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# Retinal Thickness and Its Interocular Asymmetry Between Parkinson's Disease and Drug-Induced Parkinsonism

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## ABSTRACT




**Background:** Drug-induced parkinsonism (DIP) is common, but diagnosis is challenging. Although dopamine transporter imaging is useful, the cost and inconvenience are problematic, and an easily accessible screening technique is needed. We aimed to determine whether optical coherence tomography (OCT) findings could differentiate DIP from Parkinson's disease (PD).

**Methods:** We investigated 97 de novo PD patients and 27 DIP patients using OCT and [<sup>18</sup>F] N-(3-fluoropropyl)-2b-carbon ethoxy-3b-(4-iodophenyl) nortropane (FP-CIT) positron emission tomography. We compared peripapillary retinal nerve fiber layer thickness (pRNFLT) and macular retinal thickness (mRT) between PD and DIP patients as well as interocular differences in the pRNFLT and the mRT. Asymmetric index (%) for retinal thickness (AIRT) was calculated to measure the interocular differences between pRNFLT and mRT. The correlation between AIRT and total striatal specific/non-specific binding ratio asymmetry index (SNBRAI) was investigated in PD and DIP patients.

**Results:** No significant differences in pRNFLT and mRT values were observed between PD and DIP patients (all *P* values > 0.090). The mean SNBRAI was significantly higher in PD than in DIP (*P* = 0.008) patients; however, AIRT did not differ between PD and DIP patients in pRNFLT and mRT (all *P* values > 0.100). SNBRAI did not correlate with AIRT of pRNFLT and mRT in PD and DIP patients (all *P* values > 0.060).

**Conclusion:** Our study showed no benefit of retinal thickness and interocular asymmetry measurements using OCT for distinguishing PD from DIP in the early stages. Additional investigations are needed for confirmation.

**Keywords:** Drug-Induced Parkinsonism; Parkinson's Disease; Retina; Optical Coherence Tomography; Asymmetry; Dopamine Transporter Imaging

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The authors have no potential conflicts of interest to disclose.

**Data Availability Statement**

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

**Author Contributions**

Conceptualization: Kang SY. Data curation: Suh W, Baek SU, Oh JS, Seo SY, Kang SY. Formal analysis: Suh W, Baek SU, Oh JS, Seo SY, Kim JS, Kang SY. Investigation: Kim MS, Kang SY. Methodology: Suh W, Baek SU, Oh JS, Seo SY, Han YM, Kang SY. Supervision: Kang SY. Writing - original draft: Suh W, Kang SY. Writing - review & editing: Kang SY.

**INTRODUCTION**

Drug-induced parkinsonism (DIP) is the second most common parkinsonism after Parkinson's disease (PD) and the most common drug-induced movement disorder.<sup>1,2</sup> The prevalence of DIP has increased in Korea.<sup>3</sup> DIP is usually considered reversible by discontinuing offending drugs. However, because DIP is sometimes clinically indistinguishable from PD, diagnosis is challenging.<sup>4-7</sup>

Because of nigrostriatal dopaminergic dysfunction in PD, dopamine transporter (DAT) imaging can be used to assess and differentiate DIP from PD.<sup>8</sup> Despite the clinical benefit, DAT applicability may be limited due to cost, radiation hazard, long waiting time from isotope injection to start of imaging, and the necessity of special equipment such as positron emission tomography (PET) or single photon emission computed tomography.<sup>4</sup> Therefore, another discriminating method is needed.

Optical coherence tomography (OCT) is a non-invasive and non-contact transpupillary imaging technology providing high-resolution, cross-sectional images of the retina.<sup>9</sup> OCT advantages include low cost, no radiation hazards, and easy access.<sup>10</sup> OCT measurements were suggested as an imaging biomarker for PD because the retina can reflect brain pathology and PD-related retinal degeneration.<sup>10</sup> Although inconsistent results have been found,<sup>11,12</sup> retinal thinning in PD<sup>13,14</sup> and its correlation with disease duration and motor severity have been reported.<sup>14,15</sup>

Asymmetric motor symptoms are considered a typical feature in PD and are correlated with DAT imaging. This asymmetry correlated with interocular asymmetry of OCT findings in our previous study.<sup>9</sup> Although 13–48% of DIP patients reportedly had asymmetric onset, DIP is classically described as symmetric parkinsonism.<sup>1,16</sup> Therefore, we hypothesized that asymmetric interocular OCT findings would be more frequent in PD than in DIP subjects.

Because DIP is reversible, we hypothesized that there would be no retinal degeneration in DIP; therefore, OCT could be used to differentiate DIP from PD. The aim of this study was to explore difference in OCT imaging between DIP and PD. Because asymmetric motor symptoms are considered a typical feature in PD and are correlated with DAT imaging, we also compared the interocular asymmetry of OCT imaging between DIP and PD patients. Furthermore, we evaluated the correlation of interocular asymmetry with asymmetry of DAT findings in PD and DIP.

**METHODS****Patients**

We consecutively examined 97 patients with de novo PD and 27 DIP patients who visited our hospital from 2012 to 2021. PD was diagnosed according to the UK Brain Bank criteria.<sup>17</sup> DIP was diagnosed based on the following criteria<sup>4,18</sup>: 1) the presence of at least two of the four cardinal symptoms of parkinsonism, 2) absence of parkinsonism prior to exposure to offending drugs, 3) resolution of or significant improvement in parkinsonism within 12 months after withdrawal of offending drugs, 4) no alternative explanation for parkinsonism, and 5) normal symmetric DAT binding in the caudate nucleus and putamen on <sup>18</sup>F-fluorinated-N-3-fluoropropyl-2-b-carboxymethoxy-3-b-(4-iodophenyl) nortropane

( $^{18}\text{F}$ -FP-CIT) PET. We collected Hoehn and Yahr stage, the Unified Parkinson's Disease Rating Scale (UPDRS) part I–III, results of the Korean version of the Mini-Mental State Examination (K-MMSE) and the Korean version of the Montreal Cognitive Assessment (K-MoCA), education, disease duration, and Beck depression inventory (BDI) at diagnosis. The exclusion criteria were dementia (K-MMSE < 2.5th percentile for age and educational-appropriate norm); comorbid ophthalmic pathologies capable of affecting retinal thickness such as glaucoma, age-related macular degeneration, diabetic retinopathy, retinal vein or artery occlusion, epiretinal membrane, macular hole, and high myopia (defined as spherical equivalent > -6.0 diopters or glaucomatous optic neuropathies); media opacity impeding acquisition of high-quality OCT images; or inability to undergo OCT examination. Eyes that had undergone ocular surgery other than cataract extraction were also excluded. Glaucomatous eyes were excluded based on intraocular pressure > 21 mmHg, narrow anterior chamber angles at gonioscopy, cup-to-disc ratio > 0.6, and glaucomatous appearance of the optic discs (defined as fellow eye asymmetry in cup-to-disc ratio > 0.2, neuroretinal rim thinning, disc hemorrhages, or retinal nerve fiber layer defects).

### Ophthalmic evaluation

All participants underwent complete ophthalmologic examinations as previously described.<sup>9</sup> We obtained peripapillary retinal nerve fiber layer thickness (pRNFLT) and macular retinal thickness (mRT) using spectral-domain optical coherence tomography (SD-OCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany). The automatic eye-tracking technology maintains fixation on the retina. Only well-centered images with a signal strength > 20 dB were used for analysis. The details of SD-OCT measurements were previously described as undermentioned.<sup>9</sup> The pRNFLT was measured around the optic disc with 16 averaged consecutive circular B-scans (diameter of 3.5 mm, 768 A-scans). The pRNFLT (from the inner margin of the internal limiting membrane to the outer margin of the RNFL) was automatically segmented using Spectralis software version 5.3.3.0. pRNFLT data were collected on the RNFL in each of the superior, inferior, temporal, and nasal sectors. We acquired the mRT topographic maps *via* raster images of 31 high-resolution B scans covering a 30° × 25° area centered on the fovea. We defined the mRT as the distance between the surface line of the NFL and hyporeflective line above the retinal pigment epithelium with the automatic segmentation algorithms of the Spectralis software. Spectralis SD-OCT measured the macular thickness in 1, 3, and 6 mm circles. These were divided into 9 regions: a center circle of 500 μm radius and inner and outer rings, each divided into 4 quadrants based on the Early Treatment of Diabetic Retinopathy Study. The mRT values of the central, superior inner, inferior inner, temporal inner, nasal inner, superior outer, inferior outer, temporal outer, and nasal outer regions were reported. The mRT of each superior, inferior, nasal, and temporal area was applied to the analysis of the average value of the measured mRT at the 3 and 6 mm circles: superior 3 mm + superior 6 mm = mean superior mRT. We used the same method to calculate the mean inferior, temporal, and nasal mRT.

We calculated interocular differences of pRNFLT and mRT in both eyes, as in a previous study.<sup>9</sup> Asymmetric index (%) for retinal thickness (AIRT) was calculated using the following equation:  $(a-b/a+b) \times 2 \times 100$ , where a represents the more affected side of the eye and b represents the less affected side of the eye.

### Quantitative analysis of $^{18}\text{F}$ -FP-CIT PET

$^{18}\text{F}$ -FP-CIT PET images were obtained 180 minutes after injection of  $^{18}\text{F}$ -FP-CIT (7 mCi; 259 MBq) with a Biograph mCT S (64)-3R PET/CT scanner (Siemens Medical Solutions

USA, Inc., Malvern, PA, USA) with three-dimensional resolution of 4.42 mm full width at half-maximum. Quantitative analyses were done following previously described methods.<sup>19,20</sup> Image processing was executed using SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, London, UK) with MATLAB 2018a for Windows (MathWorks, Natick, MA, USA). We defined volumes of interest (VOIs) according to an FP-CIT PET template in standard space of the Montreal Neurology Institute (MNI) template. All reconstructed PET images were spatially normalized to Talairach space with a standard <sup>18</sup>F-FP-CIT PET template produced from <sup>18</sup>F-FP-CIT PET and T-1 MR images of 13 normal controls. As in a previous study, 12 VOIs (left and right ventral striatum, anterior/posterior caudate, anterior/posterior/ventral putamen) of bilateral striatal subregions and one occipital VOI were drawn on a co-registered spatially normalized single T-1 MR and <sup>18</sup>F-FP-CIT PET template image on MRicro version 1.37 (Chris Rorden, Columbia, SC, USA).<sup>20</sup> The striatum was segmented into the anterior caudate, posterior caudate, ventral striatum, anterior putamen, and posterior putamen.<sup>21</sup>

We determined the VOI for the ventral striatum by previously defined criteria,<sup>21</sup> and the boundary between the anterior and posterior putamen as the anterior commissure of the coronal plane. The outer boundaries of the striatal subregions were visually set by the characteristic dense grey signal of the striatum, readily distinguishing these subregions from adjacent structures. The anterior/posterior division of putamen was set by the anterior commissure in the MNI template space. A minor translation in our in-house editing software called ANTIQUE were used for the adjustment of the VOI.<sup>22</sup> We calculated DAT activity with the specific/non-specific binding ratio (SNBR), defined as mean standardized uptake value of the striatal subregions VOI – mean standardized uptake value of the occipital VOI/mean standardized uptake value of the occipital VOI.<sup>23</sup>

We calculated the total striatal SNBR asymmetry index (SNBRAI) as described in a previous study<sup>24</sup> using the following equation:  $[(R-L/R+L)] \times 2 \times 100$ , where R represents the striatum contralateral to the most affected side of the body, and L represents the striatum ipsilateral to the most affected side of the body.

### Statistical analysis

Data were expressed as mean  $\pm$  standard deviation. Demographic and clinical variables among PD and DIP were compared. The chi-square test was used for categorical variables and unpaired *t*-test for continuous variables. To use both eyes of the same participant, OCT parameters between the two groups were compared using generalized estimating equation, a statistical method that compensates for inter-eye correlation in the same participant.<sup>25</sup> We also adjusted the effect of age, disease duration, K-MMSE, education years, BDI, UPDRS part II and III. We chose these parameters, because they showed the statistical differences between two groups or possibly would affect the results, although there were no significant differences. We did not adjust the effect of K-MoCA and UPDRS part I, because these two variables were considered to be overlapped because they reflected the same clinical domain as other clinical variables (i.e., cognition and mood including depression). In the case of the AIRT of OCT parameters, PD and DIP patient comparisons were analyzed using one-way analysis of covariance (ANCOVA) for data with normal distribution and the ranked ANCOVA for data with non-normal distribution after adjusting for age and K-MMSE. Normality test was performed using skewness and kurtosis, and the acceptable values were  $< 3$  and  $< 10$ , respectively.<sup>26</sup> We assessed the relationship between AIRT and SNBRAI using Spearman ranked correlation. A *P* value  $< 0.0125$  (0.05/4) or  $< 0.0056$  (0.05/9) was considered significant after multiple

comparison corrections for correlation analysis with pRNFLT or mRT, respectively. Otherwise, a  $P$  value  $< 0.05$  was considered statistically significant. Statistical analysis was performed using IBM SPSS 27 statistics (IBM Corp., Armonk, NY, USA).

### Ethics statement

The Institutional Review Board (IRB) of Hallym University Dongtan Sacred Heart Hospital approved this study (IRB Number: 2022-03-006). All methods were performed in accordance with the Declaration of Helsinki and followed relevant guidelines and regulations. Informed consent was obtained from all participants.

## RESULTS

The patient demographics and clinical features are summarized in **Table 1**. Significant differences were found in age at examination, K-MMSE, K-MoCA, BDI, and UPDRS part I scores between PD and DIP patients. The mean age at examination was higher ( $P = 0.000$ ), the K-MMSE and K-MoCA scores lower ( $P = 0.007$ ,  $0.001$ , respectively), and BDI and UPDRS part I values higher ( $P = 0.013$ ,  $0.005$ , respectively) in the DIP group.

We observed no difference between PD and DIP patients in pRNFLT or mRT measurements (all  $P$  values  $> 0.09$ , **Table 2**). The demographics and clinical features of patients included in the asymmetric index analyses are described in **Supplementary Table 1**. Only patients with binocular examination data were included. The mean SNBRAI value was significantly higher in PD ( $12.4 \pm 9.0$ ) than in DIP ( $5.8 \pm 2.5$ ;  $F = 7.390$ ,  $P = 0.008$ ) patients; however, difference was not observed in AIRT in pRNFLT and mRT (all  $P$  values  $> 0.100$ , **Table 3**). We did not find any correlation of SNBRAI with AIRT of pRNFLT or mRT (all  $P$  values  $> 0.060$ , **Supplementary Table 2**).

## DISCUSSION

Our results did not show any significant difference in retinal thickness or interocular asymmetry of OCT measurements between PD and DIP patients. Therefore, OCT measurements might not be a proper screening tool to differentiate early stages of PD from DIP.

**Table 1.** Patients' demographic and clinical characteristics

Characteristics	PD (n = 97)	DIP (n = 27)	P value*
Age, yr	66.2 $\pm$ 10.1	73.3 $\pm$ 7.2	0.000
Women, No. (%)	60 (61.9)	17 (63.0)	1.000
Disease duration, yr	1.5 $\pm$ 1.6	1.9 $\pm$ 3.1	0.546
K-MMSE	26.1 $\pm$ 3.5	23.9 $\pm$ 4.4	0.007
K-MoCA	21.5 $\pm$ 5.2	17.5 $\pm$ 6.2	0.001
Education, yr	9.3 $\pm$ 5.1	7.2 $\pm$ 5.6	0.060
BDI	15.6 $\pm$ 10.4	21.4 $\pm$ 10.6	0.013
H&Y stage	2.2 $\pm$ 0.5	2.3 $\pm$ 0.6	0.337
UPDRS I	2.9 $\pm$ 1.9	4.5 $\pm$ 2.6	0.005
UPDRS II	8.9 $\pm$ 4.2	11.0 $\pm$ 6.4	0.133
UPDRS III	32.8 $\pm$ 10.8	35.3 $\pm$ 13.8	0.380

Values are means  $\pm$  standard deviation except where indicated.

PD = Parkinson's disease, DIP = drug-induced parkinsonism, K-MMSE = Korean version of the Mini-Mental State Examination, K-MoCA = Korean version of the Montreal Cognitive Assessment, BDI = Beck Depression Inventory, H&Y stage = Hoehn and Yahr stage, UPDRS = Unified Parkinson's Disease Rating Scale.

\* $P < 0.05$  indicates significant differences.

**Table 2.** Retina thickness between PD and DIP

Retina thickness, $\mu\text{m}$	PD (n = 97)	DIP (n = 27)	P value*
Peripapillary retina nerve fiber layer thickness			
Superior	119.0 $\pm$ 23.6	115.7 $\pm$ 22.8	0.931
Inferior	125.2 $\pm$ 24.3	124.8 $\pm$ 21.3	0.962
Temporal	75.9 $\pm$ 14.8	75.7 $\pm$ 12.3	0.593
Nasal	73.9 $\pm$ 17.2	69.0 $\pm$ 11.8	0.088
Average	98.5 $\pm$ 14.5	96.3 $\pm$ 13.1	0.812
Macular retina thickness			
Foveal	262.3 $\pm$ 24.4	279.0 $\pm$ 60.0	0.444
Inner superior	332.3 $\pm$ 18.9	332.4 $\pm$ 29.7	0.894
Outer superior	298.9 $\pm$ 35.1	292.1 $\pm$ 49.9	0.948
Inner inferior	326.1 $\pm$ 41.6	332.1 $\pm$ 65.5	0.649
Outer inferior	292.2 $\pm$ 31.6	286.7 $\pm$ 25.0	0.110
Inner temporal	323.9 $\pm$ 19.8	325.1 $\pm$ 49.5	0.496
Outer temporal	280.9 $\pm$ 16.6	285.0 $\pm$ 33.7	0.348
Inner nasal	335.6 $\pm$ 20.1	341.3 $\pm$ 50.4	0.668
Outer nasal	307.5 $\pm$ 17.7	310.3 $\pm$ 29.5	0.670
Average	306.6 $\pm$ 17.1	309.4 $\pm$ 33.2	0.926

Values are means  $\pm$  standard deviation except where indicated.

PD = Parkinson's disease, DIP = drug-induced parkinsonism.

\*P < 0.05 indicates significant differences.

**Table 3.** Interocular difference of retina thickness

Asymmetric index (%)	PD (n = 78)	DIP (n = 23)	P value*
Peripapillary retina nerve fiber layer thickness			
Superior	12.3 $\pm$ 20.4	10.0 $\pm$ 7.0	0.179
Inferior	12.3 $\pm$ 19.1	9.1 $\pm$ 9.7	0.253
Temporal	12.6 $\pm$ 14.2	8.8 $\pm$ 9.2	0.364
Nasal	15.6 $\pm$ 15.8	11.2 $\pm$ 10.7	0.137
Average	7.5 $\pm$ 11.2	5.2 $\pm$ 3.6	0.214
Macular retina thickness			
Foveal	6.3 $\pm$ 9.4	13.2 $\pm$ 18.9	0.544
Inner superior	3.5 $\pm$ 4.7	3.4 $\pm$ 5.1	0.677
Outer superior	5.5 $\pm$ 18.7	7.6 $\pm$ 21.7	0.138
Inner inferior	5.4 $\pm$ 18.5	7.3 $\pm$ 13.9	0.792
Outer inferior	5.1 $\pm$ 7.6	12.6 $\pm$ 34.0	0.401
Inner temporal	2.7 $\pm$ 4.1	13.7 $\pm$ 34.5	0.991
Outer temporal	3.0 $\pm$ 2.9	6.2 $\pm$ 9.4	0.946
Inner nasal	3.3 $\pm$ 4.8	6.5 $\pm$ 11.8	0.145
Outer nasal	2.9 $\pm$ 3.7	5.2 $\pm$ 7.5	0.150
Average	2.7 $\pm$ 3.6	5.8 $\pm$ 8.3	0.430

Values are means  $\pm$  standard deviation except where indicated.

Asymmetric index (%) was  $[(a-b)/(a+b)] \times 2 \times 100$  (for retinal thickness, a = more affected side of eye, b = less affected side of eye).

PD = Parkinson's disease, DIP = drug-induced parkinsonism.

\*P < 0.05 indicates significant differences.

The exact reason for the negative result obtained is unknown. In previous studies, variable results were also reported, although reduced retinal thickness in PD patients was frequently observed.<sup>27</sup> These discrepancies may be due to heterogeneous PD populations,<sup>28,29</sup> disease duration,<sup>28</sup> different states of disease,<sup>10,29</sup> different PD phenotype such as postural instability-gait disorder<sup>10</sup> or cognition,<sup>30</sup> and differences in imaging technologies.<sup>29</sup> The duration of PD in previous studies was  $6.7 \pm 3.6$  years (ranging from 0.7–18.4 years), longer than in our study. Although there was a discrepancy in the correlation between motor severity and retinal thickness, retinal abnormality appeared more frequently in advanced PD.<sup>10</sup> All PD patients in the present study were de novo, in the early stages of PD without dementia. Because our hospital is not a tertiary referral hospital, patients in the early stage of PD were more likely to be included.



Heterogeneous DIP populations and their causative drugs (**Supplementary Table 3**) might be another reason for the negative results because retinal structural changes were reported in psychiatric disorders such as schizophrenia and major depression.<sup>31,32</sup> The DIP patients in the present study had depression, delusion, gastrointestinal disorders, and cardiovascular disease. In addition, antipsychotics were reported to cause retinal changes.<sup>33-35</sup>

Although psychiatric disorders or antipsychotics might be influential in the retina, we assumed these influences would be symmetric because the effect of the drugs is systemic and the clinical manifestations of DIP are generally bilateral, symmetric parkinsonism.<sup>1</sup> The interocular asymmetry in PD was previously reported<sup>36</sup> and correlated with motor asymmetry.<sup>9</sup> Therefore, we hypothesized that the interocular asymmetric index might discriminate between PD and DIP patients; however, this hypothesis was not proven in this study. Furthermore, because the SNBRAI values did not correlate with the AIRT in PD patients, the clinical significance of the AIRT as a screening method should be further investigated.

The present study had several limitations. First, healthy controls were not included. It would be of interest to see how DIP differ from healthy controls when then compared to PD patients next. Second, the number of DIP patients was relatively small. However, the advantages of the study were that only de novo PD patients were included and the studied patients had no dementia or other comorbid ophthalmic pathologies. In addition, the DAT imaging data were included in the analysis. Third, age might affect our results, although we adjusted the effect of age for our analysis because DIP patients were much older than de novo PD patients. A recent population-based large study with Asian ethnic groups showed that most of the retinal layers decreased with age.<sup>37</sup>

In conclusion, the retinal thickness and the interocular asymmetry measurements do not appear useful for distinguishing PD from DIP in the early stages, and further studies with age/gender-matched de novo PD patients are needed for confirmation.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Patients' demographic and clinical characteristics<sup>a</sup>

[Click here to view](#)

### Supplementary Table 2

Spearman correlation analysis of interocular difference of retina thickness and total striatal binding potential

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### Supplementary Table 3

Medications in drug-induced parkinsonism

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## REFERENCES

1. Shin HW, Chung SJ. Drug-induced parkinsonism. *J Clin Neurol* 2012;8(1):15-21.  
[PUBMED](#) | [CROSSREF](#)
2. Yoo HS, Bak Y, Chung SJ, Lee Y, Ye BS, Sohn YH, et al. Impaired functional connectivity of sensorimotor network predicts recovery in drug-induced parkinsonism. *Parkinsonism Relat Disord* 2020;74:16-21.  
[PUBMED](#) | [CROSSREF](#)
3. Byun JH, Cho H, Kim YJ, Kim JS, Baik JS, Jang S, et al. Trends in the prevalence of drug-induced parkinsonism in Korea. *Yonsei Med J* 2019;60(8):760-7.  
[PUBMED](#) | [CROSSREF](#)
4. Sung YH, Noh Y, Lee J, Kim EY. Drug-induced parkinsonism versus idiopathic Parkinson disease: utility of nigrosome 1 with 3-T imaging. *Radiology* 2016;279(3):849-58.  
[PUBMED](#) | [CROSSREF](#)
5. Kim JS, Ryu DW, Oh JH, Lee YH, Park SJ, Jeon K, et al. Cardiovascular autonomic dysfunction in patients with drug-induced parkinsonism. *J Clin Neurol* 2017;13(1):15-20.  
[PUBMED](#) | [CROSSREF](#)
6. Koh SB, Jo YH, Kim BJ, Park MK, Park KW, Lee DH. Clinical characteristics of drug-induced parkinsonism. *J Korean Geriatr Soc* 2001;5(1):43-9.
7. Lee SH, Kim HK, Lee YG, Lyoo CH, Ahn SJ, Lee MS. Clinical features indicating nigrostriatal dopaminergic degeneration in drug-induced parkinsonism. *J Mov Disord* 2017;10(1):35-9.  
[PUBMED](#) | [CROSSREF](#)
8. Kim JM, Kim YK, Kim SE, Jeon BS. Clinical usefulness of dopamine transporter imaging. *Nucl Med Mol Imaging* 2007;41(2):152-7.
9. Baek SU, Kang SY, Kwon S, Park IW, Suh W. Motor asymmetry and interocular retinal thickness in Parkinson's disease. *J Korean Med Sci* 2021;36(6):e50.  
[PUBMED](#) | [CROSSREF](#)
10. Lee JY, Martin-Bastida A, Murueta-Goyena A, Gabilondo I, Cuenca N, Piccini P, et al. Multimodal brain and retinal imaging of dopaminergic degeneration in Parkinson disease. *Nat Rev Neurol* 2022;18(4):203-20.  
[PUBMED](#) | [CROSSREF](#)
11. Kaur M, Saxena R, Singh D, Behari M, Sharma P, Menon V. Correlation between structural and functional retinal changes in Parkinson disease. *J Neuroophthalmol* 2015;35(3):254-8.  
[PUBMED](#) | [CROSSREF](#)
12. Lee JY, Kim JM, Ahn J, Kim HJ, Jeon BS, Kim TW. Retinal nerve fiber layer thickness and visual hallucinations in Parkinson's disease. *Mov Disord* 2014;29(1):61-7.  
[PUBMED](#) | [CROSSREF](#)
13. Aaker GD, Myung JS, Ehrlich JR, Mohammed M, Henschcliff C, Kiss S. Detection of retinal changes in Parkinson's disease with spectral-domain optical coherence tomography. *Clin Ophthalmol* 2010;4:1427-32.  
[PUBMED](#) | [CROSSREF](#)
14. Altıntaş O, İşeri P, Ozkan B, Çağlar Y. Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease. *Doc Ophthalmol* 2008;116(2):137-46.  
[PUBMED](#) | [CROSSREF](#)
15. Jiménez B, Ascaso FJ, Cristóbal JA, López del Val J. Development of a prediction formula of Parkinson disease severity by optical coherence tomography. *Mov Disord* 2014;29(1):68-74.  
[PUBMED](#) | [CROSSREF](#)
16. Pieters LE, Bakker PR, van Harten PN. Asymmetric drug-induced parkinsonism and psychopathology: a prospective naturalistic study in long-stay psychiatric patients. *Front Psychiatry* 2018;9:18.  
[PUBMED](#) | [CROSSREF](#)
17. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. *Neurology* 1992;42(6):1142-6.  
[PUBMED](#) | [CROSSREF](#)
18. Jiménez-Jiménez FJ, Ortí-Pareja M, Ayuso-Peralta L, Gasalla T, Cabrera-Valdivia F, Vaquero A, et al. Drug-induced parkinsonism in a movement disorders unit: a four-year survey. *Parkinsonism Relat Disord* 1996;2(3):145-9.  
[PUBMED](#) | [CROSSREF](#)
19. Lee E, Lee JE, Yoo K, Hong JY, Oh J, Sunwoo MK, et al. Neural correlates of progressive reduction of bradykinesia in de novo Parkinson's disease. *Parkinsonism Relat Disord* 2014;20(12):1376-81.  
[PUBMED](#) | [CROSSREF](#)



20. Oh M, Kim JS, Kim JY, Shin KH, Park SH, Kim HO, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. *J Nucl Med* 2012;53(3):399-406.  
[PUBMED](#) | [CROSSREF](#)
21. Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, et al. Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D<sub>2</sub> receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* 2001;21(9):1034-57.  
[PUBMED](#) | [CROSSREF](#)
22. Oh JS, Oh M, Chung SJ, Kim JS. Cerebellum-specific 18F-FDG PET analysis for the detection of subregional glucose metabolism changes in spinocerebellar ataxia. *Neuroreport* 2014;25(15):1198-202.  
[PUBMED](#) | [CROSSREF](#)
23. Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 2007;27(9):1533-9.  
[PUBMED](#) | [CROSSREF](#)
24. Zijlmans J, Evans A, Fontes F, Katzenschlager R, Gacinovic S, Lees AJ, et al. [<sup>123</sup>I] FP-CIT SPECT study in vascular parkinsonism and Parkinson's disease. *Mov Disord* 2007;22(9):1278-85.  
[PUBMED](#) | [CROSSREF](#)
25. Mello LG, Bissoli LB, Saraiva FP, Maia RP, Monteiro ML. retinal layers and choroid measurements in Parkinson's disease with or without pramipexole treatment. *Mov Disord* 2020;35(12):2357-9.  
[PUBMED](#) | [CROSSREF](#)
26. Kline RB. *Principles and Practice of Structural Equation Modeling*. 3rd ed. New York, NY, USA: Guilford Press; 2011.
27. Zhou WC, Tao JX, Li J. Optical coherence tomography measurements as potential imaging biomarkers for Parkinson's disease: a systematic review and meta-analysis. *Eur J Neurol* 2021;28(3):763-74.  
[PUBMED](#) | [CROSSREF](#)
28. Alkabie S, Lange A, Manogaran P, Stoessl AJ, Costello F, Barton JJ. Optical coherence tomography of patients with Parkinson's disease and progressive supranuclear palsy. *Clin Neurol Neurosurg* 2020;189:105635.  
[PUBMED](#) | [CROSSREF](#)
29. Tsironi EE, Dastiridou A, Katsanos A, Dardiotis E, Veliki S, Patramani G, et al. Perimetric and retinal nerve fiber layer findings in patients with Parkinson's disease. *BMC Ophthalmol* 2012;12(1):54.  
[PUBMED](#) | [CROSSREF](#)
30. Pillai JA, Bermel R, Bonner-Jackson A, Rae-Grant A, Fernandez H, Bena J, et al. Retinal nerve fiber layer thinning in Alzheimer's disease: a case-control study in comparison to normal aging, Parkinson's disease, and non-Alzheimer's dementia. *Am J Alzheimers Dis Other Dement* 2016;31(5):430-6.  
[PUBMED](#) | [CROSSREF](#)
31. Clémence-Fau M, Schwan R, Angioi-Duprez K, Laprévote V, Schwitzer T. Retinal structural changes in mood disorders: the optical coherence tomography to better understand physiopathology? *Prog Neuropsychopharmacol Biol Psychiatry* 2021;108:110080.  
[PUBMED](#) | [CROSSREF](#)
32. Jerotic S, Ignjatovic Z, Silverstein SM, Maric NP. Structural imaging of the retina in psychosis spectrum disorders: current status and perspectives. *Curr Opin Psychiatry* 2020;33(5):476-83.  
[PUBMED](#) | [CROSSREF](#)
33. Faure C, Audo I, Zeitze C, Letessier JB, Robert MP. Aripiprazole-induced chorioretinopathy: multimodal imaging and electrophysiological features. *Doc Ophthalmol* 2015;131(1):35-41.  
[PUBMED](#) | [CROSSREF](#)
34. Fornaro P, Calabria G, Corallo G, Picotti GB. Pathogenesis of degenerative retinopathies induced by thioridazine and other antipsychotics: a dopamine hypothesis. *Doc Ophthalmol* 2002;105(1):41-9.  
[PUBMED](#) | [CROSSREF](#)
35. Zhuo C, Ji F, Xiao B, Lin X, Chen C, Jiang D, et al. Antipsychotic agent-induced deterioration of the visual system in first-episode untreated patients with schizophrenia maybe self-limited: findings from a secondary small sample follow-up study based on a pilot follow-up study. *Psychiatry Res* 2020;286:112906.  
[PUBMED](#) | [CROSSREF](#)
36. Shrier EM, Adam CR, Spund B, Glazman S, Bodis-Wollner I. Interocular asymmetry of foveal thickness in Parkinson disease. *J Ophthalmol* 2012;2012:728457.  
[PUBMED](#) | [CROSSREF](#)
37. Chua J, Tham YC, Tan B, Devarajan K, Schwarzhans F, Gan A, et al. Age-related changes of individual macular retinal layers among Asians. *Sci Rep* 2019;9(1):20352.  
[PUBMED](#) | [CROSSREF](#)