAR: parotid.
*$p<0.05$.

tablished SjD patients, median symptom duration was 11 years and median time after diagnosis was 5 years, and as a result salivary gland function was already at a reduced, lower level. Thus, it seems that in established SjD patients salivary gland rest function does not change further over time. These findings are in line with results from Gannot *et al*. and Theander *et al*. where also no significant changes in salivary flow were observed after the disease had established (8, 23).

At individual level, a proportion of patients showed decrease of total Hocevar score or increase of UWS/SWS in time. We could only detect that patients who presented with a decreased total Hocevar score at Y2 had at baseline statistically significant higher UWS. Likewise, patients with ≥25% improvement of UWS between BL and Y2 had lower total Hocevar scores and less hypoechogenic areas in all 4 major salivary glands. The abovementioned findings suggest that baseline UWS or a total Hocevar score might predict a milder course of glandular disease.

Similarly, the subjective dryness assessments (PROMs) did not show significant changes after Y2 and Y5. Despite the small reduction in SMSL saliva production, no evident change in xerostomia complaints was reported. Theander *et al*. and Pijpe *et al*. described a similar outcome in that, at follow-up, no statistically significant changes in PROMs were reported (7, 23). We found moderate correlations between UWS, SWS, Hocevar score, and OMERACT scores at all timepoints, verifying the conclusion of Mossel *et al*. that these parameters are complementary measurements in SjD (24). This confirms earlier findings by Hammenfors *et al*. and Lee *et al*. that higher ultrasound scores are associated with lower saliva production, representing more damaged salivary glands (25, 26). While in our study fair associations were observed between UWS, SWS and the questionnaires, changes in objective measurements did not correlate with changes in PROMs. A possible explanation for this might be that patients in later stages of the disease have adapted better to a decreased saliva production or that, after some time, some habituation occurs.

The main strength of our study is the relatively large, prospective and standardised cohort of SjD patients, which provides a broad reflection of SjD patients from daily clinical practice. All measurements were performed using standardized methods making them

reproducible for future studies. A limitation of our study is the small patient group at Y5 compared to the patient group that has completed BL and Y2. The reason for this is that patients have not reached the Y5 visit yet. Furthermore, a rather large proportion of the participants in this study already had a longer duration of symptoms at baseline. Thus, the changes that may occur shortly after onset of SjD may not be observed in this cohort of SjD patients from daily clinical practice. Since all assessments were only performed at BL, Y2 and Y5 visits of the RESULT cohort, data was not always available directly before and after the start of (b) DMARDs, which makes it difficult to analyse the effect of treatment on major salivary gland functioning. While a subgroup analysis of patients using DMARDs was performed, besides SWS in the non-DMARD group at Y2, no statistically significant differences were observed. This difference in SWS appears to be an incidental finding with little clinical significance since it was only observed at one measurement in a relatively small patient group.

The RESULT cohort will be continued for up to 10 years. It will be of interest to assess if changes in SGUS scores, sialometry and PROMs remain constant over 10 years of follow-up, as these long-term data are lacking too. In addition, next to grey-scale SGUS, it would be interesting to longitudinally assess changes of the colour Doppler signal in the major salivary glands of patients with SjD. Currently, the role of colour Doppler in diagnosing SjD and monitoring disease activity is still unknown (27). Prospective studies investigating changes in major salivary glands vasculature using SGUS colour Doppler are eagerly awaited.

In conclusion, in this cohort of SjD patients from daily clinical practice with longstanding symptoms and SjD diagnosis, we showed that SGUS scores, sialometry and PROMs related to xerostomia, did not change up to five years of follow-up.

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