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Salivary Gland Uptake on ^{18}F-FP-CIT PET as a New Biomarker in Patients With Parkinsonism

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Objective: ^{18}F-FP-CIT positron emission tomography (PET) is known for its high sensitivity and specificity for evaluating striatal dopamine transporter (DAT) binding. Recently, for the early diagnose of Parkinson's disease, many researchers focused on the diagnosis of synucleinopathy in organs involved in non-motor symptoms of Parkinson's disease. We investigated the feasibility of salivary gland uptake on ^{18}F-FP-CIT PET as a new biomarker in patients with parkinsonism.

Materials and Methods: A total of 219 participants with confirmed or presumed parkinsonism, including 54 clinically diagnosed idiopathic Parkinson's disease (IPD), 59 suspected and yet undiagnosed, and 106 with secondary parkinsonism, were enrolled. The standardized uptake value ratio (SUVR) of the salivary glands was measured on both early and delayed ^{18}F-FP-CIT PET scans using the cerebellum as the reference region. Additionally, the delayed-to-early ratio (DE_ratio) of salivary gland was obtained. The results were compared between patients with different PET patterns.

Results: The SUVR in early ^{18}F-FP-CIT PET scan was significantly higher in patients with IPD pattern compared that in the non-dopaminergic degradation group (0.5 ± 0.19 vs. 0.6 ± 0.21, $P < 0.001$). Compared with the non-dopaminergic degradation group, the DE_ratio was significantly lower in patients with IPD (5.05 ± 1.7 vs. 4.0 ± 1.31, $P < 0.001$) or atypical parkinsonism patterns (5.05 ± 1.7 vs. 3.76 ± 0.96, $P < 0.05$). The DE_ratio was moderately and positively correlated with striatal DAT availability in both the whole striatum ($r = 0.37$, $P < 0.001$) and posterior putamen ($r = 0.36$, $P < 0.001$).

Conclusion: Parkinsonism patients with an IPD pattern exhibited a significant increase in uptake on early ^{18}F-FP-CIT PET and a decrease in the DE_ratio in the salivary gland. Our findings suggest that salivary gland uptake of dual-phase ^{18}F-FP-CIT PET can provide diagnostic information on DAT availability in patients with Parkinson's disease.

Keywords: Parkinson disease; ^{18}F-FP-CIT PET; Salivary gland uptake; Non-motor symptoms

INTRODUCTION

Parkinsonism is a comprehensive clinical syndrome characterized by bradykinesia, stiffness, tremors, and postural instability [1]. The most representative form of parkinsonism, idiopathic Parkinson's disease (IPD), is characterized by progressive dopaminergic neuronal loss of the substantia nigra and abnormal accumulation of alpha-synuclein in the form of Lewy bodies [2,3]. It is vital to differentiate IPD from other forms of parkinsonism because appropriate treatment through early diagnosis leads to superior prognoses [4]. The most common reasons for misdiagnosis are drug-induced parkinsonism (DIP), vascular parkinsonism (VP), essential tremors (ETs), and atypical parkinsonian syndromes including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). In some cases, Alzheimer's disease or Lewy body dementia can cause diagnostic errors [5].

Patients with IPD are known to suffer from numerous non-motor symptoms (NMSs) such as sensory abnormalities, behavioral changes, sleep disorders, autonomic dysfunction, fatigue, and motor function problems [6]. Multiple efforts

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have been made to prove synucleinopathy in organs involved in these non-motor functions, including salivary glands and the gastrointestinal tract [7-10]. However, adequate diagnostic accuracy has not yet been achieved due to the absence of effective staining methods and morphologically defined staining types, absence of submucosal tissue on many slides, relatively small amounts of submucosal tissue, and scarcity of neuronal elements in typically small intestinal specimens [11-14].

The salivary gland is a promising target for pathologic confirmation of clinical diagnosis in patients with IPD [15]. Because the salivary gland is close to the skin, obtaining a biopsy is relatively easy. Dopaminergic nerves, which are associated with salivary secretion, are an attractive target for the histological confirmation of IPD. After successful salivary gland biopsies in several studies, synucleinopathy was confirmed in some patients with IPD, raising expectations of the diagnostic potential through salivary gland biopsies [16,17]. However, the invasive nature of such biopsies may present limitations for the widespread application of the technique.

The presynaptic striatal dopamine transporter (DAT) is correlated with the density of dopamine neurons in the striata [18,19]. DAT imaging with several types of tracers has revealed high sensitivity, specificity, and the ability to distinguish degenerative parkinsonism from other non-degenerative diseases. N-3-Fluoropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) is currently used as a representative DAT positron emission tomography (PET) tracer.

Numerous studies have investigated the clinical role of DAT PET using ^{18}F-FP-CIT in patients with parkinsonism; however, none have examined the role of salivary gland uptake on DAT PET. In this study, we aimed to investigate the feasibility of salivary gland uptake on ^{18}F-FP-CIT PET scans as a new biomarker in patients with parkinsonism.

MATERIALS AND METHODS

This study was approved by the institutional review board of Ewha Womans University Seoul Hospital (No. 2022-06-035). The requirement for written informed consent was waived due to the retrospective nature of the study.

Subjects

Patients with suspected parkinsonism who underwent dual-phase ^{18}F-FP-CIT PET/computed tomography (CT) between March 2019 and July 2020 were retrospectively enrolled. All the patients were diagnosed at a movement disorder clinic. The diagnosis of suspected IPD was based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [20]. In addition, structural magnetic resonance imaging scans were assessed to exclude other neurological diseases, including cerebromalacia due to old infarction and normal pressure hydrocephalus. Clinical information on age, sex, motor symptoms, and Hoehn-Yahr (H-Y) stages was investigated. The severity of motor symptoms was evaluated using the motor portion of the Unified Parkinson Disease Rating Scale Part III (UPDRS III) by a movement disorder specialist.

For Z-score calculation, a separate group of 30 patients over 40 years of age was selected among the subjects who showed normal findings on ^{18}F-FP-CIT PET. Neurological examination revealed no evidence of pathologic movement disorder.

^{18}F-FP-CIT PET/CT Image Acquisition

All ^{18}F-FP-CIT PET scans were acquired using a dedicated PET/CT scanner (Discovery MI with LightBurst Digital 4-Ring Detector, GE Medical Systems), which obtains images with a three-dimensional resolution of 2.3 mm at full width and half maximum at the center of the field of view. All subjects were instructed to fast for at least 6 h before the scan. Early emission scan acquisition was performed from 0 to 10 min after a 185 MBq injection of ^{18}F-FP-CIT in dynamic mode, and delayed-emission scan acquisition began 120 min after injection and was performed for 20 min in static mode. Both emission scans were made after each CT scan, which was performed in spiral mode at 120 kVp and 250 mA. PET images were corrected for attenuation and reconstructed onto a 512 x 512 matrix using the Q. Clear reconstruction algorithm with a β value of 350.

Analysis of ^{18}F-FP-CIT PET/CT Images

All ^{18}F-FP-CIT PET images were assessed both visually and semiquantitatively. The images were first assessed visually by two independent, board-certified nuclear medicine physicians, one with 20 years of clinical experience in nuclear medicine and one with 10 years of experience. Both were blinded to clinical and diagnostic information. The visual interpretation criteria for a diagnosis of parkinsonism were based on the pattern of DAT loss in the striatum and classified as IPD, atypical parkinsonism, VP, or non-dopaminergic degradation (non-DD). The pattern of non-DD, even in DAT densities without any deficit in both striata, was considered symmetric, and decreased DAT densities on one

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or both sides of the dorsal posterior putamen were observed in IPD patients, with an anteroposterior gradient and relative preservation of the ventral putamen. For atypical parkinsonism, DAT densities were decreased in the posterior putamen without preservation of the ventral putamen for MSA and in the entire putamen, including both caudate nuclei, for PSP.

Semiquantitative analysis measuring the specific to non-specific binding ratio (SNBR) of striatal lesions on ^{18}F-FP-CIT PET was conducted using MIMneuro (MIM Software Inc.). Volumes of interest (VOIs) were automatically allocated to the striatum and occipital areas, allowing for calculations of the following ratios of uptake (represented as z-scores based on a normal database produced by our institute): striatum/occipital cortex, caudate nucleus/occipital cortex, putamen/occipital cortex, anterior putamen/occipital cortex, posterior putamen/occipital cortex, and the caudate to putamen and anterior to posterior putamen ratios. Each VOI segmentation was carefully checked visually and manually modified, if necessary, to correspond to the anatomical structures.

The standardized uptake value ratio (SUVR) of the salivary glands on ^{18}F-FP-CIT PET was measured using MIM Encore (MIM Software Inc.). Both parotid glands were selected to represent ^{18}F-FP-CIT uptake in the salivary glands. A sphere with a diameter of 65 mm was drawn on each parotid gland, and the VOI was automatically defined using a 40% threshold. The cerebellum was used as a reference tissue, a sphere with a diameter of 12 mm was drawn on each cerebellar lobe, and the left and right average values were used as reference tissue uptake values. The average uptake ratio of the parotid glands was calculated by dividing the average uptake value of the glands by that of the cerebellum. The volume of the parotid gland was estimated using the target volume from the VOI and the 40% threshold. Representative images of VOIs for salivary glands in both early and delayed scans are illustrated in Supplementary Figure 1.

Statistical Analyses

Descriptive statistics included the mean ± standard deviation or frequency for each clinical characteristic. The SUVR results in the salivary glands were compared between patients with different PET patterns, including IPD, atypical parkinsonism, VP, and non-DD. Student's *t*-tests and Mann–Whitney U tests were used to compare quantitative variables with or without a normal distribution, respectively, between the groups. Fisher's exact test was used to test the differences between categorical variables. Correlations between two variable distributions were analyzed using the Pearson correlation coefficient (PCC). Analyses were conducted using R software (version 4.02, www.Rproject.org), and the ggplot2 package was used to plot the correlation matrix. All statistical tests were two-sided, with a significance level of 0.05. Given the exploratory nature of the study, no adjustment was made for multiple comparisons.

RESULTS

Participants

A total of 219 participants were enrolled in this study. The demographic and clinical characteristics of the participants are summarized in Table 1. The average age was 73.09 ± 8.59 years, and 41.6% were male. The mean H-Y stage was 2.41 ± 1.37, and the mean UPDRS III score was 24.96 ± 16.61. Among these patients, 54 were clinically diagnosed with IPD (H-Y, 2.12 ± 0.97; UPDRS III, 22.72 ± 15.7), 59 were suspected and had not yet been diagnosed due to a lack of follow-up time (H-Y, 2.91 ± 1.23; UPDRS III, 30.35 ± 15.64), and 106 had secondary parkinsonism (H-Y, 2.31 ± 1.6; UPDRS III, 23.75 ± 17.59), including DIP, VP, and ET. The age of IPD patients was significantly lower than that of patients with secondary parkinsonism ($P < 0.001$). There was no significant difference in the H-Y and UPDRS III motor scores between these groups. The SNBR of the whole striatum or substriatal lesions in patients with IPD was significantly lower than that of patients with secondary parkinsonism (-2.1 vs. -0.37; whole striatum, $P < 0.001$).

Salivary Gland Uptake on ^{18}F-FP-CIT PET

In PET-based diagnosis, the SUVR in early ^{18}F-FP-CIT PET images of patients with IPD pattern was significantly increased compared with patients in the non-DD group (0.5 ± 0.19 vs. 0.6 ± 0.21, $P < 0.001$). In addition, the delayed-to-early ratio (DE_ratio) of salivary glands was significantly lower in patients with IPD or atypical parkinsonism pattern compared to those with non-DD (IPD, 5.05 ± 1.7 vs. 4.01 ± 1.31, $P < 0.001$; atypical parkinsonism, 5.05 ± 1.7 vs. 3.76 ± 0.96, $P < 0.05$). Representative images are shown in Figure 1. There were no significant differences in the SUVR of salivary glands between the non-DD and VP groups (Table 2).

The DE_ratio of salivary glands on ^{18}F-FP-CIT PET images was moderately and positively correlated with striatal DAT availability, including the whole striatum ($r = 0.37$, $P < 0.001$) and posterior putamen ($r = 0.36$,

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Table 1. Demographic Data and Clinical Characteristics

	Clinical Diagnosis				
	Total	IPD	NYD	SP	*P* (IPD vs. SP)
Dermographic characteristics					
Number	219	54	59	106	
Age (yr)	73.09 ± 8.59	68.96 ± 10.08	72.59 ± 8.97	75.46 ± 6.45	< 0.001
Sex (female:male)	128:91	30:24	30:29	69:37	0.151
H-Y stage	2.41 ± 1.37	2.12 ± 0.97	2.91 ± 1.23	2.31 ± 1.60	0.136
UPDRS III score	24.96 ± 16.61	22.72 ± 15.70	30.35 ± 15.64	23.75 ± 17.59	0.133
SNBR of substrial lesions (Z scores)					
Whole striatum	-1.27 ± 1.57	-2.10 ± 1.01	-1.88 ± 1.50	-0.37 ± 1.28	< 0.001
Caudate	-0.84 ± 1.37	-1.14 ± 1.15	-1.19 ± 1.43	-0.34 ± 1.26	< 0.001
Putamen	-1.47 ± 1.71	-2.59 ± 0.96	-2.22 ± 1.58	-0.36 ± 1.28	< 0.001
Anterior putamen	-1.18 ± 1.42	-1.79 ± 1.00	-1.73 ± 1.35	-0.41 ± 1.19	< 0.001
Posterior putamen	-1.64 ± 1.93	-3.10 ± 0.97	-2.49 ± 1.76	-0.31 ± 1.35	< 0.001
Caudate/putamen	1.95 ± 2.93	4.46 ± 2.30	3.19 ± 3.05	-0.01 ± 1.41	< 0.001
Anterior putamen/posterior putamen	1.82 ± 3.34	5.02 ± 3.02	2.92 ± 3.57	-0.24 ± 1.39	< 0.001

The values are expressed as mean ± standard deviation or number unless otherwise indicated. The specific to non-specific binding ratio (SNBR) score was calculated in 218 patients, excluding one patient with data errors. Hoehn-Yahr (H-Y) stage and Unified Parkinson Disease Rating Scale Part III (UPDRS III) motor scores were calculated in 49 IPD, 50 NYD, and 77 SP patients. IPD = idiopathic Parkinson's disease, NYD = not yet diagnosed, SP = secondary parkinsonism

P < 0.001) (Fig. 2). The salivary gland SUVRs themselves did not correlate closely with striatal DAT availability. However, a negative correlation was evident between the salivary SUVR in early ^{18}F-FP-CIT PET scans and striatal DAT availability, and a positive correlation was observed between the salivary SUVR in delayed scans and striatal DAT availability, although the correlation coefficient was low (Supplementary Table 1).

DISCUSSION

In this study, we investigated the uptake pattern of salivary glands in ^{18}F-FP-CIT PET in patients with parkinsonism. Salivary gland uptake as revealed by early phase ^{18}F-FP-CIT PET in patients with a parkinsonism pattern was significantly increased, and the DE_ratio was significantly decreased. These results suggest that the increased compensatory blood flow observed were due to dopaminergic nerve degeneration of the salivary glands in patients with degenerative parkinsonism, including those with IPD and atypical parkinsonism. In addition, salivary gland uptake in the delayed images compared with early scans decreased, suggesting the possibility of dopaminergic nerve degradation of the salivary glands. Our findings indicate that salivary gland uptake using dual-phase ^{18}F-FP-CIT PET can provide diagnostic information on DAT availability and suggest that it can be used to evaluate non-motor organs in patients with IPD and atypical parkinsonism.

However, the diagnostic performance of salivary gland uptake in ^{18}F-FP-CIT PET could not distinguish IPD from atypical parkinsonism easily. Increased blood flow and decreased DE_ratio of salivary glands were common in both patients with IPD and atypical parkinsonism patterns. In addition, no significant differences were observed between these groups. As these changes in salivary gland uptake were presumed to be caused by the degeneration of dopaminergic neurons, it is thought that the same pattern appeared in the disease groups in which dopaminergic neuronal regression occurs.

A positive correlation was evident between quantified DAT availability in striatal subregions and the SUVR of the salivary glands. The DE_ratios of salivary glands in ^{18}F-FP-CIT PET images were moderately and positively correlated with striatal DAT availability, including the whole striatum and posterior putamen. When compared by group, some patients in the group showing IPD patterns tended to experience a greater reduction in the DE_ratio than in the whole striatum (WS) z-score, and the presence of these patients may weaken the correlation coefficient (Supplementary Fig. 2). However, salivary gland SUVRs themselves did not correlate well with striatal DAT availability. Higher-than-normal WS z-scores in some patients in the conserved DAT group may explain these results. These patients exhibited high z-scores compared to other patients showing normal striatal

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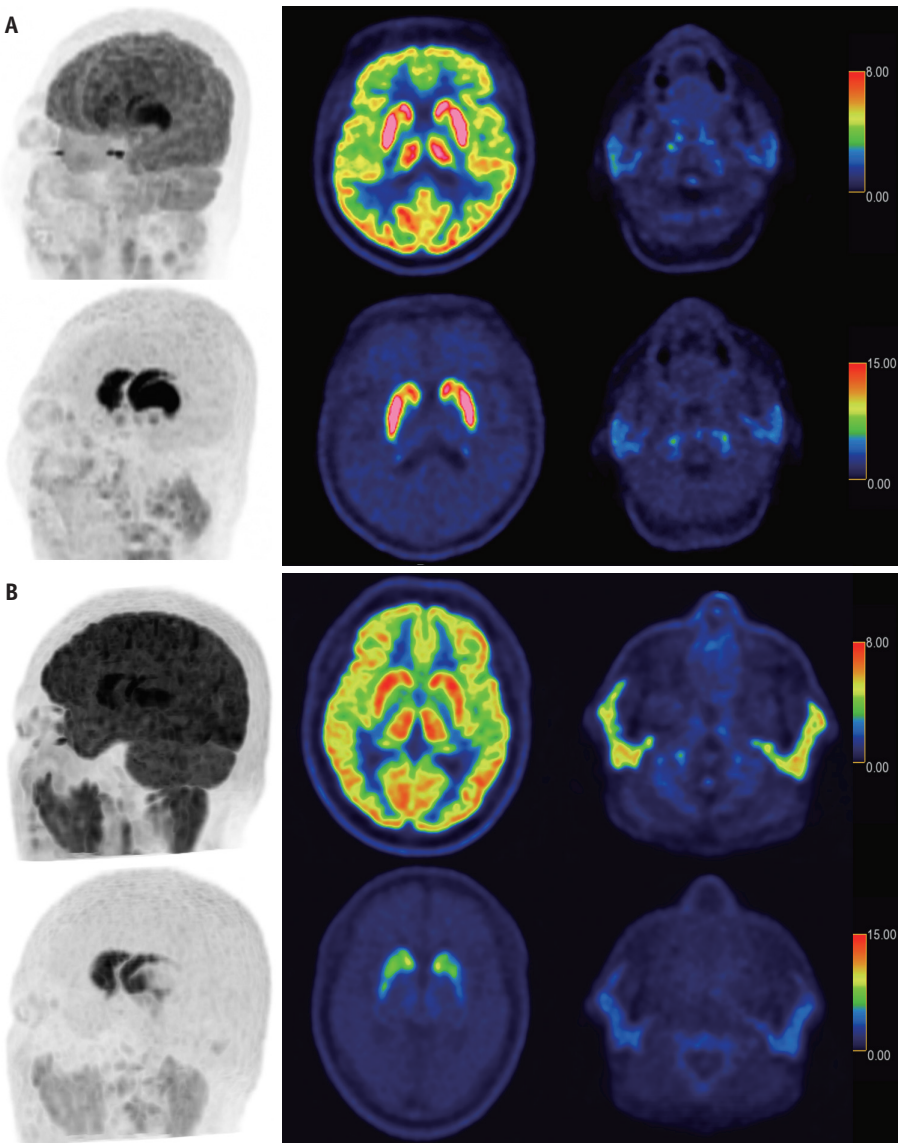

Fig. 1. Examples of maximum intensity projection (MIP) and axial images of the early (first row) and delayed phase (second row) ^{18}F-FP-CIT positron emission tomography (PET) in patients with drug-induced parkinsonism (DIP) **(A)** and idiopathic Parkinson's disease (IPD) **(B)**. In IPD patients, the salivary gland uptake of the early scan (**B**, first row; standardized uptake value ratio [SUVR], 0.86) was significantly increased compared with that of the DIP patient (**A**, first row; SUVR, 0.43). The average delayed-to-early ratio of the salivary gland was 4.83 in the DIP patient and 2.86 in the IPD patient.

DAT binding, but without a proportional increase in the salivary gland SUVR. This discrepancy is thought to weaken the correlation coefficient. In addition, the possibility of prodromal parkinsonism in patients whose WS z-scores are normal but with decreased perfusion of the salivary glands cannot be ruled out. Therefore, long-term observation of these patient groups is required.

Our findings support the use of salivary glands as diagnostic tools for evaluating patients with Parkinson's disease. Several studies have demonstrated the presence of phosphorylated α-synuclein in the submandibular glands of patients with IPD [21-27]. These studies suggest that needle biopsy of the submandibular gland reveals synucleinopathy in early IPD and may help direct therapy in clinical practice. The initial blood flow increases and decreases in the DE_ratio of salivary glands in patients with parkinsonism shown in our study can be interpreted as a change in dopaminergic nerve degeneration of the salivary glands by α-synucleinopathy, which suggests the possibility of its use as a new biomarker for early diagnosis of prodromal parkinsonism.

It can be interpreted that the reason why salivary gland uptake in IPD patients is relatively increased in early

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Table 2. The Salivary Gland Uptake (SUVR) According to the Pattern Based on PET Images

Parameter	Salivary Glands	Pattern Based on PET Images				*P*			
		Non-DD (n = 110)	IPD (n = 86)	Aty-P (n = 7)	VP (n = 16)	Non-DD vs. IPD	Non-DD vs. Aty-P	Non-DD vs. IPD + Aty-P	Non-DD vs. VP
Early phase	Right parotid	0.49 ± 0.20	0.60 ± 0.21	0.59 ± 1.50	0.52 ± 0.18	< 0.001	0.099	< 0.001	0.484
	Left parotid	0.50 ± 0.20	0.61 ± 0.22	0.63 ± 0.13	0.56 ± 0.27	0.001	0.069	< 0.001	0.621
	Average	0.50 ± 0.19	0.60 ± 0.21	0.61 ± 1.34	0.54 ± 0.22	< 0.001	0.046	< 0.001	0.484
Delayed phase	Right parotid	2.21 ± 0.46	2.21 ± 0.58	2.14 ± 0.52	2.31 ± 0.95	0.995	0.642	0.820	0.717
	Left parotid	2.24 ± 0.47	2.27 ± 0.85	2.28 ± 0.39	2.38 ± 1.00	0.826	0.814	0.995	0.604
	Average	2.23 ± 0.44	2.24 ± 0.59	2.21 ± 0.44	2.34 ± 0.97	0.911	0.868	0.961	0.818
Delayed-to-early ratio	Right parotid	5.11 ± 1.74	4.02 ± 1.38	3.79 ± 1.04	4.66 ± 1.40	< 0.001	0.046	< 0.001	0.324
	Left parotid	4.99 ± 1.74	3.99 ± 1.43	3.73 ± 0.90	4.60 ± 1.38	< 0.001	0.045	< 0.001	0.422
	Average	5.05 ± 1.70	4.01 ± 1.31	3.76 ± 0.96	4.63 ± 1.36	< 0.001	0.045	< 0.001	0.354

The values are expressed as mean ± standard deviation or number unless otherwise indicated. All *P*-values are calculated against "non-DD" group. SUVR = standardized uptake value ratio, PET = positron emission tomography, Non-DD = non-dopaminergic degradation, IPD = idiopathic parkinson's disease, Aty-P = atypical parkinsonism, VP = vascular parkinsonism

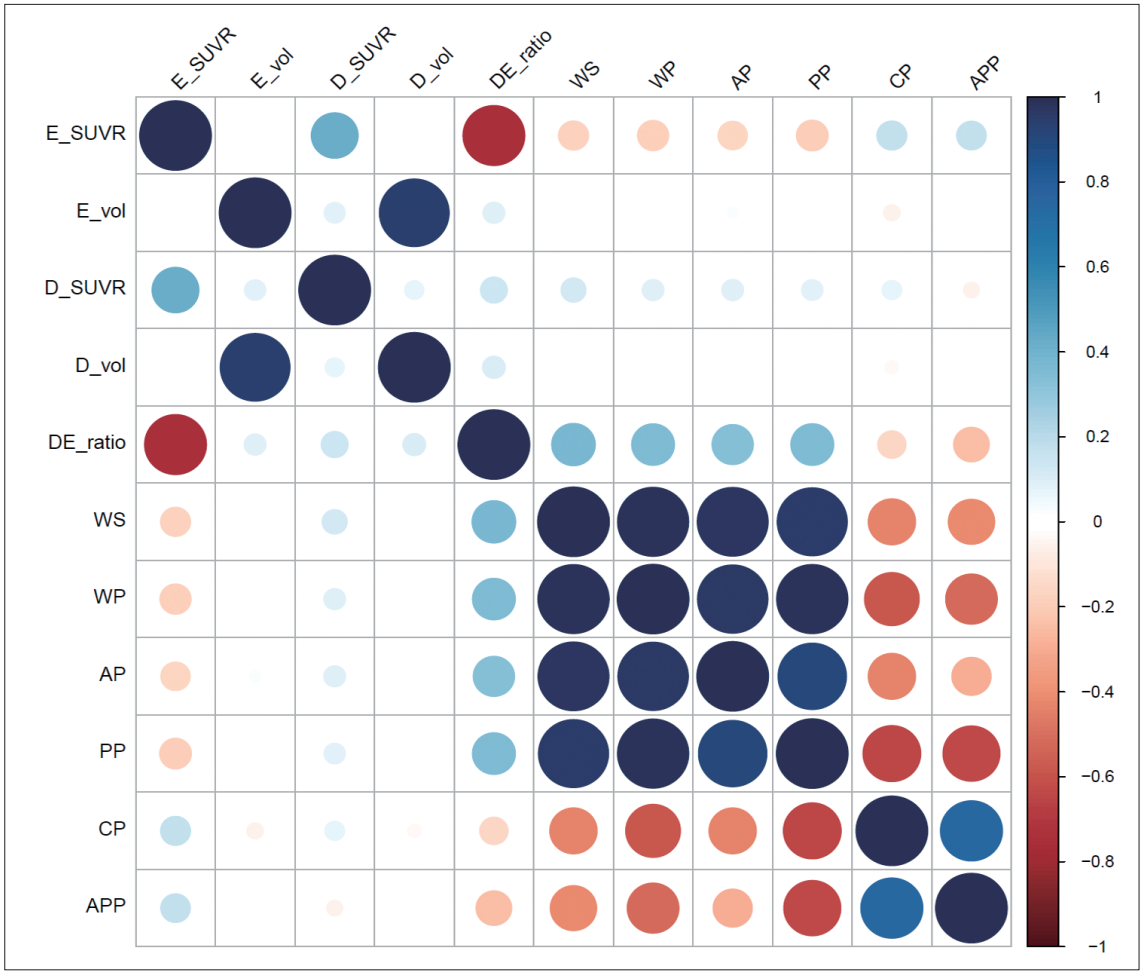

Fig. 2. Correlation plot between the salivary gland standardized uptake value ratio (SUVR) and striatal dopamine transporter (DAT) availability. There was a moderate correlation (Pearson correlation coefficient, $r = 0.37$) between the delayed-to-early ratio of salivary glands and striatal DAT availability in the whole striatum and posterior putamen. E_SUVR = salivary gland SUVmean_ratio in the early phase ^{18}F-FP-CIT positron emission tomography (PET), E_vol = salivary gland volume in the early phase ^{18}F-FP-CIT PET, D_SUVR = salivary gland SUVmean_ratio in the delayed phase ^{18}F-FP-CIT PET, D_vol = salivary gland volume in the delayed ^{18}F-FP-CIT PET, DE_ratio = delayed-to-early ratio, WS = whole striatum, WP = whole putamen, AP = anterior putamen, PP = posterior putamen, CP = the caudate-to-putamen ratio, APP = the anterior putamen-to-posterior putamen ratio

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^{18}F-FP-CIT PET scan compared to non-DD group is due to the "steal effect." However, in the early ^{18}F-FP-CIT PET scan of IPD patients, the striatal uptake reduction was not noticeable, although we have not quantified it, and it is difficult to explain the decrease in the DE_ratio as well as the lack of increase in the delayed PET scan. We would like to demonstrate this issue in future studies through striatal uptake quantification in early ^{18}F-FP-CIT PET scans.

The current study has several limitations. First, we failed to investigate the correlation between clinical diagnosis and salivary gland uptake on ^{18}F-FP-CIT PET. The 59 patients included in the study did not reach the correct clinical diagnosis because there was insufficient follow-up time to perform an accurate clinical diagnosis. Therefore, if the clinical diagnosis of these patients is determined later, the correlation between clinical diagnosis and salivary gland uptake on ^{18}F-FP-CIT PET can be investigated again. Second, we could not identify the clinical symptoms associated with dopaminergic neurodegeneration in the salivary glands of the patients. Therefore, it is necessary to investigate the symptomatic correlation related to changes in salivary gland DAT availability in patients with parkinsonism and the uptake of other organs associated with NMS in ^{18}F-FP-CIT PET. Third, we did not examine changes in salivary gland uptake according to disease severity. In fact, even within the IPD group, various increases or decreases in the DE_ratio of salivary glands were observed in the early scans; this is thought to depend on the degree of progression of the disease. Therefore, analyzing changes in salivary gland uptake through stratification according to the progression of symptoms is essential to confirm the suitability of salivary gland uptake as an early diagnostic biomarker. Finally, the pathological findings of the salivary gland itself were not investigated. For the clinical value of salivary gland uptake shown in PET images, it is essential to demonstrate changes in dopaminergic neurons inside the salivary gland. This needs to be addressed in future research.

In conclusion, parkinsonism patients with an IPD pattern exhibited a significant increase in uptake on early ^{18}F-FP-CIT PET and a decrease in the DE_ratio in the salivary gland. We also observed a moderate correlation between the DE_ratio of salivary gland uptake and striatal DAT availability. Therefore, we cautiously suggest salivary gland uptake of dual-phase ^{18}F-FP-CIT PET as a biomarker for the diagnostic evaluation of parkinsonism.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.0066.

Availability of Data and Material

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

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Seo Young Kang, Ji Young Yun, Bom Sahn Kim. Data curation: Seo Young Kang, Ji Young Yun, Yeon-Koo Kang. Formal analysis: Seo Young Kang, Yeon-Koo Kang. Funding acquisition: Hai-Jeon Yoon, Bom Sahn Kim. Investigation: Seo Young Kang, Ji Young Yun. Methodology: Seo Young Kang. Project administration: Seo Young Kang, Ji Young Yun, Bom Sahn Kim. Resources: Seo Young Kang, Byung Seok Moon, Ji Young Yun. Software: Seo Young Kang. Supervision: Ji Young Yun, Bom Sahn Kim. Validation: Hai-Jeon Yoon, Min Young Yoo, Byung Seok Moon. Visualization: Seo Young Kang. Writing—original draft: Seo Young Kang. Writing—review & editing: all authors.

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