

Assessment of Thyroid Function in Patients with Parkinson's Disease

Tamer Bayram¹, Derya Bayram², Gülbün Asuman Yüksel³, Hülya Tireli³

¹Department of Pain Medicine, Çukurova University Faculty of Medicine, Adana, Türkiye

²Department of Pain Medicine, Ankara University Faculty of Medicine, Ankara, Türkiye

³Department of Neurology, University of Health Sciences Haydarpaşa Numune Training and Research Hospital, İstanbul, Türkiye

Abstract

Introduction: The study aims to observe thyroid dysfunction, its prevalence, and the relationship between the Unified Parkinson's Disease Rating Scale (UPDRS) and thyroid function in Parkinson's patients.

Methods: Seventy patients with Parkinson's disease (PD) and 60 age- and sex-matched controls were enrolled in the study. PD patients were divided into tremor dominant-type (TDT) and akinetic-rigid-type (ART) subgroups. Serum fT₄, TSH, and Anti TPO levels of patients were retrospectively reviewed. The results of the patients were compared with the controls, and the relationship between the UPDRS score and thyroid hormone levels was observed.

Results: The mean levels of TSH and fT₄ were higher in PD patients, but the difference was not statistically significant. TDT and ART subgroups did not show differences in age, UPDRS motor score, and TSH level. Only 1 (1.42%) female patient had hypothyroidism in the TDT subgroup. Three females and 2 males had subclinical hyperthyroidism in the PD group (2 females and 2 males in TDT and 1 female in the ART subgroup). The fT₄ level and subclinical hyperthyroidism were significantly higher in the TDT subgroup than in ART. None of the patients in the PD group had hyperthyroidism or subclinical hypothyroidism. The prevalence of subclinical hyperthyroidism was higher in the PD group and the prevalence of hypothyroidism did not differ between the two groups. There was no significant relationship between the UPDRS score and thyroid hormone levels or anti-TPO.

Discussion and Conclusion: Thyroid dysfunction in Parkinson's patients may cause difficulties in the treatment and follow-up process, as thyroid hormone levels may aggravate or camouflage Parkinson's symptoms. In the study, the frequency of subclinical hyperthyroidism was higher in PD patients. The mean fT₄ level and subclinical hyperthyroidism in TDT were significantly higher than those with ART. In addition, there was no correlation between the severity of the disease and the thyroid results. Thyroid tests should be carefully evaluated to facilitate treatment regulation in Parkinson's disease.

Keywords: Hypothyroidism; parkinson's disease; thyroid dysfunction.

Parkinson's disease (PD) is a progressive disease clinically manifested by resting tremor, rigidity, bradykinesia, and impaired postural reflexes^[1]. Usually, in the late stages, autonomic dysfunctions such as symptomatic orthostatic hypotension, impotence, voiding-defecation problems, and dementia may be added over time^[2]. It is recognized

to be a complex syndrome with motor and non-motor (autonomic, behavioral, cognitive, and sensory) involvement patterns. Pathologically, it is mostly characterized by losses in dopaminergic neurons in substantia nigra and the presence of typical eosinophilic cytoplasmic inclusion bodies (Lewy inclusion bodies)^[1].

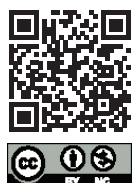
Correspondence: Tamer Bayram, M.D. Department of Pain Medicine, Çukurova University Faculty of Medicine, Adana, Türkiye

Phone: +90 531 794 16 61 **E-mail:** tmrbyrm@gmail.com

Submitted Date: 23.12.2021 **Revised Date:** 23.12.2021 **Accepted Date:** 19.01.2022

Copyright 2023 Haydarpaşa Numune Medical Journal

OPEN ACCESS This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).



In the hypothalamic-pituitary-thyroid axis, Thyroid Releasing Hormone- Thyroid Stimulating Hormone)-fT4/fT3 (free T4/free T3) hormones are constantly secreted in a controlled manner for the continuity of metabolic events with their (-) feedback effect^[3-5]. Central dopamine deficiency experienced in PD can cause disruptions in hormone secretions in the hypothalamus-hypophyseal pathway for primary or secondary reasons^[6]. Furthermore, some of the studies have reported that there might be a false decrease in TSH levels measured during the 1st h following levodopa treatment in Parkinson's patients, and therefore it was suggested that low TSH levels detected in some Parkinson's patients may be secondary to levodopa treatment^[6-8].

In PD patients, the hypothyroid symptoms may be ambiguous because parkinsonism and hypothyroidism share some common clinical features such as bradykinesia, hypomimia, hypophonia, swallowing disorders, peripheral edema, respiratory problems, dementia, depression, sleep disorders, exhaustion, fatigue, constipation, orthostatic hypotension, and sexual dysfunction^[9-12]. Some symptoms such as tremors, anxiety disorders, panic disorder, excessive sweating, cramps, paresthetic complaints, cognitive problems, dyskinesia, constipation, and intestinal problems in Parkinson's patients can also be seen in hyperthyroidism^[13].

There may be difficulties in the treatment and follow-up of Parkinson's patients with thyroid dysfunction since the signs of the disease may be aggravated or camouflaged according to thyroid hormone levels (hypothyroidism, hyperthyroidism, subclinical hypo/hyperthyroidism). However, the diagnosis of thyroid diseases can be made very clearly with laboratory results.

The main purpose of this study is to determine thyroid dysfunction, its prevalence, and its contribution to PD in Parkinson's patients, and also to observe the relationship between Unified PD Rating Scale (UPDRS) score and thyroid test results.

Materials and Methods

Seventy patients aged between 33 and 87 years with a diagnosis of PD who applied to the Movement Disorders Outpatient Clinic of Haydarpaşa Numune Training and Research Hospital between January 2000 and June 2015 were included in the study. Patient files and laboratory results were reviewed retrospectively. Ethical approval was obtained from the Medical Ethics Committee of Haydarpaşa Numune Training and Research Hospital (dated

26/10/2015, numbered 2699). This study was conducted in accordance with the Declaration of Helsinki. PD patients were divided into tremor dominant-type (TDT), akinetic-rigid-type (ART), and mixed-type (MXT) subgroups. Serum fT4, TSH, and Anti TPO (anti-thyroid peroxidase antibodies) levels were used to analyze thyroid function. The measurements were made before taking the first dose of levodopa in the morning to prevent TSH levels from being affected. The diagnosis of Parkinson's was made clinically according to the diagnostic criteria of the UK PD Society Brain Bank^[14]. The UPDRS motor scoring was used to evaluate PD severity.

Patients with a history of chronic disease (diabetes mellitus, hypertension, heart disease, cancer, etc.) were excluded from the study, as the thyroid and hypothalamic-pituitary hormone axis could be affected. The control group consisted of 60 age- and sex-matched healthy patients, and fT4, TSH, and Anti-TPO tests were performed in the controls.

Thyroid function tests (TFT) were performed on the Beckman Coulter Access Immunoassay System Unicel DX1-800 device with the chemiluminescent immunoassay method. The normal interval of this method was: free T4 (fT4): 0.92–1.83 ng/dL, sensitive TSH: 0.5–4 mIU/mL.

According to values determined by the Guidelines of the Society of Endocrinology and Metabolism of Türkiye on the Diagnosis and Treatment of Thyroid Diseases^[15]. (Hypothyroidism: fT4 < 0.92 ng/dL, sTSH > 4 mIU/mL, Subclinical hypothyroidism: fT4=0.92–1.83 ng/dL, sTSH > 4 mIU/mL, Hyperthyroidism: fT4 > 1.83 ng/dL, sTSH < 0.5 mIU/mL, Subclinical hyperthyroidism: fT4=0.92–1.83 ng/dL, sTSH < 0.5 mIU/mL, Anti-TPO reference value: 0–5.6 IU/mL).

According to the results, the patients were divided into groups normal, hypothyroid, subclinical hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism. Anti-TPO values of patients were recorded. The mean level of fT4 and TSH in Parkinson's patients were compared with the control group. The correlation between disease severity and thyroid test results was analyzed.

Statistical Analyses

IBM SPSS (version 22) Statistics program was used for the analysis of data. Descriptive data were expressed as mean±standard deviation. Pearson correlation test was used to evaluate the correlation of thyroid hormone levels with the UPDRS score. A p≤0.05 was considered to be significant.

Results

Of the 70 Parkinson's patients, 43 were male and 27 were female. The mean of the UPDRS score was 32.8 ± 5.3 . PD patients were divided into the (TDT, $n=58$), and (ART, $n=12$) subgroups. Because of the common characteristics of the tremor dominant and mixed type groups, these two groups were combined and analyzed together ($n=58$). Age, UPDRS score, and results of thyroid function tests are shown in Table 1.

There was no significant difference in age, UPDRS motor score, and TSH level between the TDT and ART groups. The ft4 level in the patients with TDT was significantly higher than those with ART.

The anti-TPO positivity rate did not differ significantly be-

Table 1. Clinical and demographic comparison of ART and TST subgroups

	TDT (n=58)	ART (n=12)	p
Age(years)	69.53 ± 8.7	65 ± 9.3	0.65
UPDRS score	32.09 ± 13.5	33.3 ± 15.21	0.753
ft4	1.45 ± 0.8	1.03 ± 0.5	0.035
TSH	1.98 ± 0.35	2.07 ± 1.2	0.157
Anti TPO (+)	5 patients	1 patient	0.145

PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale; TDT: Tremor-dominant type; ART: Akinetic-rigid type.

Table 2. Clinical and demographic comparison of PD and control groups

	Patient (n=70)	Control (n=60)	p
Age	67 ± 11.59	69.13 ± 8.74	0.133
ft4	1.09 ± 0.2	1.05 ± 0.14	0.075
TSH	2.02 ± 0.8	1.31 ± 0.73	0.155

ft4: Free T4; TSH: Thyroid-stimulating hormone.

tween the two groups. The control group consisted of 60 healthy individuals, 38 males and 22 females. Detailed clinical information is shown in Table 2.

The mean level of ft4 and TSH were 1.09 ± 0.2 ng/dL (min 0.58-max 1.85) and 2.02 ± 0.8 mIU/mL (min 0-max 3.04) in the PD patients and were 1.05 ± 0.11 ng/dl (min 0.73-max 1.33) and 1.31 ± 0.73 mIU/mL (min 0.39-max 3.1) in the control group, respectively. The mean level of TSH and ft4 were higher in PD patients than in the controls; however, they didn't reach statistically significant levels ($p=0.155$, $p=0.075$ respectively). Anti-TPO was positive in 6 (8.6%) PD patients (4 females and 2 males) and was positive in 8 (13.3%) controls (6 females and 2 males).

Thyroid function tests were abnormal in 6 (8.57%) PD patients. Sixty-four (91.42%) PD patients had normal thyroid function. Only 1 (1.42%) female patient had hypothyroidism in the TDT subgroup. Three females and 2 males had subclinical hyperthyroidism in the PD group (2 females and 2 males in TDT and 1 female in the ART subgroup). Subclinical hyperthyroidism was significantly higher in the TDT subgroup ($p<0.05$). None of the patients in the PD group had hyperthyroidism or subclinical hypothyroidism. The ft4 level and subclinical hyperthyroidism were significantly higher in the TDT subgroup than in ART. The prevalence of subclinical hyperthyroidism was higher in the PD group than in the control group and the prevalence of hypothyroidism did not differ between two groups. There was no significant relationship between the UPDRS score and thyroid hormone levels or anti-TPO ($p=0.15$).

In the controls, 2 (3.33%) females had subclinical hyperthyroidism. The results of 58 subjects (96.66%) were normal, as shown in Table 3.

Table 3. Thyroid function tests in Parkinson's patients and control group

	Parkinson's patients group			Control group		
	Male (n=43)	Female (n=27)	Total (n=70)	Male (n=38)	Female (n=22)	Total (n=60)
Normal TFT	41	23	64	38	20	58
Abnormal TFT	2	4	6	0	2	2
Hypothyroidism	0	1	1	0	0	0
Hyperthyroidism	0	0	0	0	0	0
Subclinical hyperthyroidism	2	3	5	0	2	2
Subclinical hypothyroidism	0	0	0	0	0	0

TFT: Thyroid function tests.

Discussion

This study suggested a relationship between thyroid hormone levels and PD. It was observed that the prevalence of subclinical hyperthyroidism in PD patients was higher than in controls ($p < 0.05$). The fT4 level and subclinical hyperthyroidism were significantly higher in the TDT subgroup than in the ART subgroup. In addition, there was no significant correlation between the UPDRS score and thyroid hormone levels or anti-TPO.

Idiopathic PD and thyroid disease might have common clinical symptoms. Bradykinesia, hypomimia, hypophonia, swallowing disorders, gastrointestinal motility disorders, and peripheral edema may occur in both PD and hypothyroidism. Moreover, tremors and over sweating in PD patients might be observed in hyperthyroidism. Although tremors differ in morphology and frequency in PD and hyperthyroidism, both diseases may exacerbate or camouflage each other's symptoms. These similarities in clinical presentation may result in difficulties in treatment regulation in PD.

Thyroid diseases have been reported as endocrine dysfunction frequently associated with PD^[16]. An increase has been shown in the fT4 level in the early stage PD,^[17] and both hyperthyroidism and hypothyroidism have been more commonly reported in PD patients than in the control group^[18].

According to the hypothesis of a study performed by Foster et al.,^[19] iodine deficiency plays a role in the development of PD and thyroid diseases, as in Alzheimer's disease. On the other hand, in the study of Otake et al.,^[20] the disturbance in hypothalamic-hypophyseal hormone secretion due to hypothalamic dysfunction in PD was considered to play a role in the development of thyroid diseases.

Central dopamine deficiency, experienced in PD due to widespread loss of dopaminergic neurons, may cause irregularities in hormone secretion in the hypothalamic-hypophyseal axis due to direct or indirect reasons. There is a mutual interaction in hormone levels due to this close relationship between dopamine and thyrotropic hormone levels^[21]. Dopamine modulates the hypothalamic-hypophyseal axis and thus increases growth hormone release and decreases prolactin release. The decrease in prolactin levels causes changes in TSH secretions^[22].

Recently, Tan et al.^[9] suggested that thyroid hormone levels in euthyroid PD patients were lower than in controls. In our Parkinson's patient group, thyroid hormone levels were higher than the control group and this difference

did not reach a statistically significant level. Although there was no consensus among previous studies regarding the high prevalence of hypothyroidism in Parkinson's patients, some investigators (Berger and Kelly, 1981) reported a high prevalence of hypothyroidism in PD^[6]. However, Tandeter et al.^[23] could not exhibit in their study that the prevalence of hypothyroidism in PD was higher than in the control group. In addition, in the study of Johannessen et al.,^[24] the prevalence of hypothyroidism was not different in PD patients and the control group and only 1 patient developed hypothyroidism in the follow-up of PD, similar to our study. Hypothyroidism was detected in only 1 (1.42%) female patient in the TDT subgroup in our study. Huber et al.^[25] also have shown that the prevalence of hypothyroidism was not common in Parkinson's patients; however, they have stated that male Parkinson's patients had more thyroid dysfunction and the prevalence of subclinical hyperthyroidism was higher as in our study. Subclinical hyperthyroidism prevalence was higher in the TDT subgroup than in the ART subgroup ($p < 0.05$). Five patients (7.14%, 3 females and 2 males) had subclinical hyperthyroidism, and male patients with PD tended to have higher thyroid dysfunction. Moreover, supporting our result, Tandeter also reported that compared with normals, subclinical hyperthyroidism is more prevalent in PD patients, and the free thyroxine (fT4) levels are elevated in the de novo, medication-free PD patients^[23].

It has been shown that thyroid hormone level is closely associated with motor symptoms in PD patients^[26]. We found that the mean level of fT4 in the TDT subgroup was significantly higher than in the ART subgroup. Tan et al.^[9] also reported the fT3 level was negatively correlated with UPDRS motor score and suggested that patients with lower fT3 levels may have a greater risk to develop severe diseases and the multivariable logistic regression analysis of their study showed that there was no significant relationship between the thyroid function and the disease motor subtype. However, Umehara et al.^[26] reported the thyroid hormone level, especially the free triiodothyronine level, was closely related to motor symptoms in patients with de novo PD, the decreased free triiodothyronine level was associated with akinetic-rigid motor subtype. On the other hand, we also found no correlation between UPDRS scores and thyroid function tests. Further studies are needed to clarify how thyroid hormone levels have functional roles and effects on motor and non-motor symptoms.

Subclinical hypothyroidism/hyperthyroidism may be detected incidentally in asymptomatic patients. In the study

of Huber et al.,^[25] 34% of subclinical hypothyroidism patients developed hypothyroidism in the 10-year follow-up, and even in patients with normal thyroid function tests, the presence of thyroid autoantibodies significantly increased the risk of developing hypothyroidism. Six (8.6%) Anti-TPO positive PD patients included in our study had normal thyroid function tests but their thyroid status may change over time.

When evaluating serum TSH levels in Parkinson's patients, the point to be considered is that dopamine causes a temporary decrease in serum TSH levels in blood samples taken in the 1st h following dopaminergic treatment. This important detail underlines the importance and reliability of taking blood samples before taking the first levodopa dose in the morning^[8]. This effect tends to be more significant in males, and it is considered that this is due to a primary or a secondary reason affecting the hypothalamic function levels of Parkinson's patients^[20]. In light of this information, blood samples for thyroid were taken from our patients before the first dose of levodopa in the morning.

It is known that hypothyroidism and PD have significant effects on gastrointestinal motility. Thyroid dysfunction impairs gastric emptying and small intestine motility^[27,28]. Drug absorption will also be impaired in these cases with both PD and hypothyroidism. This will cause fluctuations in Parkinsonian movements, high-dose drug use, or using a great number of antiparkinsonian drugs in a Parkinson's patient with hypothyroidism^[28].

Garcia et al.^[12] detected autoimmune thyroiditis and hypothyroidism in a Parkinson's patient with an increasing number of on-off periods after 7 years of diagnosis. It was observed that the frequency of on-off periods decreased by only adding levothyroxine to the treatment without changing the levodopa dose in the Parkinson's patient who was not receiving levothyroxine treatment. Pharmacological studies have shown that the "off" state coincides with decreases in plasma levodopa levels^[29]. Therefore, on-off periods of Parkinson's patients with hypothyroidism have been treated by only adding levothyroxine to the treatment without changing levodopa treatment.

There were some limiting factors in our study. Firstly, it was a retrospective study with 70 Parkinson's patients. Further studies with larger sample sizes may be required to understand the relationship between these two diseases, which have a high co-occurrence. Parkinson's patients in our study were currently receiving antiparkinsonian therapy and their clinical status was stable.

Conclusion

It was observed that the prevalence of subclinical hyperthyroidism was higher in patients with PD than in controls ($p < 0.05$). In addition, the fT4 level and subclinical hyperthyroidism were significantly higher in the TDT subgroup than in the ART subgroup. PD and thyroid dysfunction might affect each other's symptoms. Considering this association, it is aimed to emphasize that the detection of thyroid dysfunction in PD is important in treatment regulation. Various previous studies have suggested different results for the correlation between PH and thyroid function. It is important to evaluate thyroid function at disease onset and during follow-up to avoid unnecessary treatment for PD.

Ethics Committee Approval: Ethical approval was obtained from the Medical Ethics Committee of Haydarpaşa Numune Training and Research Hospital (dated 26/10/2015, numbered 2699). This study was conducted in accordance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: T.B., D.B.; Design: G.A.Y., T.B.; Supervision: H.T., D.B.; Materials: D.B., H.T.; Data Collection or Processing: T.B., D.B.; Analysis or Interpretation: D.B., H.T.; Literature Search: D.B., T.B.; Writing: D.B., T.B.; Critical Review: G.A.Y., T.B., D.B., H.T.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Jankovic J. Pathophysiology and clinical assessment of parkinsonian symptoms and signs. In: Pahwa R, Lyons K, Koller WC, editors. Handbook of Parkinson's disease, 4th ed. New York: Taylor and Francis Group; 2007. p.79–104.
2. Marino BLB, de Souza LR, Sousa KPA, Ferreira JV, Padilha EC, da Silva CHTP, et al. Parkinson's disease: A review from pathophysiology to treatment. *Mini Rev Med Chem* 2020;20:754–67.
3. Wartofsky L, Klubo-Gwiedzinska J. Thyroid storm (Thyrotoxic crisis). In: Luster M, Duntas L, Wartofsky L, editors. The thyroid and its diseases. New York: Springer, Cham; 2019.
4. Ünal G. Tiroid hastalıkları. 1.baskı. İ.Ü. Cerrahpaşa Tıp Fakültesi Yayınları; 2000;3:28–64.
5. Burch HB. Drug effects on the thyroid. *N Engl J Med* 2019;381:749–61.
6. Berger JR, Kelley RE. Thyroid function in Parkinson disease. *Neurology* 1981;31:93–5.
7. Wingert TD, Hershman JM. Sinemet and thyroid function in Parkinson disease. *Neurology* 1979;29:1073–4.
8. Ladenson PW, Cohen HD, Singer PA, Ain KB, Bagchi N, Bigos ST, et al. Screening for thyroid dysfunction in the elderly—reply. *Arch Intern Med* 2001;161:130.

9. Tan Y, Gao L, Yin Q, Sun Z, Man X, Du Y, et al. Thyroid hormone levels and structural parameters of thyroid homeostasis are correlated with motor subtype and disease severity in euthyroid patients with Parkinson's disease. *Int J Neurosci* 2021;131:346–56.
10. Tandeter HB, Shvartzman P. Parkinson's disease camouflaging early signs of hypothyroidism. *Postgrad Med* 1993;94:187–90.
11. García-Moreno JM, Chacón-Peña J. Hypothyroidism and Parkinson's disease and the issue of diagnostic confusion. *Mov Disord* 2003;18:1058–9.
12. García-Moreno JM, Chacón J. Hypothyroidism concealed by Parkinson's disease. *Rev Neurol* 2002;35:741–2.
13. Kim HT, Edwards MJ, Lakshmi Narsimhan R, Bhatia KP. Hyperthyroidism exaggerating parkinsonian tremor: A clinical lesson. *Parkinsonism Relat Disord* 2005;11:331–2.
14. Daniel SE, Lees AJ. Parkinson's disease society brain bank, London: Overview and research. *J Neural Transm Suppl* 1993;39:165–72.
15. Türkiye Endokrinoloji ve Metabolizma Derneği. Tiroid hastalıkları tanı ve tedavi klavuzu. 2020. Available at: https://file.temd.org.tr/Uploads/publications/guides/documents/20200929134733-2020tbl_kilavuzf527c34496.pdf?a=1. Accessed Aug 7, 2023.
16. Bonuccelli U, D'Avino C, Caraccio N, Del Guerra P, Casolaro A, Pavese N, et al. Thyroid function and autoimmunity in Parkinson's disease: A study of 101 patients. *Parkinsonism Relat Disord* 1999;5:49–53.
17. Aziz NA, Pijl H, Frölich M, Roelfsema F, Roos RA. Diurnal secretion profiles of growth hormone, thyrotrophin and prolactin in Parkinson's disease. *J Neuroendocrinol* 2011;23:519–24.
18. Munhoz RP, Teive HA, Troiano AR, Hauck PR, Herdoiza Leiva MH, Graff H, et al. Parkinson's disease and thyroid dysfunction. *Parkinsonism Relat Disord* 2004;10:381–3.
19. Foster HD. Disease family trees: The possible roles of iodine in goitre, cretinism, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases and cancers of the thyroid, nervous system and skin. *Med Hypotheses* 1987;24:249–63.
20. Otake K, Oiso Y, Mitsuma T, Hirooka Y, Adachi K. Hypothalamic dysfunction in Parkinson's disease patients. *Acta Med Hung* 1994;50:3–13.
21. Rabey JM, Vardi Y, Ravid R, Ayalon D. Dissociation of thyrotropin and prolactin responsiveness to thyrotropin releasing hormone stimulation in L-dopa treated parkinsonian patients. *Horm Res* 1981;15:78–87.
22. Kimber J, Watson L, Mathias CJ. Neuroendocrine responses to levodopa in multiple system atrophy (MSA). *Mov Disord* 1999;14:981–7.
23. Tandeter H, Levy A, Gutman G, Shvartzman P. Subclinical thyroid disease in patients with Parkinson's disease. *Arch Gerontol Geriatr* 2001;33:295–300.
24. Johannessen AC, Boye A, Pakkenberg H. Thyroid function in patients with Parkinson's disease. *Acta Neurol Scand* 1987;75:364–5.
25. Huber G, Mittrache C, Meier C, Guglielmetti M, Huber P, Staub JJ. Long-term study of subclinical hypothyroidism: Spontaneous course and predictors of manifest hypothyroidism. *Schweiz Med Wochenschr [Article in German]* 1998;128:1902–5.
26. Umehara T, Matsuno H, Toyoda C, Oka H. Thyroid hormone level is associated with motor symptoms in de novo Parkinson's disease. *J Neurol* 2015;262:1762–8.
27. Yaylali O, Kirac S, Yilmaz M, Akin F, Yuksel D, Demirkan N, et al. Does hypothyroidism affect gastrointestinal motility? *Gastroenterol Res Pract* 2009;2009:529802.
28. Bozeman T, Anuras S, Hutton T, Ghandour E, Mikesla C. Abnormal motility of the gastrointestinal tract in Parkinson's disease. *Am J Gastroenterol* 1990;85:1264.
29. Fahn S. "On-off" phenomenon with levodopa therapy in Parkinsonism. Clinical and pharmacologic correlations and the effect of intramuscular pyridoxine. *Neurology* 1974;24:431–41.