ORIGINAL ARTICLE

Parkinson's disease and thyroid dysfunction: Effects on severity and risk of cognitive impairment

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ABSTRACT

Keywords: UK Parkinson's Disease Society Brain Bank Diagnostic Criteria, Thyroid hormones, Antithyroid Antibodies, and Cognitive Functions

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Background: Parkinson's disease is a neurological condition and it is considered a serious public health issue. **Objective:** The study objective was to assess thyroid function in people with Parkinson's disease and explain how it relates to the degree and likelihood of cognitive impairment. **Methods:** From June 2021 to July 2022, forty Parkinson`s disease patients were recruited from our University Hospitals who had been diagnosed consecutively using the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria. A complete neurological examination and history collection were performed on the patients in order to estimate the severity of their Parkinson's disease Using the Unified Parkinson's Disease Rating Scale (UPDRS). Their mental capacity was tested using The Mini-mental State Examination (MMSE) and The Montreal Cognitive Assessment (MoCA). **Results:** According to our investigation, all thyroid measures were within normal bounds. We found a negligible connection between the UPDRS score and the levels of antithyroid antibodies and thyroid hormones. Our patients had mild cognitive impairment, according to reports. The levels of thyroid stimulating hormone and cognitive performance were positively correlated. **Conclusion**: we believe that individuals exhibiting deteriorating symptoms that cannot be attributed to disease progression or resistance to medication modification should have their thyroid function checked.

INTRODUCTION

After Alzheimer's disease, Parkinson's disease (PD) is regarded as the second most prevalent neurodegenerative ailment worldwide [1]. It results in cognition impairment, depression, and motor dysfunction including bradykinesia, tremor, stiffness, and postural instability [2].

The thyroid hormone is a key regulator of neurotransmission and controls neurodevelopment [3]. As well as neurodegenerative illnesses like Parkinson's disease (PD), hypothyroidism has been linked to gastrointestinal, musculoskeletal, cardiovascular, and neurosensory disorders [4,5].

Do persons who have Parkinson's disease have a higher risk of thyroid disorders than those who do not? The reason for the connection is currently under investigation. Numerous researchers speculate that it could be related to the fact that thyroid hormone synthesis and dopamine creation share a lot of the same biochemical precursors and are connected by certain enzymatic and hormonal signalling activities [6,7]. Parkinson's disease subtypes are associated with aberrant thyroid hormone levels, which, if untreated, can exacerbate symptoms.

Epidemiological data have indicated a connection between PD and hypothyroidism [8]. Similar genes contribute to both diseases, and epidemiological data links thyroid disorders with Parkinson's disease. This suggests that the two diseases may have a same pathophysiological mechanism [9].

How thyroid dysfunction might increase the risk of any neurodegenerative condition is yet unclear. In fact, a number of observational studies have examined the link between PD and thyroid dysfunction, with contradictory findings [8,10,11].

The objective of the current study was to assess thyroid function in Parkinson's disease patients and determine its relationship to the degree and likelihood of cognitive impairment.

PATIENTS AND METHODS

1- Study Plan:

This research was a cross-sectional observational study that took place between July 2021 and June 2022 on 40 Parkinson's disease patients.

2- Study Subjects:

The patients, whose ages varied from 45 to 85 years, with a mean age of 62.8 +/- 9.5 years, were chosen from the Neuropsychiatric Department's outpatient clinics at our university hospitals between July 2021 and June 2022.

Inclusion Measures:

Patients qualified for the trial if they met the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria for PD diagnosis (Huges et al 1992).

Exclusion Measures:

Patients with Parkinson's disease (PD) have secondary parkinsonism (caused by brain tumors or a history of previous cerebrovascular strokes), disturbed consciousness, psychosis, and medical issues such as renal failure, liver cell failure, respiratory failure, endocrine impairment, autoimmune diseases, and history of acute or chronic inflammatory diseases.

3- Study tools

All patients underwent the following assessment:

A. Clinical assessment

Complete medical and neurological examination during which age, sex, disease period, and presence of comorbidities (such as smoking, dyslipidemia, diabetes mellitus, history of hypertension, or any cardiac issues) were clinically and demographically recorded. PD diagnosis was based on criteria from brain banks. Using the Unified Parkinson's Disease Rating Scale (UPDRS), the severity of PD was evaluated, Fahn S, Elton RL (1987) UPDRS program members Parkinson’s Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB (eds) Recent

developments in Parkinson's disease, vol. 2, Macmillanm Healthcare Information, Florham Park, pp 153–163
. The Mini-mental State Examination (MMSE) Arevalo-Rodriguez I, Smailagic N, Roque-Figuls M, et al; Folstein, M., Folstein, S.E., McHugh, P.R. (1975)
and The Montreal Cognitive Assessment (MoCA) Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005).
were used to evaluate cognitive function.

B. Biochemical evaluation

1- Routine laboratory tests, such as those for the HBA1C, liver, kidney, and total lipid profiles were done on automated chemistry analyzer; AU 480 Beckmen Coulter.

2- Serum sample for thyroid function (Thyroid stimulating hormone (TSH), free triiodothyronine (T3), and free thyroxin (Free T4)) concentrations were collected at the outpatient clinic at 9: 00 am. Sample analysis has been done on Cobas e411; ROCHE Diagnostics.

3- Serum levels of antithyroid antibodies (Antithyroperoxidase (ATPO) and antithyroglobulin (AG))

C. Radiological examination:

To rule out secondary causes of parkinsonism and parkinsonian plus syndrome, Brain CT/MRI was performed.

Ethical Considerations

The faculty of medicine at our university's institutional ethics committee gave the current study its permission. Our Medical Faculty's IRB committee gave its approval for the project. All patients received thorough explanations of the study's goals, procedures, and cost-benefit analysis. Upon approval to participate in the study, each participant gave their written permission. The Declaration of Helsinki's guiding principles guided the study's conduct.

Statistic evaluation

The SPSS version 23 will be used to analyse every piece of data. For categorical variables, descriptive statistics will be used using frequency and cross tabulations. For numerical variables, means and standard deviations will be calculated. We will compare independent categorical variables using the chi-square test. If chi-square conditions are not met, , pearson correlation will be used to compare the groups. For comparing numerical data with a normal distribution, the Student's t-test will be used; for numerical data without a normal distribution, the Mann-Whitney U-test will be run. All comparisons will be two-tailed, with the P-value set at 0.05.

RESULTS

In this study, 40 Parkinson's disease (PD) patients—20 men and 20 women—were enrolled from the neuropsychiatric outpatient clinics of our university hospitals. Their age varied from 45 to 85

years with mean ± SD (62.8 ± 9.5 years). Their disease period lasted 8.9± 3.2 years (within a range of 3 to 20 years).

We discovered that 10% of our patients had a positive family history of the condition. 32.5% of them had consanguineous marriages, which was observed (**Table 1**). The most common comorbidity among our patients (47.5%) was dyslipidemia. Of the patients we had, 22.5% smokers. Their UPDRS mean total score was 45.8±21.3 (the range was 12–104), indicating mild to moderate Parkinson's disease manifestations in our individuals. The MMSE and MOCA scores for our patients indicated moderate cognitive impairment. The naming domain and orientation domain were the patient's most negatively impacted cognitive processes (**Table 1).**

We studied the blood levels of thyroid hormones (Free T3, Free T4), thyroid stimulating hormone (TSH), and antithyroid antibodies (Antithyroperoxidase, or ATPO, and Antithyroglobulin, or ATG) in our patients with Parkinson's disease. According to our study's findings (**Table 1**), all indicators were at ordinary values. Thyroid hormones, antithyroid antibodies, and UPDRS score did not correlate in our data (**Table 2**).

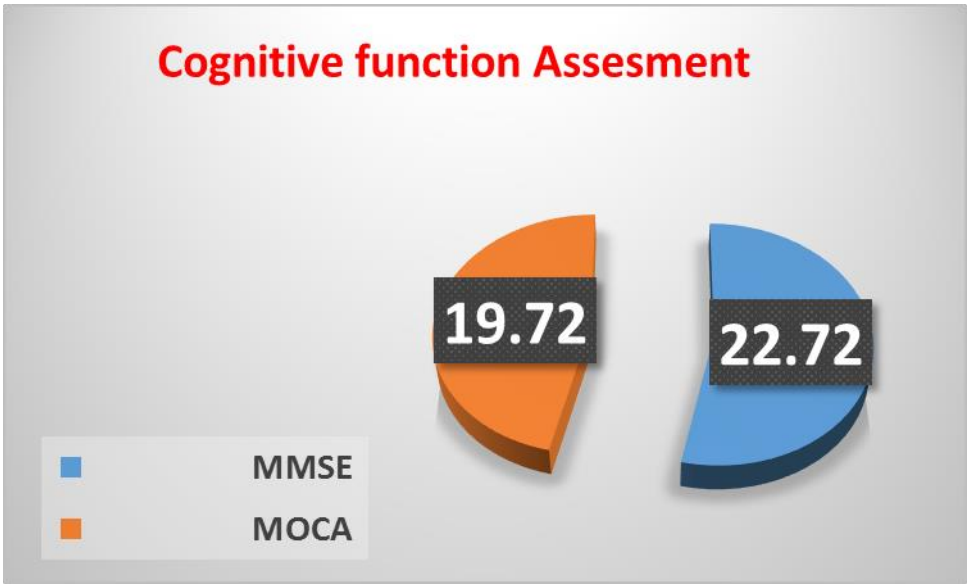
According to their MMSE and MOCA scores, our patients demonstrated mild cognitive impairment (scores of (22.72± 4.11) and (19.72 ± 6.82), respectively) (**Table 1** and **Figure 1**). Naming and orienting were the cognitive processes that were most impacted (**Figure 2**). In our investigation, there was a statistically significant positive link between TSH levels and cognition, especially in two cognitive domains (attention, working memory, and abstract thinking) (P< 0.05) (**Table 3** and **Figure 3**).

Table1: *the research group's demographic information*

Parameters	Study group (No =40)
Sex (M/F) (No; %)	(20; 50% / 20; 50%)
Age (y) (Mean ± SD; Range)	62.8 ± 9.5 (45-85)
Duration (y) (Mean ± SD; Range)	8.9 ± 3.2 (3-20)
Positive Family history	4 (10%)
Positive Consanguinity	13 (32.5%)
Comorbidity (No; %) DM HTN IHD Dyslipidemia Smoking	 8 (20 %) 12 (30 %) 5 (12.5 %) 19 (47.5%) 9 (22.5 %)
UPDRS score (Mean ± SD; Range) Total score Mentation, behavior and mood subscore Activities of daily living subscore Motor examination subscore	 45.8 ± 21.3 (12-104) 4 ± 2.6 (1-11) 11.2 ± 7.7 (3-27) 30.6 ± 13.9 (7-67)
Cognitive function assessment MMSE (Mean ± SD; Range) MOCA (Mean ± SD; Range)	 22.72 ± 4.11 (14- 29) 19.72 ± 6.82 (6-30)

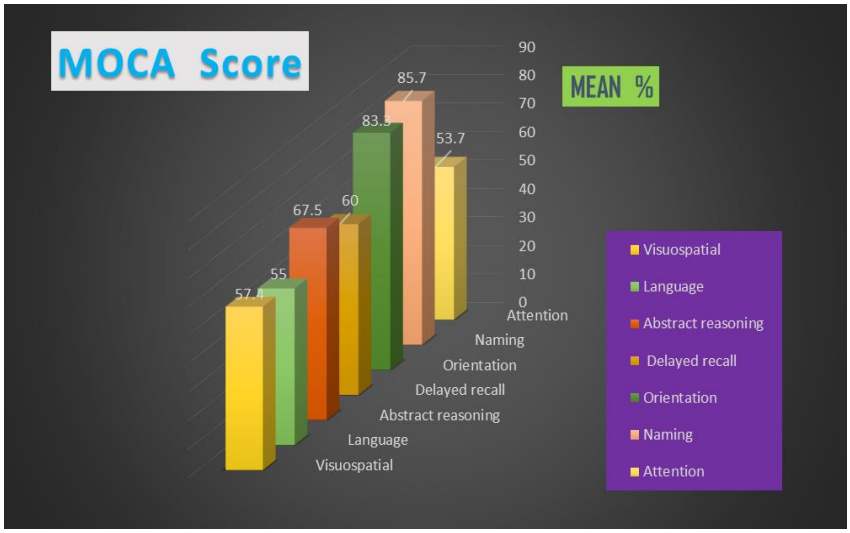
Thyroid hormones Free TSH (IU/ml) Free T3 (IU/ml) Free T4 (IU/ml)	 1.5 ± 1.04 4.9 ± 1.9 13.8 ± 6.1
Ant thyroid antibodies ATPO (IU/ml) ATG (IU/ml)	 8.1 ± 8.3 18.9 ± 18.6

DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic Heart Disease, UPDRS:The Unified Parkinson's Disease Rating Scale
p-value is significant if <0.5



MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment

Figure 1: *displays the study group's overall MMSE and MOCA scores for the assessment of cognitive function.*



MOCA: Montreal Cognitive Assessment

Figure 2: *depicts the percentage of cognitive domains of MOCA that were negatively impacted in the research group's assessment of cognitive function.*

Table 2: *the relationship between thyroid function tests and the Unified Parkinson's Disease Rating Scale (UPDRS) score in the research group.*

Thyroid function Tests	Mentation, behavior and mood subscore (0/16)	Activities of daily living subscore (0/52)	Motor Examination subscore (0/108)	Total Score (0/176)
TSH				
R*	0.033	0.138	0.332	0.261
P-Value**	0.897	0.584	0.179	0.296
T3				
R*	-0.146	-0.165	-0.031	-0.084
P-Value	0.563	0.512	0.903	0.741
T4				
R*	0.031	-0.121	-0.081	-0.085
P-Value	0.904	0.632	0.749	0.738
ATPO (IU/ml)				
R*	0.072	0.165	-0.071	0.022
P-Value	0.659	0.308	0.661	0.893
ATG (IU/ml)				
R*	0.149	0.235	-0.016	0.093
P-Value	0.359	0.	0.920	0.570

*Pearson correlation was used. **P ≤ 0.05 is considered significant

ATPO: anti–thyroid peroxidase autoantibodies, ATG: anti-thyroglobulin autoantibodies

Table 3: *the relationship between the research group's TSH, free T3, free T4, and cognitive performance.*

Cognitive function assessment		TSH		Free T3		Free T4	
		R*	P-Value**	R	P-Value	R	P-Value
MMSE		0.250	0.318	0.028	0.913	0.163	0.519
MOCA	Visuospatial	-0.188	0.456	0.047	0.854	0.146	0.564
	Naming	0.097	0.702	0.058	0.819	0.104	0.680
	Attention	0.315	0.048*	0.090	0.722	0.090	0.722
	Language	0.100	0.692	0.192	0.446	-0.105	0.678
	Abstract reasoning	0.441	0.004*	0.054	0.831	-0.018	0.943
	Delayed recall	0.160	0.526	0.065	0.799	0.052	0.837
	Orientation	0.154	0.542	-0.039	0.879	0.120	0.634
	Total	0.164	0.515	0.077	0.763	0.089	0.726

*Pearson correlation was used. **P ≤ 0.05 is considered significant

MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment

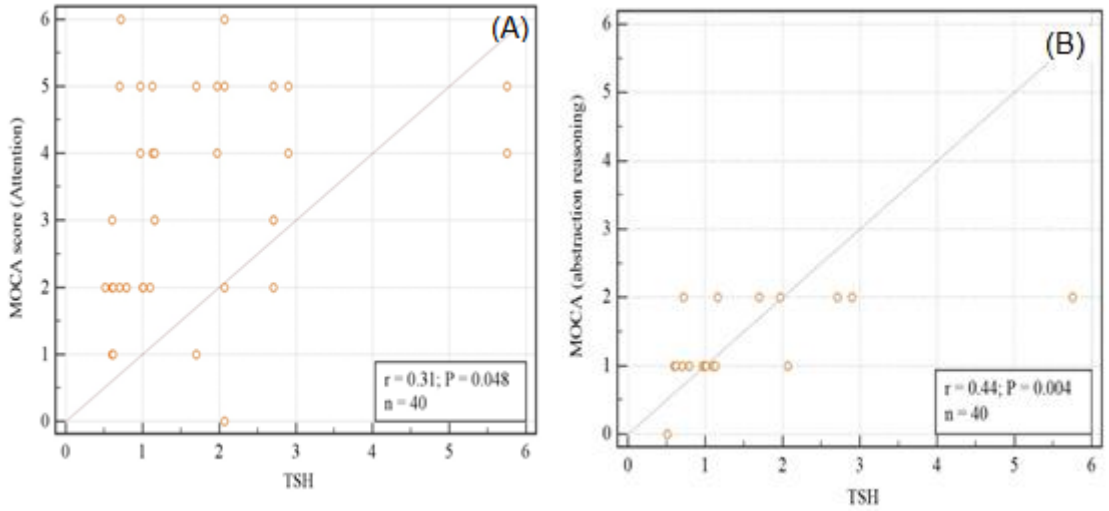


Figure 3 (A,B): *Correlation between TSH and cognitive function as measured by MOCA score in the study group.*

DISCUSSION

After Alzheimer's disease, PD is the second most prevalent neurodegenerative condition [12]. The "classic Parkinson's triad" refers to the association of the three primary motor abnormalities, which are akinesia/bradykinesia, muscular stiffness, and resting tremor [13].

Numerous organ systems, including the nervous system, depend heavily on thyroid hormones for proper growth and operation [14]. Increased basal metabolism and oxygen consumption brought on by high TH levels might result in oxidative stress [15].

The etiology of Parkinson's disease (PD) and the death of dopaminergic neurons both depend on oxidative stress [16]. In the early stages of Parkinson's disease (PD), elevated oxidative stress is a risk factor for dopaminergic cell loss [17]. Thyrotrophic hormone levels and dopamine levels interact. Parkinson's disease results in central dopamine insufficiency, which either directly or indirectly results in aberrant hormone secretion in the hypothalamo-pituitary pathway. Normally, dopamine regulates the hypothalamo-pituitary axis, boosting the release of growth hormone and inhibiting the production of prolactin. Low prolactin levels have an impact on TSH secretions as well [18].

After levodopa medication, TSH levels in Parkinson's patients have been seen to decrease, and low TSH levels found in certain PD patients were thought to be caused by levodopa treatment. T4 and T3 concentrations in the brain are still limited despite significant alterations in circulation. This suggests that even small changes in T4 might have an effect on how the CNS functions [18].

In the present study, we assessed thyroid function in Parkinson's disease patients and looked into the relationship between thyroid hormones, Parkinson's disease severity, and cognitive performance in Parkinson's disease patients.

We discovered that 10% of our patients had a positive family history of the condition. Our findings were consistent with a Pakistani research in which 9% of patients were found to have a family history of Parkinson's disease (PD) [19].

In certain parts of the world, such as the Middle East (including Egypt), North Africa, and Asiatic countries, where intrafamilial unions together account for around 20–50% of marriages [20], consanguineous unions are considered traditional and revered unions. In the current study, consanguineous marriages were found in 32.5% of the participants. According to Tufail and Hassan, patients with consanguineous marriages had a greater chance of developing Parkinson's disease (PD) than controls. PD is more likely to occur in first-degree relatives of PD patients than in second- or third-degree relatives [19].

Comorbidities have significant effects on the clinical care and health outcomes of PD patients. The most prevalent co-morbidity in our research was dyslipidemia, followed by hypertension and diabetes mellitus. Our patients had ischemic heart disease in around one-fourth of them. Our findings, which were in line with those of Gil-Prieto et al., showed that unspecified essential hypertension, diabetes mellitus, unspecified hyperlipidemia, a depressive condition, atrial fibrillation, and urinary tract infection were the most common comorbidities [21]. According to another research, cerebrovascular illness, hypertension, diabetes, chronic pulmonary disease, and paralysis were the most common comorbidities among PD patients [22].

A little more than half of our participants had dyslipidemia. Conflicting findings from the few studies that have examined the impact of dyslipidemia on cognitive function in PD to date have been reported [23]. They came to the conclusion that there is no clear and convincing correlation between cholesterol levels and declines in motor or cognitive function in advanced PD. Huang et al. discovered, however, that increased TG was linked to PD-MCI, notably with worsened visuospatial and executive functioning. Even more debatable and intriguing is the effect of cholesterol in cognition [24].

22.5% of the participants in the current research smokers. Prior studies have consistently shown a substantial negative relationship between smoking cigarettes and the advancement of Parkinson's disease (PD) [25,26], showing that smoking delays the beginning of PD and lowers the risk of PD by 41–58%. Although the precise mechanism is still unknown, several researchers have hypothesized that this reverse connection is connected to a pathophysiological explanation based on an imbalance between nicotinic cholinergic and dopaminergic neurotransmitter systems in the nigrostriatal pathway [27].

We looked at the thyroid profile in PD patients, which included measuring the serum levels of thyroid hormones (Free T3, Free T4), thyroid stimulating hormone (TSH), and antithyroid antibodies (Antithyroperoxidase, or ATPO, and Antithyroglobulin, or ATG). We discovered that all parameters were within normal ranges. That such people have subclinical hypothyroidism is the second theory that could apply. Our findings were consistent with those of Tan et al. [7], who found no significant variation in thyroid function among PD patients. Additionally, no differences in TSH, fT3, or fT4 concentrations between patients with PD and healthy controls were reported in previous investigations [28].

However, thyroid dysfunction in PD patients was observed by other investigations. According to Munhoz et al.'s research, 13.7% of the PD patients they evaluated had hypothyroidism, compared to 10.8% of the control group, and statistical analysis did not reveal a significant difference [29]. However, other measurements showed decreased thyroid hormone levels in PD patients when compared to healthy controls, and even after correcting for confounding variables, the fT3 level was shown to be adversely connected with the severity of the condition [7].

Although hypothyroidism was more common in PD patients than in controls, Fernández et al. did not find these differences to be statistically significant. It may be inferred that hyper- and hypothyroidism, the two most common thyroid dysfunctions, are not more common in PD [30]. Patients with hypothyroidism had a markedly elevated risk of Parkinson's disease, according to Chen et al. [8]. Chorea and dystonia are movement disorders and PD risk factors associated with hyperthyroidism [31,32]. Both hypothyroidism and hyperthyroidism were significantly linked to an elevated risk of Parkinson's disease (PD), according to a systematic review and meta-analysis [33]. Dopaminergic neurons are known to be affected negatively by hypothyroidism, which may help to explain why the condition is linked to an increased risk of Parkinson's disease (PD). Additionally, increased oxidative stress and neuroinflammation associated with hypothyroidism were linked to the beginning and development of Parkinson's disease (PD) [34, 35]. However, The association between TH and PD was not discovered in the current investigation.
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The association between TSH, fT3, fT4, ATPO, and ATG levels and the UPDRS total score or any of its three components was shown to be statistically insignificant. Nevertheless, this was clinically significant since it revealed the existence of subclinical hypothyroidism, which may be linked to a

more severe case of Parkinson's disease. Antithyriod antibody tests and further thyroid hormone assays were strongly advised.

Contradicting our findings, Tan et al.'s investigation on correlation analysis found a strong negative association between fT4 and UPDRS motor score [7]. Additionally, they discovered that patients with tremor-dominant type (TDT) or mixed type (MXT) had considerably greater fT4 levels than patients with akinetic-rigid type (ART).

According to a different research by Umehara and his colleagues, post-synaptic sympathetic dysregulation, which is mediated by α-synuclein in PD patients, can be the cause of reduced serum free T3 levels having a strong negative correlation with UPDRS motor score [36].

In agreement with our findings, OCAK et al. found no connection between Parkinson's patients' motor symptoms and their TSH, fT3, or fT4 levels [18]. However, they vary from us in that we employed the modified Hoehn and Yahr scale (mHYS) to evaluate the staging of motor symptoms.

A minor cognitive impairment affected our patients. The disorder of α-synuclein, amyloid protein, and cholinergic differences all played a role in the development of cognitive impairment in Parkinson's disease. We found that name and orienting were the patient's cognitive functions that were most negatively impacted in our group. In contrast to us, earlier research by Svenningsson et al., which showed that verbal memory deficiencies and frontal/executive abnormalities were linked to the emergence of PDD[37].

We found a statistically significant positive link between our patients' cognitive impairment and TSH levels in the current investigation. Previous research has not been able to establish a meaningful connection between T3 and cognitive performance [38].

In contrast to our findings, Choi et al. conjectured, contrary to our results, that an increase in fT4 may be more closely associated with cognitive impairment because of the significant correlations shown between fT4 concentrations and general cognition and executive function in PD patients [38]. Two studies provided evidence in favor of this hypothesis: one examined pathology and found that higher levels of total and fT4 were associated with a higher risk of Alzheimer's disease, as well as a higher number of neocortical neuritic plaques and neurofibrillary tangles [39, 40]. The other study used magnetic resonance imaging and found that high fT4 was linked to atrophy of the amygdala and hippocampus on imaging.
In early PD without dementia, Choi et al. hypothesize that elevated fT4 causes an increase in neocortical neuritis plaques and neurofibrillary tangles, which in turn leads to poor performance on cognitive function tests [38].

Levothyroxine, a bioactive hormone used as a T4 replacement, has been shown in certain studies to have neuroprotective benefits by promoting the proliferation of microglial processes, which improves motor function in PD animal models [41]. Levothyroxine may either have neuroprotective effects or adverse effects on cognitive function, which is the subject of considerable debate.

The findings of this study concluded that Parkinson's disease may have coexisted with a normal level of thyroid hormones. Furthermore, we were unable to show any relationship between illness severity and cognitive impairment using ft3 and ft4, despite a substantial association between TSH and cognitive impairment. Since treating thyroid dysfunction is expected to enhance the cognition of PD patients, understanding the potential relationship between thyroid hormones and cognitive impairment is crucial. Future studies are required to determine if subclinical thyroid illness is the

source of greater or lower ft4, ft3 levels, or whether they are a result of cognitive impairment or worsening motor symptoms in PD.

The differences between our study and other studies were rather varied. The different results might be the consequence of different sample selection methods, different cognitive function tests, fewer thyroid function indicators, and a smaller sample size. There is a need for more prospective follow-up studies with larger sample sizes, repeated evaluation of numerous thyroid function indicators with appropriate testing times (early in the morning before the first dose of treatment), and adequate evaluation of factors affecting cognitive function. To examine the effectiveness of thyroid replacement treatment for Parkinson's patients, more study is required.

ABBREVIATIONS

UPDRS: UK Parkinson's Disease Society Diagnostic Criteria for Brain Bank
Mini-mental state examination (MMSE)
Montreal Cognitive Assessment (MOCA)
T3 is short for triiodothyronine.
Free T4 is thyroxin.
TSH stands for thyroid stimulating hormone.
Antithyroperoxidase, or ATPO
Antithyroglobulin, or ATG
Mild cognitive impairment (MCI)
Computer tomography: CT
Magnetic resonance imaging: MRI

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