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ORIGINAL PAPER

Ultrasonography of the salivary glands in the diagnosis of Sjögren's syndrome secondary to rheumatoid arthritis – a probabilistic approach

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ABSTRACT

Introduction and aim. To evaluate the role of salivary gland ultrasound (SGUS) in differentiating rheumatoid arthritis (RA) patients with or without Sjogren's syndrome (SS) using a probability method and to study the relation between secondary SS (sSS) and RA disease characteristics.

Material and methods. One hundred RA patients with disease duration ≥5 years underwent detailed history taking, examination, routine laboratory testing, Schirmer's test, unstimulated salivary flow rate and SGUS of the 4 major salivary glands using Salaffi and Outcome Measures In Rheumatoid Arthritis Clinical Trials (OMERACT) scores.

Results. Patients sum with probabilities for sSS ≤20% and ≥80% were (39/100) before and (90/100) after SGUS with a highly significant difference ($p<0.001$).There was significantly more frequent carpal tunnel syndrome (CTS), longer RA disease duration and higher anti-cyclic citrullinated peptide antibodies (anti-CCP) in RA patients with sSS compared to those without($p<0.05$). There was highly significant agreement between Salaffi and OMERACT scores in gland evaluation by kappa test. The highest ultrasound OMERACT score of SG showed significant positive correlation with both Disease Activity Score-28-Erythrocyte Sedimentation Rate (DAS-28 ESR score) and ESR in RA patients.

Conclusion. Secondary SS is frequent in RA patients especially in association with longer disease duration, higher anti-CCP antibody titer and CTS. SGUS is a useful tool that helps diagnosing and grading the severity of SS in RA. SS severity correlates with RA disease activity.

Keywords. rheumatoid arthritis, salivary gland ultrasound, secondary Sjogren's syndrome

Introduction

Determining the exact prevalence of Sjogren's syndrome (SS) is very difficult as the diagnostic criteria frequently change. Although SS was looked upon as a rare disease in the past, it is now regarded as the second most common autoimmune disease after rheumatoid arthritis (RA).[1]

RA is the most common connective tissue disease associated with SS. RA may present with several extra-articular manifestations which might include sicca symptoms which are important for the diagnosis of secondary SS (sSS). However, other symptoms of SS are usually mild and uncommon.[2,3] RA patients with sSS have a worse course with higher morbidity and mortality than RA patients without sSS.[4]

Salivary gland ultrasound (SGUS) is an effective, easy, safe, non-invasive, and inexpensive tool to assess

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parotid and submandibular salivary gland parenchymal abnormalities accompanying SS.[5] Introduction of novel treatments necessitates finding tools for the early diagnosis of the disease.[6]

The most specific finding in ultrasound is the parenchymal inhomogeneity. Several US scores were developed considering other items as glandular size, posterior gland border, contour regularity, cyst size, echogenic bands, and hypoechogenic zones.[7]

Aim

This study aimed to evaluate the role of salivary gland US in differentiating RA patients with or without SS by using probability method and to study the relation between sSS and RA disease characteristics.

Material and methods

This cross-sectional study included 100 RA adult patients diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for RA.[8] Disease duration of RA was 5 years or more. They were recruited randomly from the rheumatology outpatient clinic and inpatient internal medicine department, Ain Shams University Hospitals between January 2021 and January 2023. Patients with other connective tissue diseases, history of head and neck radiation, hepatitis viral infections, acquired immunodeficiency disease (AIDS), pre-existing lymphoma, sarcoidosis, graft versus host disease, use of drugs including anticholinergics, neuroleptics, antidepressants, antihypertensive drugs or those with known other primary or secondary salivary glands diseases were excluded from the study.

Ethics approval

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ain Shams Univeristy in 2019 (FWA00017585).

For all patients detailed medical history and clinical examination with assessment of RA disease activity by Disease Activity Score 28 (DAS 28- ESR) were done.[9] Laboratory workup included: Complete blood count (CBC) measured on a Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare diagnostic, Erlangen, Germany), erythrocyte sedimentation rate (ESR) by placing sample into sedimentation measurement stand (BD Seditainer™ Manual ESR BD), C-reactive protein (CRP) was measured quantitatively (0004956842190c501V9.0) by Immunoturbidimetric assay using Roche/Hitachi Cobas c systems, reference value <5mg/L, rheumatoid factor (RF, 0020764574322c501V8.0) was measured quantitatively by an immunoturbidimetric assay using Roche/Hitachi Cobas c systems, reference value <14 IU/mL and anti-cyclic citrullinated peptide (anti-CCP, 0511567100V4) was measured by electrochemiluminescence immunoassay "ECLIA", Roche diagnostic, GmbH, Mannheim, Germany, reference value <20 IU/mL. Anti-Ro (SSA) antibodies performed using ELISA for all patients to exclude SS/RA overlap with cutoff for positive value ≥20 IU/mL.[10] Schirmer's test without topical anesthesia was performed by placing The end of a special filter paper strip inside the lower eyelid of each eye. The eyes were closed gently for 5 minutes without rubbing, Both eyes were tested at the same time. The paper was removed after 5 minutes, its moisture was measured. A score < 10 mm in 5 minutes is accepted as normal. A score of less than 5 mm in 5 minutes indicates a tear deficiency[11] and unstimulated salivary gland flow rate test (USSFR) were performed by asking the patient to spit all saliva possible over 15 min without gustatory provocation. A volume of <1.5 mL of saliva in 15 min is considered abnormal.[12]

Salivary glands ultrasound (both parotids (PG) and submandibular (SMG)) was done using both qualitative and quantitative assessment by both Salaffi and Outcome Measures In Rheumatoid Arthritis Clinical Trials (OMERACT) scores.[13,14] All ultrasound scans were performed by 2 expert rheumatologists (the first and third authors) who were blinded to the clinical data to minimize bias and used 3–13 linear array transducer and E-Saote Mylab Six machine. Length and width were measured in the longitudinal and transverse planes for the parotid and SMG, and the surface area was computed as (length × width)/2, Normal parotid gland surface area is around 3–4 cm^2, normal SMG surface area around 1–2 cm^2.[15]

According to the Salaffi score, grade 0=normal homogeneous glands; grade 1=small hypoechogenic areas without echogenic bands; grade 2=multiple hypoechogenic areas measuring 2 mm with echogenic bands; grade 3=multiple hypoechogenic areas measuring 2–6 mm with hyperechogenic bands; and grade 4=multiple hypoechogenic areas measuring >6 mm or multiple calcifications with echogenic bands.[13]

According to the OMERACT score; grade 0=normal appearing SG parenchyma, grade 1=minimal change: mild inhomogeneity without hypo/anechoic areas, grade 2=moderate change: moderate inhomogeneity with focal hypo/anechoic areas, grade 3=severe change: diffuse inhomogeneity with hypo/anechoic areas occupying the entire gland surface.[14]

The patient was considered abnormal if at least one parotid or one SMG showed an US score of at least 1. Then the highest score for each gland and patient (Salaffi & OMERACT scores) was recorded. Also, the sum score (simple addition) of the four and the three glands scores (Salaffi & OMERACT scores respectively) for each patient was calculated.

The diagnostic role of US for SS in RA was evaluated by probability method depending on an expert rheumatologist evaluation before and after parotid and SMG US using 5 points scale with 80 % or more meaning very high probability and 20% or less meaning very unlikely.[16] Thus parameters for SS diagnosis were: 1) symptoms of dry eye, 2) dry mouth, 3) positive Schirmer's test and 4) abnormal USSFR, in 5) RA duration ≥ 5 years (long standing RA). For example those with RA more than 5 years, positive symptoms of dry eye and dry mouth, and abnormal both Schirmer's and USSFR tests were considered as having ≥ 80% probability of secondary SS before US . On the other hand, those with RA more than 5 years, positive symptoms of dry eye and dry mouth, and normal or borderline both Schirmer's and USSFR tests were considered as having 40-60% probability of secondary SS before US. After US showed abnormality, according the reported number and severity /grade of salivary glands abnormality in each patient, we increased the probability of SS by 20-40%. To our knowledge, despite commonly used in clinical practice and search work no proved validation was available from previous studies .

Ultrasound was also used to detect dominant hand metacarpophalangeal joints (MCP) erosions by using the Power Doppler (PD) ultrasound device MyLab^{TM}-Six (E-Saote company) with 6–18 MH probe, PD pulse repetition frequency was 500–750 Hz. The first through the fifth MCP joints of the dominant hands were scanned. Each joint was scanned in both the longitudinal and transverse planes from radial to ulnar sides on both volar and dorsal aspects. A definite ultrasound erosion was defined as a cortical "break" or defect with an irregular floor seen in longitudinal and transverse planes. The sizes of definite erosions were measured using electronic calibers and a semiquantitative scale (small erosion≤2 mm, moderate erosion=2–4 mm, and large erosion≥4 mm).[17] The sum of number of erosions per patient was recorded as erosion index and used to reflect the joint damage.

Statistical analysis: Data was coded and entered using statistical package SPSS version 2021 (IBM, Armonk, NY, USA). Data was summarized using number and percent for qualitative variables, mean±SD for quantitative variables. Comparisons between groups were done using Chi-square tests or Fisher exact tests when appropriate for qualitative variables. Comparison between quantitative normally distributed variables was done using independent sample T-tests, analysis of variance (ANOVA) with multiple comparison post Hok test. Comparison between quantitative variables which were not normally distributed were done using Kruskal Wallis test and Mann-Whitney test. Correlations were done to test for linear relation between variables. Kappa agreement measures were used to test for agreement between variables. p value ≤0.05 was considered as statistically significant.

Results

The commonest extra-articular manifestations of RA among the enrolled patients were carpal tunnel syndrome (CTS) in 62% of patients, rheumatoid nodules in 9%, generalized lymphadenopathy in 8%, and interstitial pulmonary fibrosis (IPF) in 6% of patients. All RA patients were on disease modifying antirheumatic drugs (DMARDS) (conventional, biologic and targeted synthetic), and steroids. Table 1 shows RA patients characteristics.

Table 1. Characteristics of the enrolled 100 RA patients*

Parameter n (%) or mean±SD (range)		RA patients (n=100)
Gender (F/M)		99/1
Age (years)		43.64±9.08 (25–65)
Disease duration (years)		11.3±4.89 (5–27)
No. swollen joints		0.93±1.94 (0–12)
No. tender joints		9.4±8.17 (0–28)
VAS (0–100)		50±25.51 (10–90)
DAS-28 ESR score		4.78±1.45 (1.6–7.3)
Remission (<2.6)		8
Low disease activity (2.6-3.2)		11
Moderate disease activity (>3.2-5.1)		36
High disease activity (>5.1)		45
ESR (1st hour in mm)		37.48±19.47 (8–100)
CRP (mg/L)		7.23±3.92 (2–22)
Rheumatoid factor (RF) (IU/mL)	Positive	96
		60.2±50.26 (8–328)
anti-CCP antibodies (IU/mL)	Positive	99
		130.75±79.74 (10–363)
WBCs (10^3 cells/mL)		6.68±2.27 (3.8–13.4)
Hb (g/dL)		11.2±1.19 (8–13.9)
PLT (10^3 cells/mL)		261.74±77.74 (122–436)
AST (U/L)		21.97±5.84 (12–40)
ALT (U/L)		17.98±5.14 (10–35)
Serum creatinine (mg/dl)		0.75±0.16 (0.4–1.2)

* No. – number, VAS – visual analogue scale, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, anti-CCP – anti-cyclic citrullinated peptide, WBCs – white blood cells, Hb – hemoglobin, PLT – platelets, AST – aspartate aminotransferase, ALT – alanine transaminase

By musculoskeletal US, erosions were detected at 111 out of 200 examined sites and in 48 out of 100 patients, 88.2% of these erosions were metacarpal versus 11.7% at proximal phalanx. Erosion index mean±SD was 1.13±1.66 with range 0–7. Fifteen/111 erosions (13.5%) were detected in first MCP joints in 100 RA patients, mostly radial, In second MCP joints, 47 erosions (42.3%) mostly radial, in third MCP joints, 14 erosions (12.6%) mostly dorsal and radial, in fourth MCP joints, 3 erosions (2.7%) mostly dorsal and in fifth MCP joints, 32 erosions (28.8%) mostly ulnar.

Regarding sSS,72% of the enrolled patients had SS positive parameters; 58% had dry eyes, 45% had dry mouth, 39% had positive Schirmer's test, 35% had abnormal USSFR. SS symptoms duration ranged from 0

to 3 years with mean of 0.92±0.75. Two patients only had just positive anti-Ro antibodies.

Using these parameters to propose a probability of sSS in RA before and after SGUS, the results were as follows: Before SGUS the probability of sSS was ≤20% (highly unlikely) in 26% of patients, ≥80% (highly likely) in 13% of patients, 20-40% in 26% of patients, 40-60% in 21% of patients and 60-80% in 14% of patients. After SGUS, the probability of sSS was ≤20% in 51% of patients, ≥80% in 39% of patients, 20-40% in 5% of patients, 40-60% in 1% of patients and 60-80% in 4% of patients. Tables 2 and 3 show SGUS findings in 100 RA patients and Kappa agreement test between Salaffi and OMERACT scores of 4 salivary glands.

Table 2. Salivary gland ultrasound findings among the enrolled 100 RA patients

Parameter n (%) or mean±SD		Left parotid	Right parotid	Left submandibular	Right submandibular
Contour	Regular	99	99	97	96
	Irregular	1	1	3	4
Inhomogeneity	Positive	27	27	32	29
	Negative	73	73	68	71
Echogenic bands	Positive	27	23	10	9
	Negative	73	77	90	91
Posterior border	Visible	95	97	98	98
	Invisible	5	3	2	2
Surface area (mm^2)		10.28±2.99	9.79±2.88	9.79±2.88	4.8±1.09
Spot size (mm)		1.68±0.75	1.87±1.32	1.87±1.32	1.33±0.58
Salaffi score	Normal (0)	80	77	72	73
	Abnormal	20	23	28	27
	1	1	1	2	3
	2	10	11	18	17
	3	9	11	8	7
	Total score	0.48±1	0.56±1.07	0.62±1.04	0.58±1.01
OMERACT score	Normal (0)	73	73	68	71
	Abnormal	27	27	32	29
	1	9	6	7	5
	2	17	17	23	22
	3	1	4	2	2
	Total score	0.46±0.81	0.52±0.92	0.59±0.91	0.55±0.90

The kappa agreement test between the Salaffi and OMERACT scores showed a highly significant agreement between the 2 scores in detection of normal and abnormal glands (Table 3). Both scores detected normal glands in 57 patients and abnormal glands in 39 patients. However, there was a disagreement between the two scores in only 4 RA patients, in whom abnormality was detected by OMERACT score only. Regarding the left parotid gland, both scores detected 73 normal and 20 abnormal glands, with 7 glands recorded as abnormal by OMERACT score only. Also in the right parotid gland, both scores detected 73 normal and 23 abnormal glands, with 4 glands recorded as abnormal by OMERACT score only. As for the left submandibular gland, both scores detected 68 normal and 28 abnormal glands, with 4 glands recorded as abnormal by OMERACT score only. In right submandibular gland, both scores detected 71 normal and 27 abnormal glands, with 2 glands recorded as abnormal by OMERACT score only.

Table 3. Ultrasound findings of all four salivary glands and Kappa agreement test between Salaffi and OMERACT scores of 4 salivary glands

		n (%) or mean±SD (range)
Normal/abnormal patient by Salaffi score	Normal	61
	Abnormal	39
Normal/abnormal patient by OMERACT	Normal	57
	Abnormal	43
Highest Salaffi score	0	61
	1	3
	2	15
	3	21
	0.96±1.27 (0–3)	
Highest OMERACT score	0	57
	1	7
	2	29
	3	7
	0.86±1.06 (0–3)	
Sum scores of 4 glands per patient by Salaffi score		2.22±3.35 (0–12)
Sum scores of 4 glands per patient by OMERACT score		2.10±2.93 (0–10)
No. of glands affected per patient		1.13±1.45 (0–4)
	0	57
	1	3
	2	22
	3	6
	4	12

Kappa agreement test between Salaffi and OMERACT scores of 4 salivary glands

		RA patients by Salaffi score		p	Kappa
		Abnormal n (%)	Normal n (%)		
RA patients by OMERACT score	Abnormal	39 (100)	4 (6.6)	<0.001	0.9
	Normal	0	57 (93.4)		

Patients with probabilities for SS ≤20% and ≥80% were considered certain or near certain for secondary SS and their sum before SGUS was 39/100 and after SGUS was 90/100, with a highly significant difference ($p<0.001$). On the other hand, patients with probabilities 40–60% were considered uncertain or vague; and were recorded in 21/100 of patients before SGUS and in 1/100 of patients after SGUS with a highly significant difference ($p<0.001$), as shown in Figure 1.

There was a statistically significant more CTS, longer RA disease duration and higher anti-CCP antibody titer in RA patients with secondary SS compared to those without secondary SS ($p<0.05$). Also, there was statistically highly significant higher percentage of RA patients with secondary SS who had longer SS symptoms duration, dry eye, dry mouth compared to RA patients without secondary SS ($p<0.001$), as shown in table

4. None of RA patients without SS had positive Schirmer's test or abnormal USSFR. No significant difference between the 2 groups in surface area of the 4 salivary glands measured by US (p>0.05), data not shown.

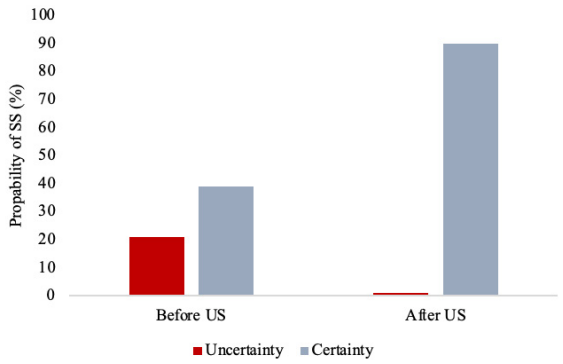


Fig. 1. Comparison between percent of RA patients in area of certainty (with probabilities for SS ≤20% and ≥80%) and uncertainty (with probabilities for SS 40–60%) before and after SGUS

Table 4. Comparison between RA patients with and without secondary SS after SGUS

RA parameters n (%) or mean±SD		RA patients without SS (probability ≤20%) (n=51)	RA patients with SS (probability ≥80%) (n=39)	P
RA disease duration (years)		10.35±4.82	12.36±4.61	0.02
anti-CCP antibody (IU/mL)		114.71±74.99	154.66±79.65	0.01
SS symptoms duration (years)		0.47±0.5	1.46±0.72	< 0.001
Dry eye		20 (39.2%)	29 (74.4%)	<0.001
Dry mouth		14 (27.5%)	29 (74.4%)	<0.001
Schirmer's test	Positive	0 (0%)	32 (82.1%)	< 0.001
	Negative	51 (100%)	7 (17.9%)	
USSFR	Positive	0 (0%)	32 (82.1%)	< 0.001
	Negative	51 (100%)	7 (17.9%)	
Carpal tunnel syndrome	Positive	23 (45.1%)	32 (82.1%)	< 0.001
	Negative	28 (54.9%)	7 (17.9%)	

Despite higher percentage of RA patients with secondary SS compared to those without secondary SS as regards active RA (94.9% versus 88.2%), positive RF (97.4% versus 94.1%), ESR (mean ,42.03 versus 34.24), CRP (mean, 7.8 versus 6.9 mg/L) and presence of erosions (46.2% versus 43.1%), differences did not reach statistical significance. Also, there was no statistically significant difference between RA patients with and without secondary SS as regards age, gender, disease activity, number of swollen joints, number of tender joints, VAS, DAS 28-ESR, RF titre, anti-CCP antibody positivity, drug intake including steroids and erosion presence or index (p>0.05) (data not shown).

There was a statistically significant difference between RA patients with different grades of disease activity measured by DAS28-ESR score as regards right PG OMERACT score being highest in patients with high disease activity, p=0.04.

Table 5. Correlation between mean of DAS28-ESR score, ESR, CRP and salivary glands US scores (Salaffi and OMERACT) in 100 RA patients*

	DAS28-ESR score		ESR		CRP	
	r	p	r	p	r	p
Left PG Salaffi score	0.07	0.43	0.1	0.2	0.1	0.08
Left PG OMERACT score	0.15	0.11	0.1	0.1	0.1	0.2
Right PG Salaffi score	0.2	0.04	0.1	0.09	0.2	0.04
Right PG OMERACT score	0.2	0.01	0.1	0.06	0.2	0.02
Left SMG Salaffi score	0.06	0.5	0.08	0.4	0.02	0.8
Left SMG OMERACT score	0.05	0.56	0.1	0.2	0.06	0.5
Right SMG Salaffi score	0.1	0.07	0.1	0.07	0.03	0.7
Right SMG OMERACT score	0.1	0.1	0.1	0.1	0.05	0.5
Highest Salaffi score	0.1	0.1	0.1	0.07	0.1	0.3
Highest OMERACT score	0.1	0.04	0.2	0.02	0.1	0.1
Sum scores of 4 glands per patient by Salaffi score	0.1	0.1	0.1	0.08	0.09	0.3
Sum scores of 4 glands per patient by OMERACT score	0.1	0.06	0.1	0.06	0.1	0.08
No. of glands affected per patient	0.1	0.07	0.1	0.09	0.1	0.2

* No. – number, ESR – erythrocyte sedimentation rate, DAS-28 – Disease Activity Score 28, CRP – C-reactive protein, PG – parotid gland, SMG – submandibular gland

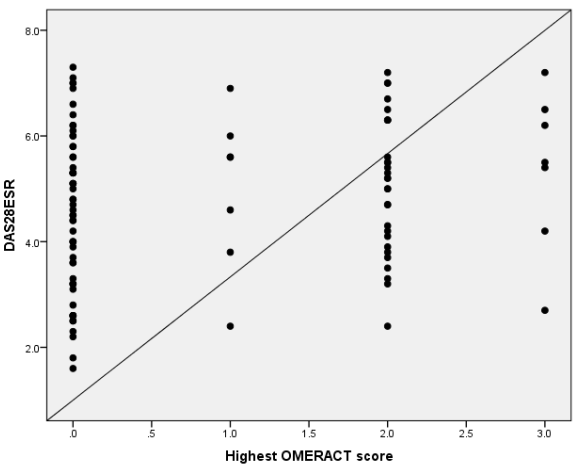


Fig. 2. Correlation between highest OMERACT score and disease activity measured by DAS28-ESR in 100 RA patients

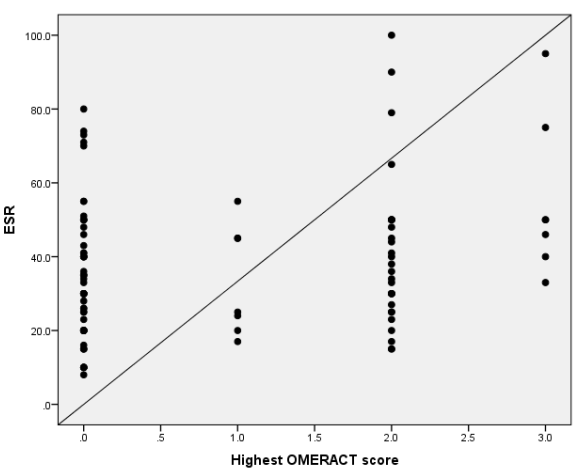


Fig. 3. Correlation between highest OMERACT score and ESR in 100 RA patients

A higher percentage of RA patients with active disease had dry eye, dry mouth, longer SS mean symptoms duration, positive Schirmer's test and abnormal USSFR. However, values did not reach statistical significance,($p>0.05$) (data not shown).

Table 5 and Figures 2 and 3 show correlations between mean of DAS28-ESR score, ESR, CRP and salivary glands US scores (Salaffi and OMERACT) in 100 RA patients.

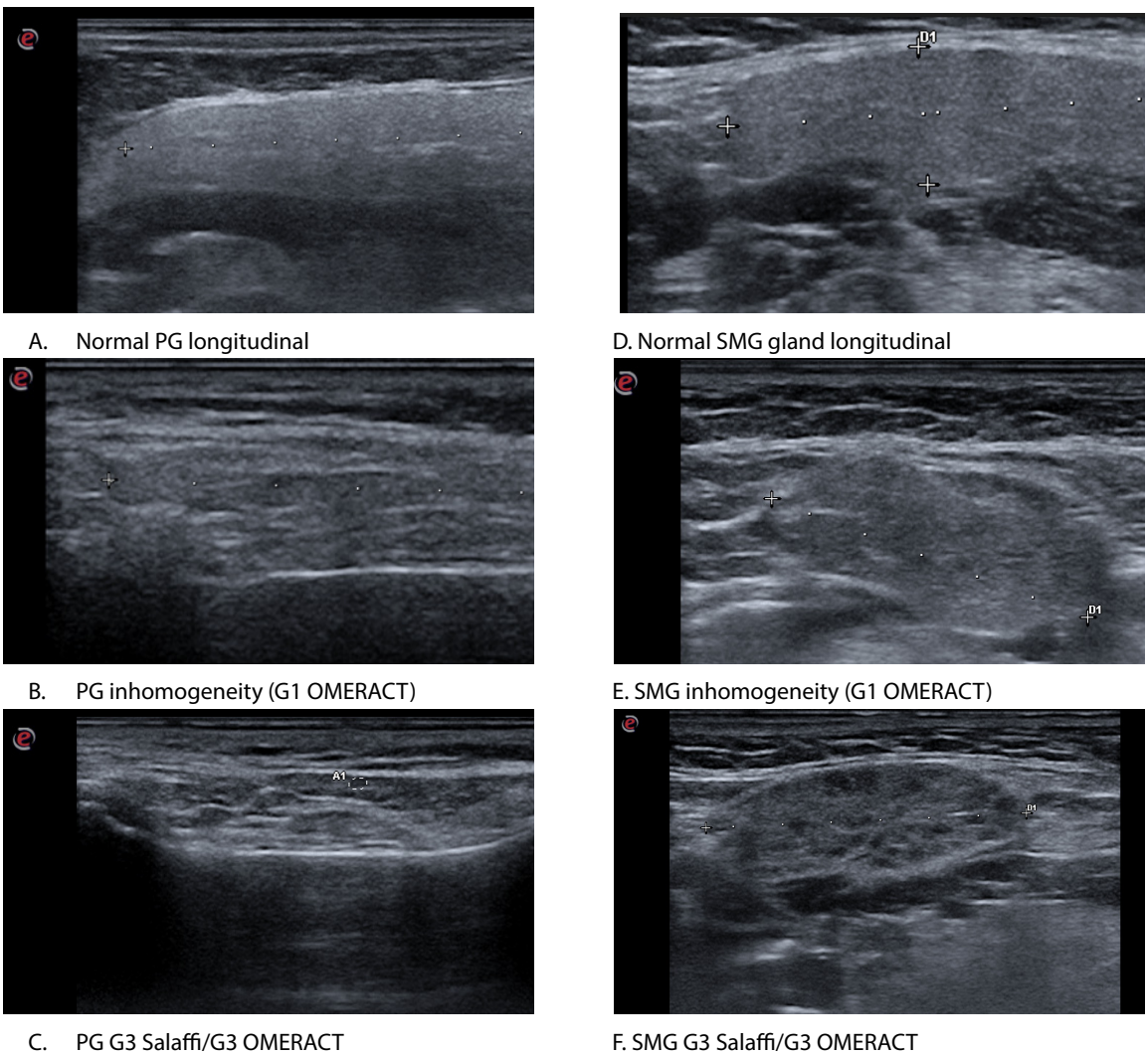
According to major salivary glands ultrasound, Figure 4 shows US images of normal PG, SMG, and abnormal glands by Salaffi and OMERACT scores.

Discussion

Based upon the recent 2016 ACR/EULAR classification criteria for SS, diagnosis of SS depends largely on the presence of anti-Ro antibodies and minor salivary gland biopsy which is invasive and inconvenient.[18] New modalities are required to support SS diagnosis. SGUS of the major salivary glands is very promising given its wide availability, ease, rapidity, reproducibility, and safety being nonivasive with no radiation exposure.[19] Typical SGUS findings in SS are oval anechoic or hypoechoic lesions with hyperechogenic bands.[20]

In the current study there was female predominance (F:M ratio=99:1), their mean ages were 43.64±9.08 years. Similar demographic data were found by Nawata et al.[21] (65.3% females and 34.7% males), Rabault et al.[22] (81% females and 19% males) and Sparks et al. (82% females and 18% males).[23] As for the mean ages, similar results were found by Naseri et al. (49.46±11.81), Hammer et al. (53.3±13.2), and Hajiabbasi et al. (48.3±13).[2,24,25] These findings reflect the already established epidemiological incidence of RA in middle aged females.

Using two US semiquantitative scores; Salaffi and OMERACT to detect the presence and grade the severity of salivary glands involvement by SS, 39% of RA patients were recorded to have at least one abnormal gland by Salaffi versus 43% by OMERACT.[13,14] Furthermore, there was a highly significant agreement between the 2 scoring systems with more abnormal glands detected by OMERACT scoring system, reflecting its better sensi-



A. Normal PG longitudinal

D. Normal SMG gland longitudinal

B. PG inhomogeneity (G1 OMERACT)

E. SMG inhomogeneity (G1 OMERACT)

C. PG G3 Salaffi/G3 OMERACT

F. SMG G3 Salaffi/G3 OMERACT

Fig. 4. Longitudinal U/S images of A: normal PG, and B: SMG, and D: abnormal glands by Salaffi and OMERACT scores (B, C, E, and F)

tivity for early diagnosis of salivary glands abnormality.

In Salaffi et al., among the 77 patients with SS, 66 (85.7%) had abnormal US findings by Salaffi score.[26] The findings of parotid and SMG were in concordance with each other and were equally frequent with sensitivity of 75.3% and specificity of 83.5%. In Rabault et al., among 98 patients in their study with assessment of SGUS using OMERACT score, they found that 22.5% had at least one salivary gland scored grade 1, 7.1% had at least one salivary gland scored grade 2 and only one patient 1% had a parotid gland scored 3.[22] In Robin et al., 88% of the patients with abnormal SGUS by OMERACT score met the ACR/EULAR 2016 and American-European Consensus Group (AECG) 2002 classification criteria for the diagnosis of SS with sensitivity of 52.4% and specificity of 90%.[27] Zabotti et al., found that SGUS OMERACT score was reliable for the major salivary glands evaluation in SS, even if carried out by properly instructed less-expert sonographers.[28]

In our study, before US, the number and percent of RA patients with high likelihood of having SS (≥80% probability) and not having SS (≤20% probability) together were considered certain, they were 39% which increased after SGUS to 90% with high statistically significant difference. On the other hand, the percent of RA patients with undetermined /vague probability of having SS (40-60% probability) decreased from 21% to 1% after SGUS with high statistically significant difference making SGUS a valuable tool for diagnosis and screening of SS.

In agreement, Elghamry et al. stated that SGUS is a very helpful tool in detection of SG abnormalities in patients with RA and SS. Jousse-Joulin et al. found that SGUS had similar weight compared to minor items (anti-Ro, positive Schirmer's test, dry mouth and salivary flow rate<0.1 mL/min) and its addition improves the performance of the 2016 ACR/EULAR classification criteria for SS diagnosis.[29,30]

Zabotti et al. and El-Barbary et al., found SGUS of RA patients to be a reliable, promising tool that could be used as a practical noninvasive and sensitive technique for early detection of pathological changes for sSS in RA patients.[28,31] Theander and Mandl reported that, SGUS using a simplified score for assessment of parenchyma inhomogeneity was highly specific for SS and offered the advantage of identifying patients with severe disease or at risk of lymphoma.[32]

Furthermore, Takagi et al. stated that incorporating the SGUS criteria as an alternative to one of the three ACR classification items achieved 91% sensitivity, 96% specificity, which was comparable to that of the original ACR classification for diagnosing SS.[33]

Several studies have compared SGUS with other established tests for the diagnosis of salivary gland affection in SS. Milic et al., stated that SGUS findings could replace sialoscintigraphy in American European classification criteria (AECC) for the diagnosis of SS. Shimizu et al., found that SGUS could replace sialography for SS screening.[34,35] In addition, El Miedany et al. found that the SGUS findings agreed well with the MRI findings, concluding that SGUS could replace MRI as a routine diagnostic test.[36] In 1013, Ali et al., in their study on 196 patients, reported a significant correlation between US scores of major salivary glands and focal scores of minor salivary glands biopsy in Sjogren's syndrome group and the sialadenitis group suggesting a uniform disease process. This correlation was absent for the non-salivary gland disease group.[37] To our knowledge, no previous studies utilized probability method in diagnosis of SS, however, they used SGUS in comparison to sialography, biopsy or other methods.

In the current study, there was a significant association between presence of SS and longer RA duration, presence of CTS and higher anti-CCP antibody titer. Despite higher percent of RA patients with active disease, higher ESR and CRP in RA patients with SS compared to those without SS, values didn't reach statistical significance. These findings partially agree with El-Barbary et al. who found that the duration of RA in patients with SS was longer than patients without SS but no significant difference between RA patients with and without SS regarding anti-CCP titer, DAS28-ESR score, ESR and CRP levels.[31]

Haga et al. found no significant difference between RA patients with and without SS regarding RA disease duration, anti-CCP titer, DAS28-ESR score, ESR and CRP levels.[38] In Antero et al., they found no relation between the presence of sSS and RA disease activity (p=0.31) or RA duration (p=0.95).[39] In Lafitte et al. only 4 out of 25 SS patients had CTS.[40]

We compared RA patients with active disease with those in remission and compared RA patients with different grades of disease activities, only significantly higher mean right parotid gland OMERACT score was reported in patients with high disease activity. The small number of RA patients in remission (8) may account for this. However, this may reflect an association between RA disease activity and SS severity especially in the right parotid gland.

Similarly, Das et al. found that RA patients with changes on SGUS had higher disease activity scores than those without changes.[41] However, in Haga et al. there were no significant differences between RA patients with and without sSS regarding disease activity measured by DAS28.[38]

In the present study, the association between RA disease activity and SS severity in SG was confirmed by the presence of a significant correlation between right parotid gland scores by both Salaffi and OMERACT (severity of SS) and DAS-28 ESR score and CRP (RA activity). Furthermore, there was a significant positive

correlation between DAS28-ESR and ESR and the highest OMERACT score in RA patients. In agreement, Rabault et al., reported a significant correlation between RA disease activity (by DAS28 score) and SGUS abnormalities according to OMERACT scoring system.[22] However, in Elghamry et al., there was no significant correlation between RA disease activity (by DAS28 score) and SGUS severity of SS in RA patients with sSS that may be explained by low disease activity by DAS28 score in RA patients in their study.[29]

In this work, a higher percentage of RA patients with active disease had dry eye, dry mouth, longer SS mean symptoms duration, positive Schirmer's test and abnormal USSFR. However, values did not reach statistical significance. This agrees with Haga et al., who found no significant correlation between DAS-28 score and sicca symptoms or the presence of SS.[38] Also, Fujita et al. found that RA activity had no significant association with the presence of dry eye.[42] On the other hand, Uhlig et al. found that reduced tear or saliva production were related to RA disease activity.[43]

In the current study, there was no significant relation between RA disease severity (as reflected by positivity and mean RF titer and by presence of and the mean erosion index) and any of SS related parameters. In agreement, Uhlig et al. found no significant relation between RA disease severity (RF positivity or joint erosions and deformity) and sicca symptoms.[43] Haga et al., found that the concentration of RF was higher in RA patients without versus with SS, but not being significant.[38]

Study limitations: Limitations to this work include that: although OMERACT scoring system proved superiority in detection of more abnormal glands with just inhomogeneity, hence helping early diagnosis of SS, its use may result in overestimation and over diagnosis especially in the submandibular gland where it showed confusing images due to similar homogeneity with the surrounding structures.[44] To overcome this, OMERACT scoring system should be included within a diagnostic algorithm in clinical practice. Our proposed diagnostic algorithm for secondary SS in RA includes: RA duration ≥5 years (1 point), dry eye (1 point), dry mouth (1 point), +ve Schirmer test (3 points), abnormal USSFR test (3 points), OMERACT score by ultrasound (sum scores for 4 glands, range 0–12), with total score 0–21, to be tested for validity and the threshold cutoff score for diagnosis of secondary SS in RA. Also, we used probability method to propose the diagnosis of SS in RA patients which although it depends on Clinical judgement (derived from clinician's diagnostic skill and clinical experience, draws from memory of encountered cases, instinctive, fast, always available) and clinical prediction rules (quantifies the relative importance of various clinical data points when evaluating a patient for a specific disease, facilitates identifying which information is important to obtain and helps in the interpretation of the clinical information), however, it has limitations that it is dependent on clinician's diagnostic skill and experience, prone to cognitive biases with high variability of estimates from clinician to clinician compared to deterministic method with gold standard.[45] This was part of our objectives to avoid invasive diagnostic tool (SG biopsy) by adding the value of salivary gland ultrasound.

Conclusion

RA is frequently associated with sSS especially in cases with longer disease duration, higher anti-CCP antibody titer and CTS. SGUS is a useful tool that helps diagnosis and grading of severity of SS in RA. Ultrasound OMERACT score proved superiority in detection of salivary gland abnormality allowing early diagnosis and is better correlated with disease activity compared to Salaffi score.

Declarations

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Author contributions

Conceptualization, M.M.A.G.; Methodology, M.M.A.G. and C.S.M. ; Software, M.M.A.G., C.S.M. and M.A.E.A.; Validation, M.M.A.G.; Formal Analysis, M.M.A.G. and C.S.M.; Investigation, M.M.A.G., C.S.M. and M.A.E.A.; Resources, M.M.A.G. and A.A.M.K.; Data Curation, C.S.M. and R.M.H.; Writing – Original Draft Preparation, M.M.A.G. and C.S.M.; Writing – Review & Editing, M.M.A.G., C.S.M., and S.A.E.B.; Visualization, S.A.E.B. and R.M.H.; Supervision, M.M.A.G.; Project Administration, M.M.A.G.

Conflicts of interest

The authors declare no competing interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ain Shams Univeristy in 2019 (FWA00017585).

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