

Using ^{18}F -FDG and ^{68}Ga -PSMA-11 PET/CT to evaluate salivary glands in Sjögren's Disease: Implications for Treatment Stratification

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Abstract

Objectives

To investigate the associations of ^{18}F -FDG PET/CT and ^{68}Ga -PSMA-11 PET/CT parameters with salivary gland ultrasonography abnormalities and unstimulated whole salivary flow rate in patients with Sjögren's disease.

Methods

Twenty-three patients with SjD who had undergone ^{18}F -FDG PET/CT within the previous 6 months subsequently underwent ^{68}Ga -PSMA-11 PET/CT. FDG SUVmax, FDG SUVmean, PSMA SUVmax, PSMA SUVmean, PSMA-based functional glandular volume (PSMA-GIVol), and PSMA-based total glandular activity (PSMATotGIAct; PSMA SUVmean $\times$ PSMA-GIVol) were calculated for each parotid and submandibular gland and compared with SGUS scores and UWSFR.

Results

PSMA SUVmax, PSMA SUVmean, and PSMATotGIAct were lower in glands with higher SGUS scores, while PSMA-GIVol showed a decreasing trend, particularly in the submandibular glands. FDG uptake showed gland-dependent patterns: higher uptake was observed in parotid glands with higher OMERACT and selected Høcevar abnormalities, whereas lower uptake was observed in submandibular glands with higher OMERACT and hypoechoic area scores. UWSFR showed no significant association with ^{68}Ga -PSMA-11 PET/CT parameters, but correlated positively with FDG uptake in both parotid and submandibular glands.

Conclusion

^{68}Ga -PSMA-11 PET/CT and ^{18}F -FDG PET/CT appear to provide complementary information in SjD. Lower PSMA uptake may reflect structural glandular damage, whereas FDG uptake patterns, particularly their association with preserved salivary flow, may indicate residual metabolic activity and retained functional potential.

Key message

1. Lower ^{68}Ga -PSMA-11 uptake was associated with more severe SGUS abnormalities.
2. ^{18}F -FDG uptake showed gland-dependent patterns and correlated with salivary flow.
3. Dual-tracer PET/CT may help define imaging phenotypes of glandular involvement in SjD.

Introduction

Sjögren's disease (SjD) is a chronic systemic condition that primarily affects the salivary and lacrimal glands. It is characterized by keratoconjunctivitis sicca and reduced salivary flow resulting from glandular inflammation, which is typically associated with focal lymphocytic infiltration on histologic assessment (1). Although salivary gland biopsy and measurements of tear and salivary flow are used in clinical practice, they have important limitations, including sampling error and physiological variability. Consequently, diagnosing early-stage SjD remains challenging due to the lack of objective markers that can reliably differentiate between active lymphocytic infiltration (potential for recovery) and end-stage fibro-fatty degeneration (permanent loss of function). Therefore, objective and non-invasive imaging modalities are needed to better evaluate disease status (2).

Non-invasive imaging modalities, including salivary gland scintigraphy, salivary gland ultrasonography (SGUS), and magnetic resonance imaging, have been widely investigated for the assessment of salivary gland involvement in SjD (3). Although scintigraphy is easy to perform and provides an objective functional assessment, its specificity is limited, as abnormal scintigraphic patterns may also be seen in other major salivary gland disorders associated with secretory dysfunction and in elderly individuals with involutionary glandular changes (4). Salivary gland ultrasonography is widely accepted for detecting

structural glandular changes and correlates with stimulated and unstimulated salivary flow rates, which serve as objective indicators of salivary gland function (5). In addition, fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) has emerged as a valuable imaging modality in a range of inflammatory diseases. FDG is a glucose analogue taken up by metabolically active cells—including activated leukocytes—reflecting increased glycolytic activity and ongoing inflammation. In SjD, ongoing inflammation in the salivary glands can be visualized using ^{18}F -FDG PET/CT, potentially providing information on disease activity and staging (6). Another promising tracer is ^{68}Ga -PSMA-11, which targets prostate-specific membrane antigen (PSMA) and demonstrates physiological uptake in several non-prostatic tissues, including the salivary and lacrimal glands (7). Recent studies suggest that ^{68}Ga -PSMA-11 PET/CT may be useful for evaluating salivary gland function and damage in SjD (8).

This prospective study investigated the relationship of ^{18}F -FDG PET/CT and ^{68}Ga -PSMA-11 PET/CT findings with SGUS abnormalities and unstimulated whole salivary flow rate (UWSFR), and explored their potential relevance for treatment stratification in SjD.

Materials and Methods

Patients

This prospective study included 23 adult patients with SjD, comprising 18 patients with primary SjD and 5 patients with associated SjD. All patients fulfilled the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for SjD. Patients under follow-up at the Rheumatology Outpatient Clinic who had undergone clinically indicated ^{18}F -FDG PET/CT within the previous 6 months were prospectively enrolled and subsequently underwent ^{68}Ga -PSMA-11 PET/CT. ^{18}F -FDG PET/CT was not part of the routine SjD assessment and had been performed for separate clinical indications, including the evaluation of unexplained elevations in acute-phase reactants, weight loss, and/or lymphadenopathy.

Exclusion criteria were prior radiotherapy to the head and neck region, active hepatitis C or HIV infection, sarcoidosis, IgG4-related disease, amyloidosis, and a history of graft-versus-host disease. The study protocol was approved by the Ethics Committee of Marmara University Faculty of Medicine (Approval No: 08.09.2023.1133). Written informed consent was obtained from all participants prior to inclusion.

Twenty-one patients underwent SGUS at enrolment. The parotid and submandibular glands were evaluated bilaterally using the OMERACT and Hocevar scoring systems. Subsequently, ^{68}Ga -PSMA-11 PET/CT was performed, and PET-derived parameters were quantified for each gland. Corresponding parameters from the previously acquired ^{18}F -FDG PET/CT scans were also recorded. PET/CT findings were then compared with SGUS abnormalities and UWSFR to examine their association with glandular involvement and function.

Major Salivary Gland Ultrasonography

SGUS was performed in 21 patients by an EULAR-certified physician (NI) using a MyLab™ 70 ultrasound system (Esaote, Genoa, Italy) equipped with a 6–18 MHz linear transducer. The evaluations were carried out with the patients in the supine position, and the examiner was blinded to the clinical data. A total of 42 parotid glands (PGs) and 42 submandibular glands (SMGs) were assessed (21 patients $\times$ 2 PGs and 2 SMGs each).

SGUS findings were evaluated using two scoring systems: the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (Grade 0–3) and the Hocevar scoring system (0–48), with higher scores indicating more severe glandular involvement. The OMERACT scoring system is a semiquantitative method based on the presence and extent of hypoechoic areas within the salivary glands, graded on a scale from 0 to 3. Hypoechoic areas are defined as millimetric, non-compressible regions without vascular flow on color Doppler imaging (9). The scoring is as follows:

- Grade 0: Normal glandular parenchyma
- Grade 1: Focal inhomogeneity

- Grade 2: Moderate inhomogeneity with focal anechoic or hypoechoic areas
- Grade 3: Diffuse inhomogeneity with anechoic or hypoechoic areas involving the entire gland (10)

In the Hocevar scoring system (0–48 points), the following components are assessed: echogenicity (0–1 point), inhomogeneity (0–3 points), number of hypoechogenic areas (0–3 points), presence of hyperechogenic reflections (0–3 points), and clearness of glandular borders (0–3 points) (11).

Each of the parameters from the OMERACT and Hocevar scoring systems was categorized into two groups: scores of 0–1 were considered as Group 1 (indicating minimal or no involvement), while scores of 2–3 were classified as Group 2 (indicating moderate to severe involvement). Because the echogenicity component of the Hocevar score is graded on a 0–1 scale, it was not included in the 0–1 versus 2–3 subgroup analyses.

¹⁸F-FDG PET/CT

All patients were instructed to fast for a minimum of 6 hours prior to the ¹⁸F-FDG PET/CT examination. Just before administration of FDG, the patient's blood glucose levels were examined and required to be below 150 mg/dL. Approximately 60 minutes after administration of 3.7 MBq/kg FDG intravenously, PET/CT images were acquired from head to midthigh using an integrated PET/CT scanner (Discovery-16 LS; GE Healthcare, Waukesha, Wisconsin, USA).

⁶⁸Ga-PSMA-11 PET/CT

All ⁶⁸Ga-PSMA-11 PET/CT images were acquired from the vertex to the mediastinum approximately 60 minutes after intravenous administration of ⁶⁸Ga-PSMA-11 at a dose of 1.85 MBq/kg. For attenuation correction and anatomical orientation, a low-dose CT scan was obtained. The PET scan was acquired in 3D mode with an emission time of 3 min per bed position (two to three bed positions). All PET images were corrected for attenuation, and the acquired data were reconstructed using an iterative algorithm.

Image Analysis of Both ¹⁸F-FDG and ⁶⁸Ga-PSMA-11 PET/CT

All ¹⁸F-FDG PET/CT and ⁶⁸Ga-PSMA-11 PET/CT images were analysed using PET Volume Computerized Assisted Reporting (PET VCAR) software (Advantage Windows Workstation 4.5). Three skilled nuclear medicine physicians assessed the PG and SMG visually and quantitatively. Discrepancies were resolved through a consensus. Representative delineation of the bilateral PG and SMG on attenuation-corrected PET/CT images is shown in Fig. 1.

A volume of interest (VOI) was drawn manually along the margin of PG and SMG on ¹⁸F-FDG and ⁶⁸Ga-PSMA-11 PET/CT examination. The maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean) were measured within the defined VOI on both PET/CT images. PSMA-based Functional Glandular Volume (PSMA-GIVol) and PSMA-based Total Glandular Activity (PSMATotGIAct=PSMA-SUVmean x PSMA-GIVol) were calculated for each PG and SMG.

Unstimulated whole salivary flow rate

Unstimulated whole saliva was collected by asking patients to lean forward and spit into a graduated tube for 15 minutes. All collections were performed in the morning between 9:00 and 11:00 AM, following at least two hours of fasting, including no eating, drinking, or smoking. The UWSFR was then calculated in millilitres per minute (mL/min).

Statistical Analysis

All statistical analyses were conducted using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) according to the distribution of data, while categorical variables were presented as frequencies and percentages. The Shapiro–Wilk test was used to assess the normality of distribution for continuous variables. To compare ¹⁸F-FDG PET/CT and ⁶⁸Ga-PSMA-11 PET/CT parameters between ultrasonographic score groups (OMERACT and Hocevar scores of 0–1 vs. 2–3), the independent samples t-test was used for

normally distributed data, and the Mann–Whitney U test was applied for non-normally distributed variables. The association between UWSFR and PET/CT variables was evaluated using Spearman's rank correlation coefficient due to the non-parametric nature of the data. As a sensitivity analysis, the comparisons were repeated by taking into account that right and left glands belonged to the same patient. A p-value < 0.05 was considered statistically significant for all analyses.

Results

The clinical and demographic characteristics of the cohort are summarized in Table 1. The mean age of the 23 patients was 57.5 ± 8.8 years, and 95% (n = 22) were female. Eighteen patients had primary SjD, and five had associated SjD (aSjD). The mean disease duration was 7.48 ± 4.7 years. UWSFR was available in 22 patients, and decreased UWSFR (≤ 0.1 mL/min) was observed in 15 patients (68%).

Table 1
Demographics and clinical, laboratory characteristics of patients with SjD

Age, years; (mean ± SD)	Patients with SjD (n = 23)
	57.5 ± 8.8
Disease duration, years; (mean ± SD)	7.48 ± 4.7
Female, n (%)	22 (95%)
Schirmer test ≤ 5/5 mm, n (%)	21 (91%)
Low UWSFR (≤ 0.1 mL/min), n/N (%)	15/22 (68%)
ANA positivity, n (%)	22 (95%)
Anti-SSA (Ro) positivity, n (%)	15 (65%)
Primary SjD / associated SjD, n	18/5
Treatment, n (%)*	18 (78%)
Hydroxychloroquine	3 (13%)
Azathioprine	1 (4%)
Mycophenolate mofetil	3 (13%)
Methotrexate	1 (4%)
Leflunomide	3 (13%)
Rituximab	1 (4%)
Pilocarpine	

Salivary gland ultrasonography (SGUS) was performed in 21 patients, yielding evaluation of 42 parotid glands (PGs) and 42 submandibular glands (SMGs). OMERACT grades and Hocevar component scores were dichotomized as 0–1 versus 2–3. In PGs, grade 2–3 inhomogeneity, hypoechoic areas, hyperechoic foci, abnormal glandular borders, and OMERACT grade 2–3 were present in 47% (n = 20), 38% (n = 16), 33% (n = 14), 9% (n = 4), and 38% (n = 16), respectively. In SMGs, grade 2–3 abnormalities were more frequent, with corresponding rates of 76% (n = 32), 52% (n = 22), 42% (n = 18), 14% (n = 6), and 52% (n = 22).

On ⁶⁸Ga-PSMA-11 PET/CT, PSMA-derived parameters were available for all 46 PGs and 46 SMGs. In PGs, PSMA SUVmax, SUVmean, and PSMATotGIAct were significantly lower in glands with higher OMERACT grades (2–3) compared with those graded 0–1 (Table 2). Similar findings were observed when glands were categorized according to Hocevar components, with consistently lower PSMA SUVmax, SUVmean, and PSMATotGIAct in the 2–3 category across inhomogeneity, hypoechoic areas, hyperechoic foci, and glandular border parameters (Table 2). In SMGs, PSMA SUVmax, SUVmean, and PSMATotGIAct were likewise reduced in

glands with higher SGUS scores (2–3) for OMERACT grade, inhomogeneity, hypoechoic areas, and hyperechoic foci. However, no statistically significant difference was observed for the glandular border parameter (Table 3). PSMA-GIVol tended to be lower in glands with higher SGUS scores, not all comparisons reached statistical significance (Tables 2–3).

Table 2
Comparison of OMERACT and Hocevar SGUS scores with ⁶⁸Ga-PSMA-11 PET/CT parameters of the parotid glands

SGUS group			SUVmax	P	SUVmean	P	PSMA-GIVol	P	PSMATotGIAct	P
OMERACT score		0–1	10.61 (7.35–11.29)	< 0.001	6.54 (3.80–7.11)	< 0.001	18.45 (16.56–24.61)	0.095	121.15 (77.37–164.41)	< 0.001
		2–3	4.38 (1.90–5.99)		2.58 (1.14–3.44)		16.03 (12.54–20.23)		0.095	
HOCEVAR	Inhomogeneity	0–1	10.61 (7.57–11.29)	0.003	6.71 (4.21–7.11)	< 0.001	19.75 (17.03–24.77)	0.056	130.37 (81.46–168.60)	< 0.001
		2–3	5.04 (2.33–6.84)		3.02 (1.29–3.99)		16.32 (13.18–20.19)		0.056	
	Hypoechoic area	0–1	10.61 (7.35–11.29)	< 0.001	6.54 (3.80–7.11)	< 0.001	18.45 (16.56–24.61)	0.095	121.15 (77.37–164.41)	< 0.001
		2–3	4.38 (1.90–5.99)		2.58 (1.14–3.44)		16.03 (12.54–20.23)		0.095	
	Hyperechoic focus	0–1	10.77 (7.66–11.41)	< 0.001	6.71 (4.45–7.15)	< 0.001	18.20 (16.08–22.99)	0.531	121.15 (79.38–158.95)	< 0.001
		2–3	4.73 (1.75–5.71)		2.83 (1.09–3.45)		19.00 (12.24–21.59)		0.531	
	Glandular border	0–1	8.46 (5.67–11.17)	0.003	5.33 (3.43–6.97)	0.003	19.08 (16.22–24.07)	0.003	90.46 (63.87–141.74)	< 0.001
		2–3	1.81 (1.53–2.09)		1.09 (0.93–1.20)		9.10 (5.28–12.24)		0.003	
PSMA-GIVol: PSMA-based functional glandular volume; PSMATotGIAct: PSMA-based total glandular activity (PSMA SUVmean × PSMA-GIVol). SGUS: salivary gland ultrasonography; p value < 0.05 was considered statistically significant. Values are presented as median (IQR).										

Table 3

Comparison of OMERACT and Hocevar SGUS scores with ^{68}Ga -PSMA-11 PET/CT parameters of the submandibular glands

SGUS group			SUVmax	P	SUVmean	P	PSMA-GIVol	P	PSMATotGIAct	P
OMERACT score		0–1	8.74 (4.22–11.20)	0.007	5.27 (2.49–7.28)	0.004	5.85 (1.99–7.71)	0.024	30.69 (4.99–54.44)	0.010
		2–3	2.99 (1.45–5.97)		1.70 (0.84–3.41)		2.50 (1.92–4.90)		4.16 (1.70–15.04)	
HOCEVAR	Inhomogeneity	0–1	11.16 (9.85–12.76)	< 0.001	7.12 (6.27–7.76)	< 0.001	6.78 (6.15–8.36)	< 0.001	50.53 (34.56–59.61)	< 0.001
		2–3	3.31 (1.16–7.39)		1.96 (0.81–4.33)		2.27 (1.47–4.88)		4.27 (1.46–20.05)	
	Hypoechoic area	0–1	8.74 (4.22–11.20)	0.007	5.27 (2.49–7.28)	0.004	5.85 (1.99–7.71)	0.024	30.69 (4.99–54.44)	0.010
		2–3	2.99 (1.45–5.97)		1.70 (0.84–3.41)		2.50 (1.92–4.90)		4.16 (1.70–15.04)	
	Hyperechoic focus	0–1	8.41 (2.10–11.09)	0.017	5.06 (1.29–6.97)	0.012	5.29 (2.59–7.42)	0.019	27.38 (3.27–53.91)	0.012
		2–3	3.52 (1.45–5.27)		2.15 (0.84–2.95)		2.15 (1.60–3.41)		4.27 (1.64–11.41)	
	Glandular border	0–1	7.04 (1.95–9.49)	0.258	4.25 (1.16–5.90)	0.195	4.98 (1.69–6.15)	0.378	20.74 (2.21–34.56)	0.297
		2–3	3.75 (1.73–4.76)		2.25 (1.12–2.71)		2.75 (2.22–3.35)		6.24 (2.46–9.15)	
PSMA-GIVol: PSMA-based functional glandular volume; PSMATotGIAct: PSMA-based total glandular activity (PSMA SUVmean × PSMA-GIVol). SGUS: salivary gland ultrasonography; p value < 0.05 was considered statistically significant. Values are presented as median (IQR).										

On ^{18}F -FDG PET/CT, FDG-derived parameters were available for 45 of 46 PGs and all 46 SMGs. One parotid gland was excluded from FDG analysis due to a history of surgery for parotid MALT lymphoma. In PGs, glands with higher OMERACT and Hocevar scores (2–3) demonstrated significantly higher FDG SUVmax and SUVmean compared with glands scored 0–1 for OMERACT grade and Hocevar parameters including inhomogeneity and hypoechoic areas. In contrast, FDG uptake did not differ significantly according to hyperechoic foci or glandular border parameters (Table 4). In SMGs, FDG SUVmax and SUVmean were significantly lower in glands with higher OMERACT scores and hypoechoic area scores, whereas no significant differences were observed for inhomogeneity, hyperechoic foci, or glandular border parameters (Table 5). Representative ^{68}Ga -PSMA-11 and ^{18}F -FDG PET/CT images are presented in Fig. 2.

Table 4
Comparison of OMERACT and Hocevar SGUS scores with ^{18}F -FDG PET/CT parameters of the parotid glands

SGUS group		SUVmax		P	SUVmean	P
OMERACT score		0–1	1.41 (1.29–1.51)	0.005	1.02 (0.86–1.10)	0.010
		2–3	1.79 (1.53–2.62)		1.19 (1.06–1.73)	
HOCEVAR	Inhomogeneity	0–1	1.37 (1.26–1.49)	< 0.001	0.98 (0.83–1.06)	0.001
		2–3	1.79 (1.48–2.58)		1.19 (1.06–1.56)	
	Hypoechoic area	0–1	1.41 (1.29–1.51)	0.005	1.02 (0.86–1.10)	0.010
		2–3	1.79 (1.53–2.62)		1.19 (1.06–1.73)	
	Hyperechoic focus	0–1	1.48 (1.33–1.85)	0.956	1.04 (0.94–1.38)	0.773
		2–3	1.52 (0.96–1.82)		1.08 (0.78–1.19)	
	Glandular border	0–1	1.48 (1.34–1.83)	0.878	1.06 (0.95–1.20)	0.878
		2–3	2.16 (0.81–3.72)		1.40 (0.71–2.21)	
SGUS: salivary gland ultrasonography; p value < 0.05 was considered statistically significant. Values are presented as median (IQR).						

Table 5
Comparison of OMERACT and Hocevar SGUS scores with ^{18}F -FDG PET/CT parameters of the submandibular glands

SGUS group		SUVmax		P	SUVmean	P
OMERACT score		0–1	1.67 (1.32–2.10)	0.037	1.29 (1.09–1.55)	0.045
		2–3	1.50 (1.02–1.68)		1.11 (0.83–1.33)	
HOCEVAR	Inhomogeneity	0–1	1.72 (1.61–2.12)	0.098	1.31 (1.15–1.42)	0.165
		2–3	1.50 (1.13–1.76)		1.18 (0.86–1.40)	
	Hypoechoic area	0–1	1.67 (1.32–2.10)	0.037	1.29 (1.09–1.55)	0.045
		2–3	1.50 (1.02–1.68)		1.11 (0.83–1.33)	
	Hyperechoic focus	0–1	1.67 (1.28–1.91)	0.062	1.27 (1.06–1.42)	0.258
		2–3	1.44 (1.13–1.63)		1.11 (0.89–1.45)	
	Glandular border	0–1	1.62 (1.16–1.83)	0.332	1.23 (0.89–1.48)	0.429
		2–3	1.50 (1.26–1.54)		1.11 (0.98–1.20)	
SGUS: salivary glandultrasonography; p value < 0.05 was considered statistically significant. Values are presented as median (IQR).						

When the analyses were repeated by accounting for bilateral glands from the same patient, the main PSMA findings remained largely unchanged. PSMA-derived parameters continued to be lower in glands with more severe SGUS abnormalities. In contrast, some FDG findings became weaker, particularly in the submandibular glands. These results are shown in Supplementary Table S1.

No statistically significant association was observed between UWSFR and ^{68}Ga -PSMA-11 PET/CT parameters. In patients with UWSFR > 0.1 mL/min, FDG SUVmax and SUVmean values in the SMGs were significantly higher than in those with UWSFR ≤ 0.1 mL/min (SUVmax: 2.10 [1.80–2.46] vs. 1.54 [1.12–1.69], $p < 0.001$; SUVmean: 1.59 [1.31–1.81] vs. 1.18 [0.85–1.34], $p = 0.002$). In the PGs, FDG SUVmean was higher in patients with UWSFR > 0.1 mL/min (1.35 [1.18–1.50] vs. 1.02 [0.92–1.20], $p = 0.022$), whereas the difference in FDG SUVmax did not reach statistical significance ($p = 0.057$). Spearman correlation analysis

demonstrated positive associations between UWSFR and FDG uptake in both PGs (SUVmax: $p = 0.485$, $p = 0.001$; SUVmean: $p = 0.541$, $p < 0.001$) and SMGs (SUVmax: $p = 0.459$, $p = 0.002$; SUVmean: $p = 0.446$, $p = 0.003$).

Discussion

Sjögren's disease is a chronic autoimmune disease that has been proposed to evolve through four stages: initiation, preclinical, asymptomatic, and overt (12). In the overt stage, glandular injury becomes severe, and progressive loss and atrophy of acinar tissue together with interstitial fibrosis, sometimes accompanied by adipose tissue replacement, lead to marked exocrine hypofunction and pronounced dryness symptoms (13, 14). Unfortunately, many patients are diagnosed at this advanced stage, limiting the effectiveness of current therapeutic options in preserving or restoring exocrine gland function (12, 15). Therefore, an important treatment strategy is to identify patients who still retain functional glandular tissue with ongoing inflammation, as patients with shorter disease duration and less advanced gland dysfunction may be more likely to benefit from intervention (16), while pilot studies suggest potential effects in selected patients (17, 18). In the present study, low UWSFR was observed in approximately two-thirds of patients, while objective dry eye was present in nearly all (91%), indicating widespread glandular dysfunction. In this context, imaging can help characterize salivary gland involvement and support the distinction between potentially reversible inflammatory activity and predominantly irreversible structural damage.

Our findings suggest that ^{68}Ga -PSMA-11 PET/CT and ^{18}F -FDG PET/CT capture distinct but complementary aspects of salivary gland involvement in SjD. PSMA parameters were significantly lower in both parotid and submandibular glands with higher OMERACT and Hocevar scores, consistent with more advanced structural glandular involvement. This interpretation is supported by a case report in which absent ^{68}Ga -PSMA-11 uptake in the lacrimal, parotid, and submandibular glands prompted further evaluation and subsequent diagnosis of Sjögren's disease (19). In addition, Li et al. reported significantly lower SUVmax and SUVmean values in lacrimal, parotid, and submandibular glands of SjD patients compared with controls using ^{68}Ga -PSMA-11 PET/CT, further supporting the utility of this modality for assessing glandular involvement (8). Lower ^{68}Ga -PSMA-11 uptake may primarily reflect reduced viable glandular tissue and more advanced structural damage.

By contrast, FDG uptake patterns, particularly their association with preserved salivary flow, may indicate residual metabolic activity in glands with retained functional potential. In PGs, higher FDG uptake in glands with higher OMERACT scores and selected Hocevar abnormalities, including inhomogeneity and hypoechoic areas, may suggest ongoing metabolic activity. Thus, grade 2–3 ultrasonographic abnormalities in PGs may not necessarily represent end-stage damage, but may also coexist with active inflammation and structural change. In SMGs, however, FDG uptake was lower in glands with higher OMERACT and hypoechoic area scores. In our cohort, SGUS abnormalities were more frequent in the submandibular glands than in the parotid glands, in keeping with recent ultrasonographic studies showing dominant submandibular involvement in primary Sjögren's syndrome and suggesting that the submandibular gland parenchyma may be affected earlier than the parotid gland (20, 21). Taken together with the positive association between FDG uptake and salivary flow, this finding may suggest reduced residual metabolically active tissue in more structurally affected SMGs.

We then explored whether these PET metrics were associated with gland function, using salivary flow as an objective reference. Our group previously reported an association between SGUS scores and salivary flow rates in SjD (5). In the current study, FDG uptake correlated positively with UWSFR in both PGs and SMGs. Moreover, SMG SUVmax and SUVmean values were higher in patients with UWSFR > 0.1 mL/min, suggesting that ^{18}F -FDG PET/CT may help identify residual metabolic activity in glands with relatively preserved salivary function. In contrast, ^{68}Ga -PSMA-11 PET/CT parameters did not correlate significantly with UWSFR, supporting the view that PSMA uptake may reflect structural glandular involvement rather than whole-saliva output. This complementary imaging pattern may help differentiate glands with residual metabolic activity despite reduced PSMA uptake (low PSMA with relatively higher FDG) from glands with predominantly structural loss (low PSMA with low FDG).

This study has several limitations, including the small sample size, the cross-sectional design, the absence of histopathological validation, and the heterogeneity of ongoing treatments, which may have influenced FDG uptake and salivary flow. Although the primary analyses were performed at the gland level, we repeated the analyses by accounting for the fact that bilateral glands were obtained from the same patient. This supported the consistency of the PSMA findings. However, some FDG associations, especially in the submandibular glands, were attenuated. Therefore, the FDG results should be interpreted more cautiously.

Nevertheless, given the limited number of studies evaluating PSMA and FDG concurrently on an ultrasound-based gland-by-gland basis, this cohort provides a meaningful contribution. Further longitudinal studies assessing treatment response and disease progression, ideally with healthy controls, are needed to clarify prognostic value and to better define physiological reference ranges for ^{68}Ga -PSMA uptake.

Conclusion

In SJD, ^{68}Ga -PSMA-11 PET/CT and ^{18}F -FDG PET/CT appear to provide complementary information on salivary gland involvement. Lower PSMA uptake and PSMATotGIAct were associated with more severe ultrasonographic abnormalities, supporting the interpretation that PSMA-based parameters may reflect structural glandular damage. By contrast, FDG uptake patterns, particularly their association with preserved salivary flow, may indicate residual metabolic activity in glands with retained functional potential. This dual-tracer approach may help define imaging phenotypes relevant to treatment stratification; however, its clinical utility should be confirmed in larger longitudinal studies.

Declarations

Conflict of interest statement:

The authors declare that they have no conflicts of interest.

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The data underlying this article will be shared by the corresponding author upon reasonable request.

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Figures

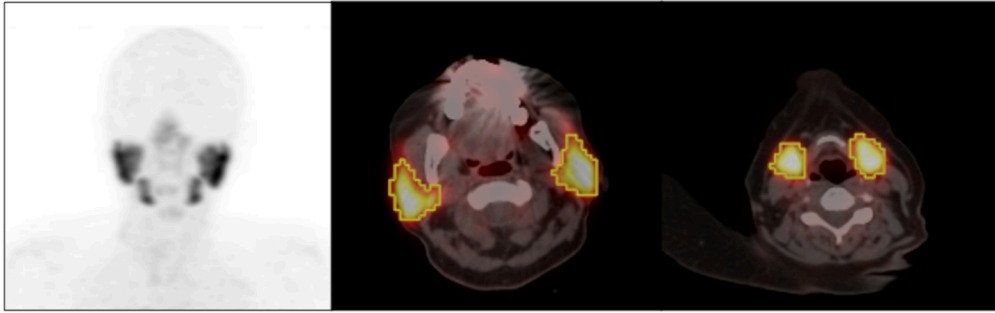


Figure 1

Representative delineation of the bilateral parotid and submandibular glands on attenuation-corrected PET/CT images.

Alt text: Attenuation-corrected PET/CT images showing representative delineation of the bilateral parotid and submandibular glands.

	18F-FDG PET/CT	68Ga-PSMA PET/CT	18F-FDG PET/CT	68Ga-PSMA PET/CT
CASE 1				
CASE 2				

Figure 2

Representative dual-tracer PET/CT findings in Sjögren's disease. In case 1, both FDG and PSMA uptake are reduced in the parotid and submandibular glands, consistent with more advanced structural glandular involvement. In case 2, both FDG and PSMA uptake are relatively preserved in the salivary glands, consistent with retained glandular activity.

Alt text: Representative dual-tracer PET/CT images in Sjögren's disease showing reduced FDG and PSMA uptake in one case and relatively preserved uptake in another case.