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# Effect of L-Dopa Therapy on Plasma Homocysteine Levels and, Consequently, on Carotid İntima-Media Thickness in Parkinson's Disease Patients

## Parkinson Hastalarında L-Dopa Tedavisinin, Plazma Homosistein Düzeyleri ve Bununla İlişkili Karotis İntima-Media Kalınlıkları Üzerine Olan Etkisi

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***ABSTRACT***

**Objective:** In this study, we investigated hyperhomocysteinemia, as well as carotid intima-media thickness (CIMT) measurements using carotid Doppler ultrasonography, in Parkinson patients on levodopa treatment.

**Methods:** This study was carried out on 23 patients with Parkinson's disease and 21 age-and gender-matched healthy volunteers. Carotid Doppler ultrasonography was performed in order to determine CIMT in all cases. In addition, plasma homocysteine, vitamin B12 and folate levels were measured. Carotid Doppler ultrasonography and homocysteine levels were repeated one year later to evaluate the rate of atherosclerosis progression.

**Results:** Although the population sample was limited, there was an increase in baseline CIMT measurements that occurred in parallel with an increase in baseline homocysteine levels in these patients. At the end of the follow-up period, a bilateral increase in CIMT was observed, which was not correlated to hyperhomocysteinemia.

**Conclusion:** In conclusion, many clinical studies on hyperhomocysteinemia caused by L-dopa therapy in Parkinson patients have been published. However, the relationship between hyperhomocysteinemia and increased risk of vascular disease is still controversial. On the basis of this result, we speculated that hyperhomocysteinemia might lead to an increase in the arterial wall thickness, but its effect on the progression of atherosclerosis is still discussable. *(Archives of Neuropsychiatry 2010; 47: 297-301)*

**Key words:** Parkinson's disease, S-adenosylhomocysteine, carotid artery diseases, atherosclerosis

***ÖZET***

**Amaç:** Bu çalışmada, levodopa tedavisi alan Parkinson hastalarında, hiperhomosisteinemi ve karotis intima media kalınlık (KIMK) değerleri karotis Doppler ultrasonografi kullanılarak araştırılmıştır.

**Yöntemler:** Bu çalışma 23 Parkinson hastası ve yaş-cinsiyet olarak benzer 21 sağlıklı gönüllü üzerinde yapıldı. Tüm olgulara, karotis arter intima-media kalınlığının araştırılması amaçlı Doppler ultrasonografi uygulandı. Bununla birlikte plazma homosistein, vitamin B12 ve folik asit düzeyleri ölçüldü. Ateroskleroz progresyonunun değerlendirilmesi amacıyla bir yıl sonra karotid Doppler ultrasonografi ve homosistein seviyeleri tekrar değerlendirildi.

**Bulgular:** Çalışmamızda örneklem sayımızın az olmasına rağmen, bu hastalarda bazal artmış homosistein düzeyleriyle paralel olarak bazal karotis intima media kalınlık (KIMK) değerlerininde artmış olduğu görüldü. Takip süresi sonunda, hiperhomosisteinemiden bağımsız olarak bilateral karotid intima-media kalınlıkları artmıştı.

**Sonuç:** Sonuç olarak, Parkinson hastalarında L-dopa tedavisinin hiperhomosisteinemiye neden olabileceği ile ilgili birçok çalışma yayınlanmıştır. Fakat hiperhomosisteinemi ile artmış vasküler hastalık riski arasındaki ilişki halen tartışmalıdır. Biz, çalışma sonuçlarımıza dayanarak, Parkinson hastalarında hiperhomosisteineminin arter duvar kalınlığı artışına neden olabileceğini, fakat ateroskleroz progresyonu üzerine olan etkisinin tartışmalı olduğunu öne sürmekteyiz. *(Nöropsikiyatri Arşivi 2010; 47: 297-301)*

**Anahtar kelimeler:** Parkinson hastalığı, s-adenozilhomosistein, karotid arter hastalıkları, ateroskleroz

## Introduction

The elevation in plasma homocysteine (Hcy) levels constitutes a risk for the progression of cardiovascular and peripheral vascular diseases that may lead to atherosclerotic and endothelial damage (1-4). Furthermore, the development of hyperhomocysteinemia has been associated with dementia and cerebrovascular diseases, as well as extrapyramidal disorders such as Huntington's disease, dystonia and Parkinson's disease (PD) (5-9).

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Metabolism of levodopa (L-dopa) takes place in the brain and peripheral regions via the enzyme catechol-O-methyltransferase (COMT) and requires S-adenosylmethionine (AdoMet) as a methyl donor for methylation reactions. After donation of the activated methyl group to an acceptor, AdoMet is converted into total Hcy by formation of S-adenosyl-L-homocysteine (AdoHcy) (10). Consequently, elevated Hcy concentrations have been reported in L-dopa-treated PD patients, indicating an increased risk of hyperhomocysteinemia due to this treatment (11).

Moreover, it is known that Hcy levels are associated with environmental factors such as lifestyle (smoking, coffee and alcohol consumption) and diet (B12 and folate deficiencies); nutritional abnormalities including certain B12 metabolism disorders; male gender; an age over 65; and diagnosis of systemic disorders such as renal or hepatic failure, diabetes mellitus (DM) and hypothyroidism (12,13).

Similarly, certain studies have identified a correlation between hyperhomocysteinemia and increased carotid intima-media thickness (CIMT), suggesting that this may be an indicator of atherosclerosis and endothelial dysfunction (3). However, there are some issues that remain unclear, including: the length of time that may be necessary for the effects of Hcy to manifest in the endothelium; when these unfavorable effects can be accurately detected and monitored in clinical practice; and the mechanisms involved in producing these detrimental effects.

This study was designed to evaluate atherosclerosis progression by determining CIMT using carotid Doppler ultrasonography. Furthermore, we investigate the relationship between CIMT and Hcy levels in PD patients on L-dopa and dopa decarboxylase inhibitor (DDI) treatment.

## Methods

Twenty-three PD patients, who attended the movement disorders outpatient clinic at Uludag University between 2006 and 2007, were included in this study. All patients were on L-dopa/DDI therapy for at least one year. The controls consisted of 21 age- and gender-matched healthy volunteers who had similar life styles, including a Mediterranean-style diet. In terms of atherosclerosis, the Turkish population was similar to the HANGİ risk group according to the Framingham system. The Framingham Heart Study investigators created a useful, risk-assessment tool based on age, gender, total LDL or high-density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure, and history of diabetes and cigarette smoking. This tool can be used to predict the risk of a first cardiovascular event. After the risk factors and fitness levels were summed, the total score was translated into the estimated absolute risk of a cardiovascular heart disease event occurring within the next 10 years (14).

We excluded from the study subjects with pathologies known to lead to a B12-folate deficiency or malnourishment, such as: gastrointestinal malabsorption, postgastrectomy, pernicious anemia, thyroiditis, diabetes, Crohn's disease, gastric carcinoma, pancreatic insufficiency, irritable bowel syndrome, sprue-related disorders and dietary deficiencies in vegetarians. Exclusion criteria also included systemic disease diagnoses such as prior stroke, systemic lupus erythematosus, chronic atrophic gastritis, renal failure, hypothyroidism, coronary artery disease, hypertension, and patients over 65 years of age.

Diagnosis for PD was based on the UK Brain Bank diagnostic criteria, and clinical data were staged with Hoehn and Yahr (H-Y) scale. Tests for Hcy and B12-folic acid levels as well as lipid profiles and thyroid function tests were performed in all patients. The fasting blood tests were carried out in the morning. The patients were then evaluated using carotid Doppler ultrasonography to determine their CIMT. One year later, this evaluation was repeated to assess atherosclerosis progression. The controls were selected from individuals who visited the cardiology outpatient clinic for a check-up and had undergone similar examinations. The 21 control subjects also underwent carotid Doppler ultrasonography to establish their risk scores. The approval for the study was granted by the institutional ethics committee, and informed consent was given by all participants before enrollment.

The groups were compared after one year in terms of clinical and laboratory data, as well as atherosclerosis progression. Those requiring close monitoring and medical therapy were identified. During the follow-up period, each patient was treated according to his/her medical situation. Medications for PD patients were changed as needed.

### Ultrasonography

All carotid Doppler examinations were performed by the same radiologist (N.B.) in Uludag University. Color Doppler ultrasonography (SSA-770A Toshiba, Tokyo, Japan) and 7-11 Hz broadband electronic linear probe (704 AT, Toshiba) were applied. With the patient in a supine position with slight cervical hyperextension, the CIMT measurements were assessed in a sagittal plane, 1 cm proximal to the carotid bulb on the posterior wall of a plaque-free region. On average, a total of three measurements were obtained from each patient, and the mean value was calculated. A mean CIMT value greater than 0.8 mm was regarded as increased (15-17). These measurements were repeated after one year by the same radiologist following the same procedure. The radiologist was blinded for any clinical data of the patients.

### Statistical Analysis

All statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL). Categorical variables are presented as numbers and percentages, and continuous variables as means, standard deviations, minimum and maximum values. Distributions of continuous variables were tested for normality with the one-sample Kolmogorov-Smirnov test. According to test results, intergroup comparisons of the mean values of continuous variables were performed using the Wilcoxon and Student's t-tests. In order to compare basal and final values, percent changes were computed and Mann-Whitney U test

was applied to compare these values between the groups. Percent change values were expressed as mean and standard deviation. A correlation analysis was carried out to establish the relationship between continuous variables, and Pearson's correlation coefficient was applied. The Chi-square test was used for intergroup comparisons of categorical variables. The results were significant at $p<0.05$.

## Results

Of the 23 patients with PD, 13 were female (56.5%) and 10 were male (43.5%) with a mean age of 59.5±7.21 years (44-64 years old). The mean disease duration was 7±3.46 years (1.5-15 years), while the mean L-dopa therapy duration was 5.17±3.28 years (Table 1) (less than 5 years, n = 8 (34.8%); greater than 5 years, n = 15 (65.2%)).

Of the 21 controls, 11 were female (52.4%) and 10 were male (47.6%) with a mean age of 59,23±5,45 years. There was no significant difference between patients and controls in terms of age and gender ($p>0.05$) (Table 1).

The mean baseline Hcy level in PD patients on L-dopa therapy was above the normal (15.84±3.78; between 9.8-25.0) (reference value for Hcy in our laboratory is 5.0-12.0 µmol/L). The mean value of baseline Hcy in the control group was 8.62±2.56. Baseline and final Hcy levels in PD patients were significantly higher than those in the control group ($p<0.05$). However, we did not observe any significant difference between baseline and final Hcy levels in the patient group ($p>0.05$) (Table 2).

The mean left-right CIMT values for the patient and control groups at baseline and after one year are shown in table 3. Left-right CIMT increased more significantly from baseline values in PD patients receiving L-dopa, compared to controls ($p<0.05$). However, when the change in bilateral CIMT ratios (results of 1-year interval measurements) were compared between the patient and the control groups, the values for the patient group were significantly increased ($p<0.05$) (Table 3). There was a significant positive correlation between the baseline Hcy levels and the left-right CIMT values for PD patients ($p<0.001$; $r = 0.764$). Hcy levels in the patient group were slightly elevated (12-15 mmol/dl) in 10 subjects (40.3%) and markedly elevated (15 mmol/dl and higher) in 11 subjects (47.8%). Baseline left-right CIMT and Hcy values, when compared to those obtained at the end of one year from both groups, did not correlate with duration of illness or L-dopa use ($p>0.05$).

Of 23 PD patients, three subjects (13%) were at H-Y stage 1, four (16%) were at stage 3, and the remaining 16 patients (61%) were at stage 2. Therefore, it was not possible to perform statistical analyses of Hcy levels and CIMT with respect to the stage of the disease. The number of subjects receiving COMT inhibitors concomitant with L-dopa therapy was 12 (52.2%). There were no significant differences in Hcy levels between patients receiving COMT inhibitors and those who were not. Similarly, their bilateral CIMT values at baseline and at the end of one year were not significantly different ($p>0.05$) (Table 4).

Next, we investigated whether gender or any of the other independent parameters, were associated with left-right CIMT and Hcy levels. Left-right CIMT values were found to be significantly higher in female patients ($p<0.05$).

Laboratory tests indicated that low-density lipoprotein (LDL), HDL and fibrinogen values were not associated with plasma Hcy levels or left-right CIMT ($p>0.05$) (Table 5).

At the end of the study, patients with elevated plasma Hcy levels and increased CIMT received folate (5 mg/d, oral intake) and B12 (500 µg/d, oral intake) as prophylactic treatment for hyperhomocysteinemia. These patients are still being followed in the outpatient clinic.

## Discussion

It has been reported that L-dopa therapy increases Hcy levels in PD patients (1-3,9). Population studies have shown a strong correlation between increased CIMT and several cardiovascular risk factors. CIMT may also be associated with atherosclerosis progression and organ damage in high-risk patients. There has been recent interest in the clinical use of CIMT measurements for detecting preclinical (asymptomatic) atherosclerosis and for identifying subjects at high risk (18,19).

**Table 1**. Main characteristic features of Parkinson's disease patients and control subjects

| Variables | L-dopa treated PD patients | Control subjects |
|---|---|---|
| Mean age (yr) | 59.5±7.21 | 59.23±5.45 |
| Female/male | 13/10 | 11/10 |
| PD duration (yr) | 7±3.46 | - |
| L-dopa treatment (yr) | 5.17±3.28 | - |

PD: Parkinson's disease, yr: year

**Table 2**. Mean values of biochemical parameters in Parkinson's disease patients and control subjects

| | L-dopa treated PD patients | | Control subjects | |
|---|---|---|---|---|
| | Basal | Final | Basal | Final |
| Mean B 12 (mmol/L) | 195.04±4.51 | 203.01±1.4 | 295.76±3.43 | 312.54±1.82 |
| Mean folate (ng/mL) | 6.8±2.31 | 7.6±2.76 | 8.4±3.82 | 8.5±1.12 |
| Mean Hcy level (µmol/Ll) | 15.84±3.78* | 15.91±5.06 | 8.62±2.56 | 8.47±1.24 |

PD: Parkinson's disease, Hcy: homocysteine, *($p<0.05$)

**Table 3**. The mean values of carotid intima-media thickness in Parkinson's disease patients and control group

| Variables | Control | Parkinson's disease |
|---|---|---|
| **Basal** | | |
| Right | 0.62±0.10 mm | 0.87±0.27 mm* |
| Left | 0.65±0.11 mm | 0.86±0.29 mm* |
| **Final** | | |
| Right | 0.64±0.11 mm | 0.98±0.26 mm* |
| Left | 0.63±0.13 mm | 0.99 ±0.27 mm * |

*($p<0.05$)

Furthermore, L-dopa use and hyperhomocysteinemia might possibly be related to increased CIMT, which is a marker for systemic atherosclerosis (3,20). Nakaso et al. not only described cases of CIMT hypertrophy in PD patients receiving L-dopa, but also revealed a correlation between Hcy levels and CIMT hypertrophy. On the other hand, although their methodology was similar to that of Nakaso et al., Hassin et al. stated that hyperhomocysteinemia did not significantly increase CIMT in their samples (3,20).

Measurement of CIMT can vary depending on the technique used, follow-up period, blood viscosity, age distribution, and psychosocial status. Therefore, there is still no consensus regarding the association between increased CIMT and hyperhomocysteinemia (21).

Unlike other studies, which were cross-sectional, we recorded CIMT values twice in one year and compared these values in order to monitor atherosclerosis progression. We observed that there was an increase in baseline CIMT values that occurred in parallel with an increase in baseline Hcy levels. We also found that while the increase in bilateral CIMT was statistically significant, the increase in Hcy levels was not significant at the end of the one-year follow-up period. Our results could be interpreted as follows: hyperhomocysteinemia might be the start of arterial wall thickness development, but its role in progression of atherosclerosis is still discussable. It should be noted that a follow-up period of one year may be inadequate for demonstrating a link between elevated Hcy values and progression of atherosclerosis by arterial wall thickness; longer follow-up periods might be necessary.

Previous studies have proposed 12 μmol/L as an upper limit for Hcy in healthy individuals. It is known that plasma Hcy levels vary diurnally and are lower during the first half of the day. It has also been suggested that Hcy has a pathologic effect on blood vessels at levels of 15-20 μmol/L, thus, constituting an independent risk factor (19,21,23). In our study, all Hcy levels in the patient group were over 12 μmol/L.

**Table 4**. Homocysteine levels and bilateral carotid intima-media thickness (CIMT) values in Parkinson's patients receiving COMT inhibitors and those who were not

| Variables | COMT inhibitors | No COMT inhibitors |
|---|---|---|
| Hcy | 16.25±3.87 | 15.41±3.84 |
| Right CIMT baseline-control | 0.92±0.27 | 0.98±0.20 |
| Left CIMT baseline-control | 0.91±0.46 | 1.02±0.66 |

Hcy: homocysteine, (p>0.05)

**Table 5**. Laboratory tests associated with plasma homocysteine levels and left carotid intima-media thickness (CIMT) value

| | Hcy | | Left CIMT | |
|---|---|---|---|---|
| | r | p | R | p |
| LDL | -0.16 | p>0.05 | 0.04 | p>0.05 |
| HDL | -0.47 | p>0.05 | 0.15 | p>0.05 |
| Fibrinogen | 0.169 | p>0.05 | 0.37 | p>0.05 |

LDL: Low-density lipoprotein, HDL: High-density lipoprotein,
Hcy: homocysteine,
r: Pearson's correlation coefficient

Nevertheless, duration of the disease and its severity did not significantly correlate with Hcy and CIMT values. The effect of entacapone on decreasing plasma Hcy levels is still controversial. While the studies carried out in Europe have proved the effectiveness of this COMT inhibitor in L-dopa-induced hyperhomocysteinemia, no correlation has been demonstrated in studies conducted in the USA (2,22,24). In accordance with the American studies, our study revealed that entacapone did not have an impact on Hcy levels and CIMT values.

Our study showed baseline hyperhomocysteinemia and increased CIMT in PD patients receiving L-dopa. However, we found no evidence of relationship between increased CIMT and Hcy at the end of the study, which may be due to the fact that a one-year follow-up is not enough to demonstrate such a correlation. Since the small sample size was a limiting factor in this study, we recommend that future studies use larger patient sample populations and longer follow-up periods.

However, we would like to underline the importance of monitoring Hcy levels during L-dopa treatment and of starting Hcy-lowering therapy or changing L-dopa with other antiparkinsonian agents in case of hyperhomocysteinemia.

In conclusion, many clinical studies on hyperhomocysteinemia caused by L-dopa therapy in Parkinson patients have been published recently. However, the relationship between hyperhomocysteinemia and increased risk of vascular disease is still controversial. In spite of the small sample size, the findings of the present study may contribute to this disputable subject.

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