

Salivary gland ^{18}F -FDG-PET/CT uptake patterns in Sjögren's syndrome and giant cell arteritis patients

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Abstract

Objective

Wide variety in salivary gland ^{18}F -FDG-uptake is observed in the general population. A general consensus about the usefulness of ^{18}F -FDG-PET/CT to detect salivary gland inflammatory conditions, such as in primary Sjögren's syndrome (pSS), is not yet clear. This study aimed to investigate whether there are differences in uptake of ^{18}F -FDG in salivary glands among two autoimmune groups [pSS, giant cell arteritis (GCA)] and a non-autoimmune group (lung cancer).

Methods

PSS patients aged ≥ 50 years who underwent ^{18}F -FDG-PET/CT were included and age-matched with GCA patients and a non-autoimmune control group (lung cancer patients). Scans were visually evaluated and quantitative analysis was performed by measuring standardised uptake values (SUV) within salivary glands and lacrimal glands. For GCA patients, arteries in the vicinity of the parotid and submandibular gland were assessed for positivity.

Results

PSS patients did not show increased ^{18}F -FDG-uptake in the parotid or submandibular gland, compared to the other two groups. For the tubarial gland, significantly higher SUV_{max} was found in the pSS patient group. Interestingly, GCA patients had significantly higher SUV_{max} in the submandibular gland than the other two groups. Visual ^{18}F -FDG-positivity of cranial arteries related to the parotid and submandibular glands was associated with significantly higher SUV_{max} in salivary glands of GCA patients.

Conclusion

Although ^{18}F -FDG-uptake was not increased in parotid and submandibular glands of pSS patients, increased ^{18}F -FDG-uptake in tubarial glands of pSS patients might indicate a role for these glands in pSS. Furthermore, parotid and submandibular glands may be affected by local vasculitis in GCA.

Key words

primary Sjögren's syndrome, giant cell arteritis, FDG, PET-CT, salivary gland, tubarial gland

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Introduction

Positron emission tomography/computed tomography (PET/CT) is a well-established imaging modality which was proven to be useful in diagnosis and follow-up of many oncological, infectious and inflammatory diseases (1-3). ^{18}F -fluorodeoxyglucose (^{18}F -FDG) is the most commonly used tracer in PET/CT-imaging. Different tissues and organs display diverse uptake patterns, depending on glucose demand and metabolic activity. A distinction between physiological and pathological ^{18}F -FDG-uptake can be made using the pattern and intensity of ^{18}F -FDG-uptake, including comparison of this uptake with ^{18}F -FDG-uptake in reference sites, such as the mediastinum or the liver (4-8).

One of the organs with a wide variety in ^{18}F -FDG-uptake in the general population are the salivary glands. Salivary gland ^{18}F -FDG-uptake is often denoted as physiological or non-specific. There are 2 major salivary glands that transport saliva through ducts into the oral cavity, the parotid and submandibular gland. Recently, the tubarial gland has sparked interest after a long period of being underexposed (9, 10). This gland is located in the nasopharynx and appears to be most akin to palatal salivary glands (11-13). Several studies demonstrated variable ^{18}F -FDG-uptake in the major salivary glands of patients without abnormal salivary gland conditions (5, 14). The meaning of ^{18}F -FDG-PET/CT uptake in inflammatory salivary gland conditions is not clear yet. Some diseases may be related to salivary gland dysfunction, and an underlying (inflammatory) salivary gland pathology cannot be ruled out in patients with visual salivary gland ^{18}F -FDG-uptake.

An autoimmune disease with clear salivary gland involvement is primary Sjögren's syndrome (pSS). This chronic, systemic autoimmune disease is characterised by reduced saliva and lacrimal fluid production, causing sicca symptoms of the mouth and eyes. Characteristic is the infiltrate of immune cells in the salivary glands, mostly located around the ducts that transport saliva (15, 16). Several studies have been conducted to determine the value

of ^{18}F -FDG-PET/CT in discriminating between pSS and individuals without pSS (17-19). At this moment, literature is conflicting, and it is not yet clear whether pSS patients show increased ^{18}F -FDG-uptake in their inflamed salivary glands.

Another autoimmune disease that shows variable ^{18}F -FDG-uptake in salivary glands is giant cell arteritis (GCA). Although GCA patients do not often present with sicca complaints, we observed, in clinical practice, highly variable and abnormal visual salivary gland ^{18}F -FDG-uptake in several GCA patients. GCA is a common large vessel vasculitis essentially affecting people over the age of 50, characterized by inflammation of the temporal artery, but the aorta and its proximal branches can also be involved (20, 21). The diagnosis of GCA relies on the presence of physical complaints such as temporal headache, jaw or tongue claudication and sudden visual loss combined with laboratory, imaging and histopathological findings. Literature describing ^{18}F -FDG-uptake in salivary glands of GCA patients is unavailable.

The instigation for this research is severalfold. Previous studies evaluated ^{18}F -FDG-uptake in salivary glands in pSS and found contradicting results. Clinically observed salivary gland ^{18}F -FDG-uptake in GCA is scarcely described in literature, and other types of vasculitis may affect the salivary glands (22, 23). ^{18}F -FDG-PET/CT also plays an increasing role in the diagnostic process and follow-up of pSS and GCA. Therefore, the main aim of this study was to investigate whether there are differences in the uptake of ^{18}F -FDG in salivary glands among pSS, GCA and non-autoimmune patients. Furthermore, correlations between PET findings and clinical parameters were evaluated.

Methods

Patient selection

Three patient groups were included for this retrospective study: (1) pSS patients, (2) GCA patients and (3) non-autoimmune patients. All included patients had glucose levels below 11 mmol/L before ^{18}F -FDG-PET/CT and were aged ≥ 50 years. Ethical approval for this non-

WMO study was waived by the local medical ethics committees of the participating centres (METc 2018/711 and 036.22 BWdV/mp). All patients were checked for objection against use of diagnostic material for research purposes in the electronic patient file system according to the Dutch law.

The pSS cohort consisted of consecutive pSS patients who underwent ^{18}F -FDG PET/CT in the University Medical Center Groningen (UMCG) between 2011 and 2022, and fulfilled the American College of Rheumatology – European League Against Rheumatism (ACR-EULAR) classification criteria for pSS (24). In most cases, PET was performed because of high clinical disease activity of pSS or suspicion of a lymphoma ($n=29$). Other indications were: suspicion of having an autoimmune disease (these patients had clinical signs of systemic disease activity/suspicion of a lymphoproliferative disorder and were retrospectively verified to have pSS at the time of FDG-PET) ($n=3$), or an indication not related to any autoimmune disease ($n=8$). PSS patients diagnosed with a malignancy, either related or not related to pSS (including pSS-associated Mucosa Associated Lymphoid Tissue (MALT) lymphomas), were excluded. If pSS patients underwent multiple ^{18}F -FDG-PET/CT scans, the first ^{18}F -FDG-PET/CT scan after pSS diagnosis was used.

Patients in the GCA and the non-autoimmune control group were selected for comparison with the pSS cohort using individual matching based on age. For each pSS patient, a GCA and non-autoimmune control patient was selected, with an age ± 5 years. The maximum differences in age between GCA and non-autoimmune control patients was also 5 years. GCA patients were selected from the GCA/PMR/SENEX (GPS) cohort in the UMCG. All GCA patients fulfilled the 2022 ACR-EULAR criteria for GCA (25). ^{18}F -FDG-PET/CT was routinely performed as part of the diagnostic work-up of GCA in the UMCG. GCA patients did not have an associated autoimmune disease or a concomitant malignancy, except for polymyalgia rheumatica (PMR). For the non-autoimmune control group, patients with

pulmonary nodules or masses, who underwent ^{18}F -FDG-PET/CT in the UMCG for primary staging during 01-12-2021 and 01-04-2022 were selected. These patients did not have a history of an autoimmune disease.

^{18}F -FDG-PET/CT scanning

All ^{18}F -FDG-PET/CT scans were performed using hybrid PET/CT camera systems (Siemens Biograph mCT 40/64 or Biograph Vision). Images were reconstructed according to standardized European EANM/EARL guidelines (26). In total, 3 MBq ^{18}F -FDG per kilogram of bodyweight was administered intravenously after a 6-hour fasting period. Imaging was performed 60 minutes post-injection. Scans were taken from the head to midthigh region in the pSS and non-autoimmune control group, and from head up to and including the knees in GCA patients. GCA patients underwent a scanning interval of 5 minutes (vasculitis PET protocol) of the head region, in contrast to pSS and non-autoimmune patients who underwent a scanning interval of 3 minutes of this region. A low dose CT (LDCT) was performed in all patients for attenuation correction.

Image analysis

Image analysis and quantification were performed with Syngo.Via VB50 (Siemens Healthineers, Erlangen). Visual and quantitative image analyses were performed by two investigators (RG and MvG), supervised by two experienced nuclear medicine physicians (AG and RS). The following glands were visually and quantitatively bilaterally evaluated: the parotid gland, the submandibular gland, the lacrimal gland and the tubarial gland. Visual assessment was performed by categorising ^{18}F -FDG-uptake into 4 groups: 0) No notable uptake; 1) uptake equal to the mediastinum; 2) uptake >mediastinum <liver and 3) uptake >liver. Abnormal visual uptake was defined as ≥ 2 for the salivary glands and ≥ 1 for the lacrimal glands, based on clinical expertise (AG and RS). In the GCA group, the following arteries of were visually analysed and scored for GCA involvement (RS): internal carotid, superficial temporal,

maxillary, transverse facial, posterior auricular, facial, submental and sublingual arteries.

Quantitative analysis was performed by drawing a volume of interest (VOI) at EARL-reconstructed images in the following structures: Salivary glands (including tubarial glands), lacrimal glands, blood pool in the descending aorta, liver, spleen and bone marrow (vertebral body lumbar 4 or lumbar 5). Standardised uptake values (SUV_{max} , SUV_{mean}) were corrected for blood pool activity and glucose levels at time of scanning. The diameters of the parotid gland, submandibular gland, liver and spleen were measured on CT-images.

Clinical parameters

Clinical parameters of pSS were collected within a maximum time frame of 1 year before or after PET scanning. The EULAR Sjögren's syndrome disease activity index (ESSDAI), consisting of 12 domains, was collected for all pSS patients (27). Time between ^{18}F -FDG-PET/CT and evaluation of the ESSDAI was 2 weeks (IQR 0-6). Calculations were performed with the glandular domain of the ESSDAI, which includes the presence of clinical swelling of the salivary or lacrimal glands, and the total ESSDAI score. Patients were divided into two groups based on low systemic disease activity ($\text{ESSDAI} < 5$) or relatively higher systemic disease activity ($\text{ESSDAI} \geq 5$). The glandular ESSDAI score was split into two groups: no activity and low or moderate activity. Since localised vasculitis in the vicinity of salivary glands could possibly be related to ^{18}F -FDG-uptake in salivary glands of GCA patients, parotid gland SUVs in GCA patients were compared between two groups based on visual positivity or negativity of the internal carotid, superficial temporal, maxillary, transverse facial and posterior auricular arteries. Submandibular gland SUVs in GCA patients were compared between two groups based on visual positivity or negativity of the facial, submental and sublingual arteries.

Statistical analysis

SPSS version 28 was used for statistics. Patient characteristics of the 3

Table I. Patient characteristics and ¹⁸F-FDG-PET/CT results of glands and other regions.

	Sjögren n=40	GCA n=40	Non-autoimmune n=40	p-value
Patient characteristics				
Female (%)	30 (75%)	24 (60%)	22 (55%)	0.157
Age at time of ¹⁸ F-FDG-PET	66.3 ± 8.9	67.13 ± 8.1	66.6 ± 7.8	0.901
Medication use at time of ¹⁸F-FDG-PET				
Methylprednisone (1000mg i.v.)	2 (5%)	2 (5%)	0 (0%)	0.544
Oral prednisone	6 (15%)	2 (5%)	0 (0%)	0.012
Dosage (mg)	5.0 (5.0-10.0)	2.5-60.0		
Other DMARDs	9 (22.5%)	0 (0%)	0 (0%)	<0.001
¹⁸F-FDG-PET/CT parameters				
Parotid gland				
Visual uptake (0-3)	0 (0-2)	0 (0-1)	0 (0-1)	0.668
Visual uptake ≥2	10 (25%)	8 (20%)	5 (12.5%)	0.401
SUV _{max} /bloodpool	1.09 (0.83-1.43)	1.09 (0.88-1.22)	0.99 (0.81-1.15)	0.375
Diameter transversal (highest)	2.86 (2.16-3.19)	2.99 (2.62-3.25)	3.43 (2.91-3.67)	<0.001
Diameter frontal (highest)	3.67 (3.19-4.33)	3.97 (3.55-4.32)	4.24 (3.82-4.72)	0.004
Submandibular gland				
Visual uptake (0-3)	0 (0-1)	2 (1-3)	1 (0-2)	<0.001
Visual uptake ≥2	6 (15.4%)	27 (69.2%)	15 (37.5%)	<0.001
SUV _{max} /bloodpool	1.10 (0.84-1.41)	1.43 (1.26-1.72)	1.20 (0.94-1.54)	<0.001
Diameter transversal (highest)	1.39 (1.05-1.83)	2.19 (1.77-2.40)	2.05 (1.75-2.28)	<0.001
Tubarial gland				
Visual uptake (0-3)	2 (1-3)	1 (0-2)	1 (0-2)	0.004
Visual uptake ≥2	29 (72.5%)	19 (47.5%)	14 (35%)	0.003
SUV _{max} /bloodpool	1.54 (1.36-1.96)	1.23 (1.06-1.48)	1.20 (0.87-1.40)	<0.001
Lacrimal gland				
Visual uptake (0-3)	0 (0-0)	0 (0-0)	0 (0-0)	0.009
	Total range: 0-2	Total range: 0-0	Total range: 0-1	
Visual uptake ≥1	6 (15%)	0 (0%)	1 (2.5%)	0.016
SUV _{max} /bloodpool	0.92 (0.79-1.08)	0.89 (0.80-0.99)	0.90 (0.80-1.05)	0.780
Other regions				
SUV _{mean} tonsil/bloodpool	1.76 (1.47-2.05)	1.74 (1.39-2.14)	1.64 (1.30-2.02)	0.520
SUV _{mean} liver/bloodpool	1.24 (1.17-1.35)	1.32 (1.23-1.43)	1.27 (1.14-1.38)	0.092
SUV _{mean} spleen/bloodpool	1.17 (1.09-1.37)	1.19 (1.06-1.29)	1.08 (1.02-1.18)	0.017
SUV _{mean} Bone marrow /bloodpool	1.11 (0.86-1.34)	1.13 (0.94-1.33)	0.92 (0.70-1.06)	<0.001
PMR (visual positivity on PET/CT)	3 (8%)	12 (30%)	0 (0%)	<0.001

groups were described using mean (± SD), median (IQR) and number (%), as appropriate. Patient characteristics were compared between groups using Chi-Square tests and One-way ANOVA. Visual assessment of the salivary and lacrimal glands was compared using Chi-Square tests and Kruskal-Wallis tests. SUVs and the diameters of the different glands were compared between the three groups using Kruskal-Wallis tests, followed by Mann-Whitney U-tests in case of significant results. Correlations between SUVs and clinical parameters were assessed by using Spearman's correlation tests 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).

Results

Patients

All three age-matched groups consisted of 40 patients. There were no statistically significant differences in gender between these age-matched groups. Patient characteristics including medication use are shown in Table I.

Visual PET analysis

Visual ¹⁸F-FDG-uptake in the parotid gland was low amongst all groups, without significant differences (Table I). The submandibular gland displayed more varied uptake patterns between groups, with significant differences between all three groups (Table I). Visual ¹⁸F-FDG-uptake in the submandibular gland was significantly higher in GCA

patients, compared to non-autoimmune patients ($p=0.006$). PSS patients had significantly lower visual ¹⁸F-FDG-uptake in the submandibular gland than non-autoimmune patients ($p<0.001$). Regarding the tubarial gland, pSS patients had significantly higher visual ¹⁸F-FDG-uptake than the other two groups (Table I). Only 7 patients showed visual ¹⁸F-FDG-uptake in the lacrimal gland, of which 6 were pSS patients. Consequently, visual uptake in the lacrimal gland was significantly higher in the pSS group (Table I).

Quantitative PET analysis

As illustrated in Figure 1, the SUV_{max} of the parotid gland was not significantly different between the three groups. The diameter of the parotid gland of pSS and GCA patients was significantly smaller than non-autoimmune patients in the transverse and frontal plane. In the submandibular gland, GCA patients had a significantly higher SUV_{max} compared to pSS and non-autoimmune patients. The transverse diameter of the submandibular gland in pSS patients was significantly lower than GCA and non-autoimmune patients (Fig. 1). The SUV_{max} of the tubarial gland was significantly higher in the pSS group compared to GCA and non-autoimmune patients (Fig. 1). No significant differences between the three groups were found regarding SUV_{max} in the lacrimal gland (Table I). No significant differences were present among the different groups when looking at the SUV_{mean} of the tonsils or liver (Table I). Regarding the spleen and the bone marrow, the SUV_{mean} among non-autoimmune patients was found to be significantly lower than in pSS and GCA patients (spleen: $p=0.015$ and $p=0.014$, bone marrow: $p=0.003$ and $p<0.001$) (Table I).

Clinical correlations

Within the pSS patient group, there were poor/fair correlations between the total ESSDAI score and SUV_{max} of the parotid ($\rho=-0.054$), submandibular ($\rho=0.096$), lacrimal ($\rho=-0.257$) and tubarial gland ($\rho=0.204$). SUV_{max} of the parotid, submandibular and lacrimal glands were not significantly different when comparing patients with

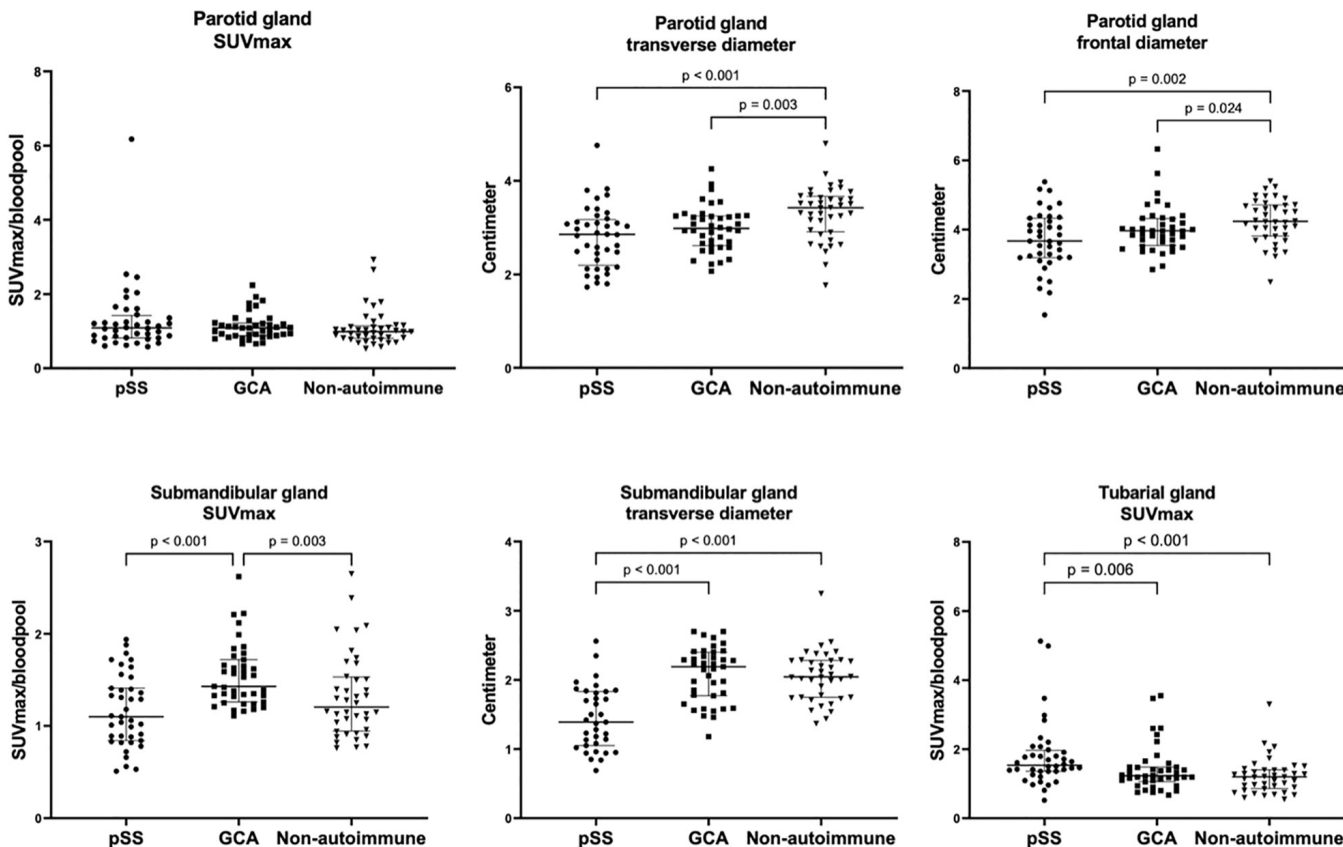


Fig. 1. SUV_{max} and diameters of parotid, submandibular and tubarial glands in pSS, GCA and non-autoimmune control patients. Median and IQR are denoted by the middle and outer horizontal lines respectively.

ESSDAI total score <5 and patients with ESSDAI total scores ≥5 (Fig. 2). However, a total ESSDAI score ≥5 was associated with a significantly higher SUV_{max} in the tubarial gland (Fig. 2). When focusing on the ESSDAI domain glandular activity, pSS patients with presence of clinical glandular swelling (either scored as low or moderate activity in this domain), displayed significantly higher SUV_{max} in the parotid and tubarial glands, compared to pSS patients without activity in the glandular ESSDAI domain (Fig. 3). No significant differences in SUV_{max} of the submandibular and lacrimal gland were found between patients with glandular activity and patients without glandular activity in the glandular ESSDAI domain. When performing a sub-analysis with pSS patients with presence of glandular activity (n=6), SUV_{max} in the parotid gland was significantly higher in pSS patients compared to GCA and non-autoimmune patients (p=0.007, p=0.003), even when a pSS patient with SUV_{max}>6 in the parotid gland (outlier)

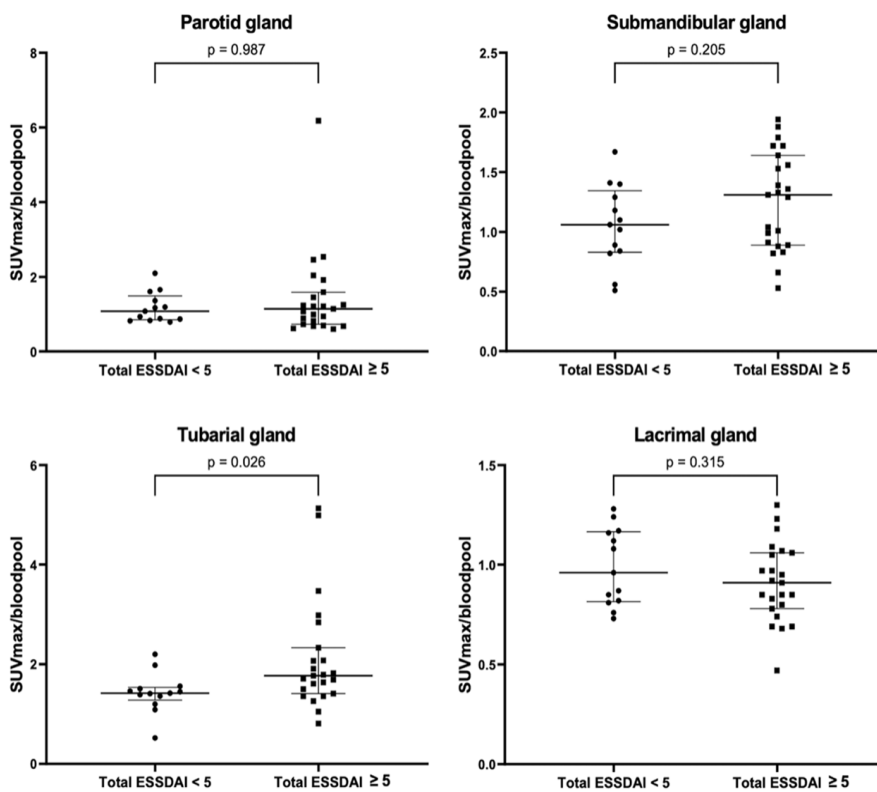


Fig. 2. SUV_{max} in salivary and lacrimal glands of pSS patients with total ESSDAI<5 and total ESSDAI≥5. Median and IQR are denoted by the middle and outer horizontal lines respectively.

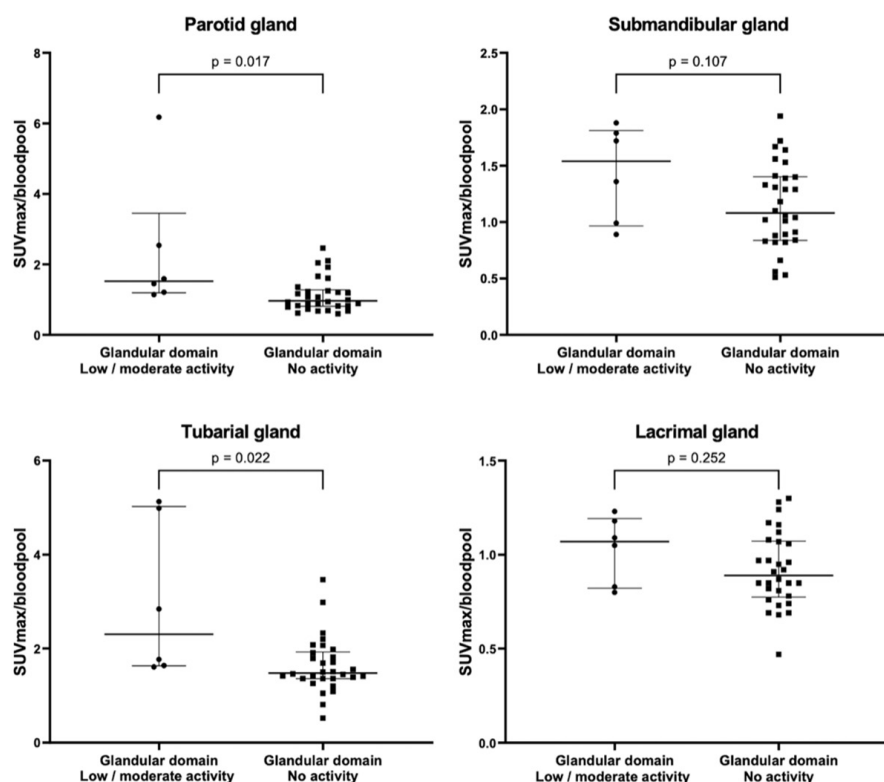


Fig. 3. SUV_{max} in salivary and lacrimal glands of pSS patients with low/moderate activity and no activity in the glandular domain of the ESSDAI. Median and IQR are denoted by the middle and outer horizontal lines respectively.

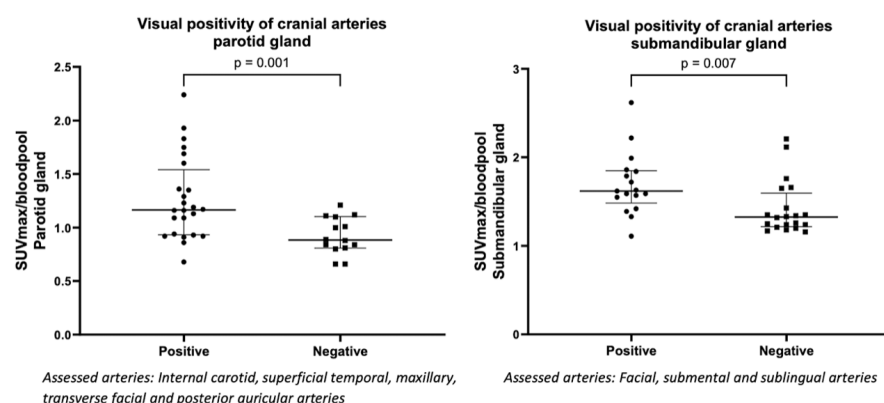


Fig. 4. SUV_{max} in parotid and submandibular glands in patients with visual positivity of cranial arteries, and in patients without positivity of cranial arteries. Median and IQR are denoted by the middle and outer horizontal lines respectively.

was excluded from the sub-analysis ($p=0.023$, $p=0.011$). Comparing these same 6 pSS patient's submandibular SUV_{max} with submandibular SUV_{max} of GCA and non-autoimmune patients gave no significant results ($p=0.841$, $p=0.415$).

No correlation was found between disease duration of pSS and SUV_{max} in the parotid gland ($\rho=-0.028$) or submandibular gland ($\rho=-0.166$). Poor correlations were found between SUV_{max}

of the parotid gland and transverse ($\rho=-0.003$) and frontal ($\rho=0.042$) diameter of the parotid gland in pSS patients. Moreover, a fair correlation was found between the transverse diameter and SUV_{max} of the submandibular gland ($\rho=0.398$) in pSS patients. A poor correlation was found between the Schirmer's score and SUV_{max} of the lacrimal gland ($\rho=-0.182$, $n=13$). Poor to fair correlations were found between unstimulated whole saliva

(UWS) and SUV_{max} of the parotid and submandibular glands ($\rho = -0.175$ and $\rho = 0.256$, $n=10$).

GCA patients with positive visual uptake of cranial arteries in vicinity of the parotid gland (internal carotid, superficial temporal, maxillary, transverse facial and/or posterior auricular arteries) demonstrated significantly higher SUV_{max} in parotid glands than patients without visual uptake of these cranial arteries (Fig. 4). For the submandibular gland, patients with visual uptake in the facial, submental and/or sublingual arteries, showed significantly higher SUV_{max} in the submandibular gland compared to GCA patients without visual positivity in these arteries (Fig. 4). Of the four GCA patients who used steroids during PET, only one patient had visual uptake of the arteries in vicinity of the parotid gland, and only one patient showed visual uptake of the cranial arteries in vicinity of the submandibular gland. Patients who used prednisone did not show lower SUV_{max} in both glands, compared to patients without using steroids ($p=0.589$, $p=0.611$).

Discussion

We present the first study evaluating the ¹⁸F-FDG-uptake in salivary glands across an age-matched population using EANM/EARL PET/CT reconstructions. We did not find increased ¹⁸F-FDG-uptake in parotid and submandibular glands of pSS patients, compared to GCA and non-autoimmune patients. However, significantly higher uptake in the tubarial glands was found in pSS patients. Interestingly, GCA patients showed significantly higher uptake in submandibular glands, both visually and quantitatively, compared to the other two groups.

The lack of significantly higher ¹⁸F-FDG-uptake in parotid glands in pSS patients contradicts previous studies. Cohen *et al.* found pathological ¹⁸F-FDG-uptake in 50% of parotid glands and 28% of submandibular glands of pSS patients (17). In that study, salivary gland uptake was more frequent and significantly higher in pSS patients compared to the control group without known head/neck pathology. Another study confirmed these findings, in a

cohort of pSS patients compared to healthy volunteers (19). On the other hand, Shimizu *et al.* found that salivary gland ^{18}F -FDG-uptake could not differentiate between pSS patients and patients with oral carcinoma without salivary gland involvement (18). These discrepancies could be explained by different scoring methods and definitions of abnormal uptake. Furthermore, previous studies did not use standardised image reconstructions, which is one of the strengths of the current study. Another explanation for the contradictory results could be differences in pSS study populations. PSS patients with a parotid gland MALT lymphoma show higher parotid ^{18}F -FDG-uptake compared to pSS patients without lymphoma (28, 29). Therefore, pSS patients with pSS-associated lymphoma were excluded in the current study. However, lymphoma patients were included in two of the previous studies (17, 18). Furthermore, Jimenez-Royo *et al.* only included patients with an ESSDAI \geq 5, whereas the current study also contained patients with lower disease activity (64% of patients with ESSDAI \geq 5), which might have influenced measured SUVs in pSS patients. Although pSS patients with ESSDAI \geq 5 did not show significantly higher SUVs in the parotid and submandibular glands compared to pSS patients with ESSDAI $<$ 5 in our cohort (Fig. 2), significant differences were found in parotid gland SUV_{max} between pSS patients with and without activity in the glandular domain of the ESSDAI (Fig. 3). Furthermore, a sub-analysis showed that the subgroup of pSS patients with glandular activity (N=6) showed significantly higher SUV_{max} in the parotid gland compared to GCA and non-autoimmune patients. Together, this indicates that pSS patients with clinical presence of glandular swelling show increased parotid gland ^{18}F -FDG-uptake compared to GCA and non-autoimmune patients, in contrast to pSS patients without presence of glandular swelling. pSS patients without clinical presence of glandular swelling and lower SUVs might have diminished inflammatory activity in the salivary glands. From MRI studies it is known that pSS

patients can display cystic changes in affected glands, which are thought to arise from destruction of the glandular parenchyma and presence of fibrosis and fatty infiltration (18, 30). Acinar atrophy and fibrosis are increased in salivary gland biopsies of pSS patients (31, 32). It is not yet clear whether increase of adipocytes is a specific histopathological finding in pSS salivary glands, or if it is age-associated (16, 33, 34). Additionally, distinctively smaller salivary glands were found in our pSS cohort versus the other two groups. Smaller volumes of salivary glands on MRI images are also associated with lower salivary flow in pSS (35). This might indicate that this pSS cohort consists of relatively many patients with atrophic glands, possibly explaining the lower than anticipated SUV_{max} in salivary glands in pSS patients. However, no correlation was found between SUV_{max} in the parotid gland and the diameter of the gland in the group of pSS patients, and pSS patients with a longer disease duration did not have lower SUV_{max}. Also, poor correlations were found between UWS and SUV_{max} of the parotid and submandibular glands. No differences were observed in FDG-uptake between patients with and without ant-SSA and/or anti-SSB antibodies. However, the small number of three seronegative pSS patients in this cohort complicates an accurate comparison. It is known that older subjects generally have lower ^{18}F -FDG-uptake in salivary glands (14). Our selected relatively older population of pSS patients aged $>$ 50 years might have attenuated any correlation between disease duration and parotid gland SUV_{max}. Together, the fact that our retrospective cohort did not include many patients with high disease activity or presence of glandular activity as measured by the ESSDAI, could have caused lower salivary gland SUVs in this cohort of pSS patients. Prospective studies with well-defined pSS study populations could further clarify the use of ^{18}F -FDG-PET/CT in pSS. Currently, ^{18}F -FDG-PET/CT seems, however, mainly effective in the diagnostic work-up of pSS-associated lymphomas and the assessment of systemic disease

activity, instead of differentiating between pSS and other diseases based on salivary gland ^{18}F -FDG-uptake (17, 28, 29).

Regarding the tubarial gland, increased ^{18}F -FDG-uptake was observed in pSS patients (Fig. 2). Furthermore, pSS patients with higher ESSDAI scores also showed higher SUV_{max} in the tubarial gland, suggesting involvement of these glands in the disease process of pSS. The clinical significance of the possible involvement of tubarial glands in pSS is still topic of debate. Increased prevalence of dry rhinopharynx has been described in pSS patients, which might be caused by tubarial gland involvement (36). Furthermore, as the tubarial glands are located in close proximity to the torus tubarius, hypofunction of these glands in pSS could predispose to eustachian tube dysfunction in pSS, as described by Pringle *et al.* (13). However, it should be noted that the amount of saliva produced by the tubarial glands, and their role in oral dryness of pSS patients is probably limited (37). A study that compared ^{18}F -FDG uptake in tubarial glands of another disease with salivary gland involvement, IgG4-related disease (IgG4-RD), found significantly higher uptake in IgG4-RD patients, compared to thyroid and tongue cancer patients (38). While some argue that adenoids may contribute to increased uptake in the tubarial glands due to overlap of both structures, adenoids tend to regress progressively after adolescent ages, minimising their influence on tubarial gland ^{18}F -FDG-uptake (39). The lack of increased ^{18}F -FDG uptake in other salivary glands in pSS suggests cautious interpretation of these tubarial gland findings in pSS. However, further investigation through post-mortem studies or biopsies in pSS patients with dryness complaints in the upper airways and rhinopharynx could be valuable (40).

The current study is the first to evaluate ^{18}F -FDG-uptake in salivary glands of GCA patients. In another type of vasculitis, granulomatosis with polyangiitis, pathological salivary gland ^{18}F -FDG-uptake was already described (41, 42). Interestingly, we observed significantly higher ^{18}F -FDG-uptake

in the submandibular gland in the GCA group compared to the other two groups. This could imply involvement of the submandibular glands in GCA. Another explanation for the increased ^{18}F -FDG-uptake in submandibular glands is local vasculitis activity. Vasculitis activity may result in ischaemia due to reduced blood flow supply, because of reduced vascular diameters. Both GCA-induced inflammation and ischaemia can induce elevated ^{18}F -FDG-uptake (43, 44). Medium sized arteries such as the facial artery tend to be involved in GCA (21, 25). As shown in Figure 4, visual positivity of cranial arteries was associated with higher SUV_{max} in both the parotid and the submandibular gland. These results confirm the possible role of localized vasculitis in the submandibular gland, and possibly also the parotid gland. No differences in salivary gland ^{18}F -FDG-uptake were found in GCA patients using prednisone. However, the number of GCA patients using prednisone at the time of PET-imaging in our cohort was small ($n=4$), making it complicated to properly compare both groups. Besides salivary glands, lacrimal glands were also analysed. Although lacrimal glands are also involved in pSS, no significant differences in SUV_{max} were found. The increased SUV_{mean} of the spleen and bone marrow in pSS and GCA patients could be a reflection of general higher inflammatory activity in these groups. Besides the characteristic glandular manifestations, pSS is a systemic, multi-organ disease, driven by both the innate as well as the adaptive immune system. Although GCA usually affects less organ systems compared to pSS, the disease also puts of strain on the innate and adaptive immune system, which is also shown by increased ESR and CRP levels in GCA patients. In conclusion, although pSS patients with presence of glandular swelling showed increased ^{18}F -FDG-uptake in the parotid gland, no differences were found in parotid gland ^{18}F -FDG-uptake between the total pSS group and the other two groups, which might be explained by our relatively large percentage of pSS patients with low disease activity. Furthermore, uptake in tubarial

glands was higher in pSS patients, indicating that the tubarial glands might play a role in the disease process of pSS. Interestingly, significant higher ^{18}F -FDG-uptake in submandibular glands of GCA patients was found, possibly as a result of involvement of the small arteries surrounding these glands. Further research is warranted to elucidate the origins of the ^{18}F -FDG-uptake in submandibular glands in GCA and tubarial glands in pSS.

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