# Dopamine Transporter Imaging Using 99mTc-TRODAT-1 SPECT in Parkinson's Disease

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**Background:** Although the decrease in striatal dopamine transporter (DAT) density has been described in North American, European, and Asian Parkinson's disease (PD) patients, studies on this issue are required in the rest of the world. This study examined the diagnostic utility of DAT imaging in Brazilian PD patients.

**Material/Methods:** Twenty PD patients (13 males, 7 females, median age: 62 years, median age at disease onset: 56 years, median disease duration: 5 years, and median UPDRS-III score: 29) and 9 age- and sex-matched healthy subjects underwent single-photon emission computerized tomography (SPECT) using 99mTc-TRODAT-1.

**Results:** PD patients showed a significant decrease in the striatum, caudate nucleus, and putamen DAT densities compared with data from healthy subjects. Striatal 99mTc-TRODAT-1 bindings had the highest diagnostic accuracy compared to those estimates from caudate nucleus and putamen. For the diagnosis of PD, a striatal 99mTc-TRODAT-1 binding cut-off value of 0.90 was associated with a sensitivity of 100% and a specificity of 89%. There was no significant difference between striatal 99mTc-TRODAT-1 binding values provided by different readers, contrary to 99mTc-TRODAT-1 binding estimates in the caudate nucleus.

**Conclusions:** Striatal DAT imaging using 99mTc-TRODAT-1 can be considered a marker for differentiating PD patients from healthy individuals, with a good interobserver reproducibility.

**MeSH Keywords:** **Molecular Imaging • Parkinson Disease – radionuclide imaging • Tomography, Emission-Computed, Single-Photon**

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## Background

Current advances in molecular imaging techniques, such as single-photon emission computerized tomography (SPECT) and positron emission tomography (PET), have allowed the functional assessment of the nigrostriatal pathway using specific dopamine radiotracers. Studies on PD have revealed that the degeneration of dopaminergic neurons in the substantia nigra leads to a decrease in the density of presynaptic dopaminergic nerve terminals and dopamine transporters (DAT) in the striatum. Striatal DAT imaging disclosed by SPECT and PET has been considered an *in vivo* biomarker of dopaminergic neuron loss in the substantia nigra, and may help to determine the diagnosis and progression of PD [1–4].

Although the decrease in striatal DAT density has been extensively described in North American, European, and Asian PD patients [5–8], few reports concerning DAT imaging are available on the rest of the world population.

The objective of this study was to examine the diagnostic utility of SPECT with $^{99m}$Tc-TRODAT-1 in Brazilian PD patients and healthy controls by means of a cross-sectional study design and receiver operating characteristic (ROC) analysis. Diagnostic accuracies of DAT density in the striatum, caudate nucleus, and putamen, as well as DAT density measurements provided by 2 independent readers, were compared.

## Material and Methods

The present investigation consisted of a prospective, non-interventional, cross-sectional study, approved by the local research ethics committee. All subjects signed the informed consent, and did not receive financial reward for participation.

Twenty patients (13 males and 7 females) with the diagnosis of PD based on the United Kingdom Parkinson's Disease Society Brain Bank criteria [9], were included in the study. Their ages varied from 43 to 76 years, with a median of 62.5 years (54; 67.5). The median age at disease onset was 56.5 years (49; 66.7) (range 38–86 years). The disease duration ranged from 1 to 15 years, with a median of 5 years (2.2; 5.7). Five patients presented with tremor-predominant PD, 9 with akinetic-rigid PD, and 6 with mixed-type PD. One patient was graded as H&Y stage 1, 9 patients as H&Y stage 2, 9 patients as H&Y Stage 3, and 1 patient as H&Y stage 4. The median UPDRS-III score, assessed during the off phase, was 29 (17.5; 35.5).

Nine age- and sex-matched healthy subjects who worked at the hospital formed the control group. There were 6 males and 3 females. Their ages varied from 43 to 57 years, with a median of 51 years (46; 54). All healthy volunteers were interviewed and examined to rule-out clinical abnormalities. No family members of PD patients were recruited for the control group. Table 1 summarizes the participants' clinical profiles.

### Brain SPECT studies

SPECT assessments using $^{99m}$Tc-TRODAT-1, a radiotracer with high selectivity and specificity for the DAT, were performed between January 2008 and December 2009. Antiparkinsonian drugs were withdrawn for at least 12 h before the examinations, although these drugs have not been demonstrated to influence brain DAT density. Subjects were scanned using a double-headed gamma camera equipped with fan beam collimators (Infinia™ Hawkeye® SPECT/CT, GE Healthcare), 4 h following intravenous injection of 814 MBq (±74) of $^{99m}$Tc-TRODAT-1. The TRODAT-1 kits, produced by the Institute of Nuclear Energy Research (Taiwan, ROC), were labeled and controlled before administration, and the radiochemical purity control was verified by solvent extraction method. Images were transferred to a Xeleris workstation

**Table 1.** Clinical profile of Parkinson's disease and healthy subjects.

| | Healthy group | PD group | p |
|---|---|---|---|
| Sex (F/M) | 3/6 (33%/67%) | 7/13 (35%/65%) | >0.05 |
| Age (years) | 51 (46; 54) | 62 (54; 67) | >0.05 |
| Literacy | 13 (10; 15.5) | 5.5 (4; 12) | <0.05 |
| Age at disease onset (years) | | 56 (49; 66) | |
| Disease duration (years) | | 5 (2; 5) | |
| UPDRS III score | | 29 (17; 35) | |
| HY stage | | 2 (2.0; 2.5) | |
| SE | | 90 (80; 90) | |

Data are expressed as median (25th and 75th percentiles); Chi-squared analysis with Yates' correction. F – female; M – male; PD – Parkinson's disease; UPDRS – Unified Parkinson Disease Rating Scale; HY – Hoehn and Yahr scale; SE – Schwab & England scale.

**Table 2.** Comparison between healthy controls and Parkinson's disease patients in terms of molecular imaging variables.

| 99mTc-TRODAT binding | Control group | | | Case group | | | p |
|---|---|---|---|---|---|---|---|
| | 25 | Median | 75 | 25 | Median | 75 | |
| Striatum | 1.03 | 1.18 | 1.41 | 0.47 | 0.58 | 0.67 | <0.05 |
| Caudate nucleus | 1.55 | 1.64 | 2.18 | 0.58 | 0.81 | 0.94 | <0.05 |
| Putamen | 0.92 | 1.22 | 1.36 | 0.34 | 0.45 | 0.50 | <0.05 |

Data are expressed as median and quartiles; Mann-Whitney test; 99mTc-TRODAT – dopamine transporter radioligand.

**Table 3.** 99mTc-TRODAT binding cut-off values in the striatum, caudate nucleus, and putamen in terms of Receiver Operating Characteristic analysis.

| 99mTc-TRODAT binding | | | Group | | p |
|---|---|---|---|---|---|
| | | | Control | Case | |
| Striatum | ≥0.90 | N | 8 | 0 | <0.05 |
| | | % | 89% | 0% | |
| | <0.90 (abnormal) | N | 1 | 20 | |
| | | % | 11% | 100% | |
| Caudate nucleus | ≥1.4 | N | 5 | 0 | <0.05 |
| | | % | 56% | 0% | |
| | <1.4 (abnormal) | N | 4 | 20 | |
| | | % | 44% | 100% | |
| Putamen | ≥0.76 | N | 8 | 3 | <0.05 |
| | | % | 89% | 15% | |
| | <0.76 (abnormal) | N | 1 | 17 | |
| | | % | 11% | 85% | |

Chi-squared analysis with Yates' correction; 99mTc-TRODAT – dopamine transporter radioligand.

(GE Medical Systems) and reconstructed taking into account the anteroposterior commissural line by using a standard back-projection technique with a Butterworth low-pass filter (cut-off frequency 0.45). Photon attenuation correction was performed using Chang's first-order correction method [10].

DAT density was calculated using binding potential from regions of interest (ROI), bilaterally drawn in the striatum, caudate nucleus, putamen, and occipital lobe, by 2 independent readers (P.B.N and I.R.B), blind to subject identity, diagnosis, and group. DAT binding potential was obtained according to the equation: (specific binding – nonspecific binding)/nonspecific binding. Data from occipital lobes were considered as a reference for nonspecific DAT binding.

### Statistical analysis

Descriptive statistical data are given as median values with lower and upper quartiles (25th and 75th percentiles, respectively).

Concerning the DAT binding potentials in the striatum, caudate nucleus, and putamen, the lowest of bilateral measures of each participant was selected for analysis. Data provided by observer 1 were randomly chosen and were considered for descriptive data.

Data distribution was assessed using the Kolmogorov-Smirnov test. For intergroup comparisons, the Mann-Whitney $U$ test was used. Chi-squared analysis with Yates' correction was used when appropriate. The cut-off values for the differentiation between PD and healthy subjects were established by receiver operating characteristic (ROC) curves. Correlations were performed using nonlinear regression analysis. To verify the interobserver reproducibility of the 99mTc-TRODAT-1 SPECT results, DAT binding potentials from both studied groups, provided by the readers 1 and 2, were compared, using the Wilcoxon signed rank test. Differences were considered significant for p values <0.05.

**Table 4.** Accuracy (area under the curve) from Receiver Operating Characteristic curve analysis of molecular imaging variables between healthy controls and Parkinson's disease patients.

| 99mTc-TRODAT binding | Area under the curve | CI < 95% | CI > 95% | p |
|---|---|---|---|---|
| Striatum | 0.998 | 0.982 | 1.001 | <0.05 |
| Caudate nucleus | 0.994 | 0.977 | 1.001 | <0.05 |
| Putamen | 0.983 | 0.945 | 1.001 | <0.05 |

Data are expressed as area under the curve and confidence intervals (CI); Asymptotic significance test; 99mTc-TRODAT – dopamine transporter radioligand.

**Table 5.** Comparison between dopamine transporter density figures provided by independent SPECT readers.

| 99mTc-TRODAT binding | N | Reader 1 | Reader 2 | p |
|---|---|---|---|---|
| Right striatum | 29 | 0.69 (0.50; 1.06) | 0.67 (0.46; 0.98) | 0.475 |
| Left striatum | 29 | 0.64 (0.52; 1.08) | 0.60 (0.48; 1.00) | 0.931 |
| Right caudate nucleus | 29 | 0.97 (0.77; 1.41) | 0.85 (0.60; 1.16) | <0.05 |
| Left caudate nucleus | 29 | 1.02 (0.79; 1.63) | 0.90 (0.61; 1.45) | <0.01 |
| Right putamen | 29 | 0.56 (0.34; 1.02) | 0.61 (0.37; 0.85) | 0.424 |
| Left putamen | 29 | 0.52 (0.35; 0.83) | 0.57 (0.31; 0.94) | 0.489 |

Data are expressed as median (25th and 75th percentiles); Wilcoxon signed rank test; 99mTc-TRODAT – dopamine transporter radioligand.

## Results

PD patients showed a significant decrease in the striatum, caudate nucleus, and putamen DAT densities compared with data from healthy subjects: 0.58 (0.47; 0.67) versus 1.18 (1.03; 1.41) (p<0.05), 0.81 (0.58; 0.94) versus 1.64 (1.55; 2.18) (p<0.05), and 0.45 (0.34; 0.50) versus 1.22 (0.92; 1.36) (p<0.05) (Table 2).

### ROC curve analysis

Regarding striatal DAT density, the cut-off value of 0.90 for indicating PD was associated with a sensitivity of 100% and a specificity of 89% (area under the curve: 0.998; p<0.05). Striatal 99mTc-TRODAT-1 binding <0.90 (defined as presynaptic dopaminergic deficit according to the current study) was found in all PD patients (100%), and in 1 (11%) of 9 healthy subjects (p<0.05). The decrease in striatal 99mTc-TRODAT-1 binding was bilateral in all PD patients.

Concerning caudate nucleus DAT density, the cut-off value of 1.40 for indicating PD was associated with a sensitivity of 100% and a specificity of 56% (area under the curve: 0.994; p<0.05). Caudate nucleus 99mTc-TRODAT-1 binding <1.40, considered as presynaptic dopaminergic deficit in this study, was found in all PD patients (100%), and in 4 (44%) of 9 controls (p<0.05).

Considering putaminal DAT density, the cut-off value of 0.76 for indicating PD was associated with a sensitivity of 85% and a specificity of 89% (area under the curve: 0.983; p<0.05). Putaminal 99mTc-TRODAT-1 binding <0.76 (defined as presynaptic dopaminergic deficit in the present study) was found in 17 PD patients (85%), and in 1 (11%) of 9 control individuals (p<0.05). Tables 3 and 4 summarize ROC curve analysis data.

### Interobserver data comparison

Taking into account the DAT density obtained from all participants, there was no significant difference between measures provided by readers 1 and 2 for the right and left striatum or the putamen. In contrast, a significant difference was found between data measured by readers 1 and 2 regarding the caudate nuclei (Table 5).

## Discussion

This investigation reports data on the diagnostic accuracy and interobserver reproducibility of SPECT using 99mTc-TRODAT-1 for evaluating the DAT densities in the striatum, caudate nucleus, and putamen in PD patients and healthy subjects. Our results proved a significant reduction in the 99mTc-TRODAT-1 binding in the aforementioned basal ganglia structures in PD patients compared with data from control individuals, which are in line with

findings of prior studies [5–7,11,12]. Analysis of ROC curves disclosed that the striatal [99mTc]-TRODAT-1 bindings presented the highest diagnostic accuracy compared to those estimates from the caudate nucleus and putamen. For the diagnosis of PD, striatal [99mTc]-TRODAT-1 binding cut-off value of 0.90 was associated with a sensitivity of 100% and a specificity of 89%. Moreover, there was no significant difference between striatal [99mTc]-TRODAT-1 binding measures provided by different readers, contrary to [99mTc]-TRODAT-1 binding estimates in the caudate nucleus.

It is worth noting that the diagnostic accuracy of striatal [99mTc]-TRODAT-1 binding, reported in the present study, refers to PD patients versus healthy subjects, and not to PD patients versus those with atypical Parkinsonian syndrome. SPECT or PET using DAT radioligands are relevant methods to identify conditions associated with loss of dopaminergic nigrostriatal nerve terminals, such as PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and dementia with Lewy bodies (DLB); this means that DAT imaging can distinguish patients with and without impairment of the nigrostriatal dopaminergic system. Therefore, in cases of parkinsonism and tremor disorders, normal striatal DAT density highlights the possibility of conditions, such as essential tremor (ET), psychogenic, vascular and drug-induced parkinsonism, as well as dystonic tremor [1,3,13]. To differentiate PD from ET, the sensitivity of SPECT using DAT tracers has been reported to be around 90% [14,15]. In a North American multicenter assessment of DAT imaging, SPECT with [123I]-β-CIT was demonstrated to reliably and effectively distinguish between individuals with Parkinson's syndrome (PD and PSP) and without Parkinson's syndrome (healthy controls and ET) [6]. According to the European Association of Nuclear Medicine guidelines [4], [123I]-FP-CIT imaging helps discriminate ET from parkinsonian syndromes related to PD, MSA, and PSP, but DAT imaging is unable to discriminate between the latter 3 conditions. Interestingly, the use of [99mTc]-TRODAT-1 for the evaluation of clinically unclear parkinsonian syndromes has been recently reported, with an accuracy of 80%, a sensitivity of 100%, and a specificity of 70% when it was compared to the definitive clinical diagnosis established about 2 years later [16].

The commonly used SPECT tracers are [123I]-FP-CIT, [123I]-β-CIT, and [99mTc]-TRODAT-1; the latter was selected for this study because [99mTc] provides suitable energy and half-life for imaging, in addition to its wide availability and lower cost, in contrast to the limited availability and higher cost of [123I] [8,12]. Although PET has advantages over SPECT in image resolution and capacity of quantification, the results of [99mTc]-TRODAT-1 SPECT were demonstrated to be comparable with the findings of [18F]-FDOPA PET [11]. Also, PET is more expensive, less widely available, more time-consuming, and more manpower-dependent. The combination of all these factors can make the use of [99mTc]-TRODAT-1 SPECT more feasible in some countries.

The main limitations of the present study are: 1) small sample, particularly of the control group (9 subjects), because it is not easy to convince healthy people to undergo radiation unnecessarily, and 2) lack of a criterion standard *in vivo* examination for definitive diagnosis of PD; the accuracy of clinical diagnosis of PD is only approximately 90% [9].

Recently, transcranial sonography has become a promising tool for the evaluation of movement disorders [17–26]. Future studies must address the utility of striatal DAT density in combination with substantia nigra hyperechogenicity, in addition to a number of non-motor signs of PD, such as depression, olfactory dysfunction, neuropsychological deficits (visuospatial processing and sequential planning), idiopathic rapid-eye-movement (REM) sleep behavior disorder, and pain [27]. At present, there is strong evidence that decreased striatal dopamine transporters uptake and SN hyperechogenicity are risk markers of PD in patients with idiopathic REM sleep behavior disorder [28].

## Conclusions

Striatal DAT imaging with [99mTc]-TRODAT-1 SPECT can be considered a biomarker for differentiating PD patients from healthy individuals, with good interobserver reproducibility. Further studies comparing PD with atypical Parkinson's syndrome are needed.

### Conflict of interest

The authors have no conflict of interest to report.

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