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The Role of Metabo-Inflammatory Syndrome and Ferropathological Processes in Atherosclerotic Plaque Formation in Parkinson's Disease: Insights from High-Resolution Carotid Duplex Analysis

Parkinson Hastalığında Aterosklerotik Plak Oluşumunda Metabo-inflamatuar Sendrom ve Ferropatolojik Süreçlerin Rolü: Yüksek Çözünürlüklü Karotis Dubleks Analizinden Elde Edilen Bilgiler

ABSTRACT

Objective: Peripheral metabo-inflammatory disturbances and ferropathological processes are closely linked to steno-occlusive pathologies in Parkinson's disease (PD), though their roles remain to be fully elucidated. This study aims to investigate cardio-metabolic risk stratification in PD in the context of peripheral metabo-inflammatory and ferropathological abnormalities, and to analyze the role of iron-related dysregulation in carotid atherosclerosis.

Method: This cross-sectional case-control study employed high-resolution carotid duplex imaging. Risk stratification for metabolic syndrome (MetS) was assessed using lipid-to-high-density lipoprotein cholesterol (HDL-C) ratios. Inter-correlative and multinomial regression analyses were performed for statistical comparison.

Results: PD patients showed a higher tendency toward cardiovascular disease (CVD) and atherogenicity. Calcified plaque formation and Type 4 stenosis patterns were significantly more prevalent (χ^2 = 21.717, χ^2 = 60.609; P < 0.001), along with altered peripheral iron correlation profiles in PD. An increased risk for MetS was also observed (cholesterol/HDL-C (P = 0.015 (z = 2.434), triglyceride/HDL-C ratio (P = 0.013 (z = 2.471)), along with augmented inflammatory hematological ratios in PD. In multinomial regression analysis, a 1-unit increase in glycated hemoglobin (HbA1c) was associated with a 1.967-fold increase in the likelihood of plaque-forming classification (Odds Ratio = 1.967). Additionally, a 1-unit increase in low-density lipoprotein cholesterol was associated with a slight decrease in risk (Odds Ratio = 0.981) (Cox-Snell = 0.266, Nagelkerke = 0.294).

Conclusion: Patients with PD demonstrated a higher risk of CVD and atherosclerotic plaque complications. A close association was observed between MetS and elevated cholesterol/HDL-C and triglyceride/HDL-C ratios. Additionally, there was an increased risk of oxidative stress-related atherothrombotic complications, driven by heightened inflammatory ratios and disturbed ferropathologic processes. However, peripheral iron disturbances did not show a significant relationship with stenosis patterns.

Keywords: Atherosclerotic plaque formation, ferropathological processes, high-resolution carotid duplex studies, inflammatory hematological ratios, intercorrelation analyses, metabolic syndrome

ÖZET

Amaç: Periferik metabolik-enflamatuar bozukluklar ve ferro-patolojik süreçler, Parkinson hastalığında (PH) steno-oklüzif patolojilerle yakından ilişkili olup halen açıklığa kavuşturulmayı beklemektedir. Bu çalışmada, PH'de kardiyo-metabolik risk stratifikasyonu periferik metabolik-enflamatuar ve ferro-patolojik bozukluklar bağlamında araştırmayı ve demirle ilişkili bozuklukların karotis aterosklerozundaki rolünü analiz etmeyi amaçladık.

Yöntem: Bu kesitsel vaka-kontrol çalışması, yüksek çözünürlüklü karotis dupleks çalışmaları kullanılarak yürütüldü. Metabolik sendrom (MetS) için risk stratifikasyonu, lipitlerin yüksek yoğunluklu lipoprotein kolesterolüne (HDL-C) oranının aritmetik olarak hesaplanmasıyla belirlendi. Karşılaştırmalı istatistiksel değerlendirme için inter-korelasyon ve multinominal regresyon analizleri kullanıldı.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Bulgular: PH hastalarının kardiyovasküler hastalık (KVH) ve aterojeniteye daha yüksek eğilim gösterdiği tespit edildi. Kalsifiye plak oluşumu ve Tip-4 stenoz paterni, anlamlı derecede daha yüksek bulundu (χ^2=21.717, χ^2=60.609, P < 0.001). Ayrıca, PH'de periferik demir korelasyon analizlerinde bozukluk gözlendi. MetS riskinin daha yüksek olduğu belirlendi (Kolesterol/HDL-C: P = 0.015, z=2.434; trigliserit/HDL-C: P = 0.013, z=2.471) ve artmış enflamatuar hematolojik oranlar tespit edildi. Multinomiyal regresyon analizinde, glikozile hemoglobin (HbA1c) düzeyinde 1 birimlik artış, plak oluşturan sınıflandırmaya ait olma olasılığında 1.967 kat artış ile ilişkilendirildi (Odds Oranı = 1.967). Ayrıca, düşük yoğunluklu lipoprotein kolesterolde (LDL) 1 birimlik artış, riskte hafif bir azalışla ilişkilendirildi (Odds Oranı = 0.981) (Cox-Snell = 0.266, Nagelkerke = 0.294).

Sonuç: PH hastalarının, KVH ve aterosklerotik plak komplikasyonları açısından daha yüksek risk taşıdığı ve Kolesterol/HDL-C ve trigliserit/HDL-C oranlarının daha yüksek olmasıyla ilişkilendirilen MetS ile yakın bir ilişki gösterdiği ortaya konmuştur. Ayrıca, artırılmış enflamatuar oranlar ve bozulmuş ferro-patolojik süreçler yoluyla oksidatif stres kaynaklı aterotrombotik komplikasyonlar için daha büyük bir risk olduğu tespit edilmiştir. Bununla birlikte, periferik demir bozukluğu ile stenoz paternleri arasında önemli bir ilişki bulunmamıştır.

Anahtar Kelimeler: Aterosklerotik plak oluşumu, ferropatolojik süreçler, inflamatuar hematolojik oranlar, interkorelasyon analizleri, metabolik sendrom, yüksek çözünürlüklü karotis dupleks çalışmaları

Iron, a fundamental element, plays a critical role in the etiopathogenesis of neurodegenerative diseases. Disruptions in iron homeostasis have been associated with progressive neuronal death and the development of various neurodegenerative disorders.[1] Iron supports several essential biological functions in brain homeostasis, including oxygen transport, DNA synthesis, mitochondrial respiration, myelin synthesis, neurotransmitter synthesis, and overall metabolism.[2] Under normal conditions, the brain's homeostatic mechanisms regulate iron concentrations across cellular compartments, preventing the toxic effects of excess free iron.[3] In healthy individuals, elevated levels of free iron are controlled through storage and excretion processes mediated by iron-regulatory protein 1/2 (IRP1/2). Iron is stored in ferritin and excreted via amyloid precursor protein (APP).[4] Additionally, iron uptake occurs through transferrin receptor 1 and divalent metal transporter 1 (DMT1). In Parkinson's disease (PD), iron homeostasis is disrupted due to the inactivation of IRP1/2, ferritin, and dysfunction of APP and DMT12.[4] This disruption leads to an accumulation of free iron in the neurons of the substantia nigra, resulting in dopamine dysregulation. The etiopathogenesis of this process is believed to involve several contributing factors, including increased permeability or dysfunction of the blood-brain barrier, a heightened pro-inflammatory state, upregulation of lactoferrin receptors in neurons and blood vessels, increased DMT1 expression in dopaminergic neurons, altered iron transport via the transferrin-transferrin receptor 2 (TfR2) pathway, and mutations in genes involved in iron binding and transport.[5] The progressive accumulation of iron in the peripheral system is thought to contribute to ischemic and atherothrombotic diseases, leading to reperfusion injury and promoting atherogenic processes, particularly within the cardiovascular system. Furthermore, iron's role in lipid-induced atherogenesis, through post-secretory oxidative modification of lipoproteins and its pro-oxidant properties as a biomolecule, has been well-documented.[6,7] Numerous studies have demonstrated central dysregulation of iron metabolism in Parkinson's disease, with iron chelation showing promise in improving clinical outcomes and mitigating central degeneration.

ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
APP	Amyloid precursor protein
BMI	Body mass index
CAD	Carotid artery disease
CCA	Common carotid arteries
CHF	Congestive heart failure
CRP	C-reactive protein
CV	Coefficients of variation
CVD	Cardiovascular disease
DM	Diabetes mellitus
DMT1	Divalent metal transporter 1
H&Y	Hoehn and Yahr Scale
HDL-C	Lipid-to-high-density lipoprotein cholesterol
HT	Hypertension
ICA	Internal carotid arteries
IHD	Ischemic heart disease
IMT	Intima-media thickness
IRP1/2	Iron-regulatory protein 1/2
LDL-C	Low-density lipoprotein cholesterol
LMR	Lymphocyte-to-monocyte ratio
MDS-UPDRS	MDS-Unified Parkinson's Disease Rating Scale
MetS	Metabolic syndrome
NLR	Neutrophil-to-lymphocyte ratio
PD	Parkinson's disease
PLR	Platelet-to-lymphocyte ratio
RBC	Red blood cell
TC	Total cholesterol
TfR2	Transferrin-transferrin receptor 2
TG	Triglycerides
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell count

Although most studies investigating the association between PD and cardio/cerebrovascular diseases lack strong evidence, current findings regarding the etiopathogenesis of these two conditions suggest that PD is associated with an increased risk of myocardial infarction, stroke, and congestive heart failure (CHF). This increased risk is thought to be related to PD-associated autonomic dysfunction and blood pressure abnormalities.[8] Metabolic syndrome (MetS) and carotid artery disease (CAD) risk stratification parameters are assessed using a risk index calculated by the ratio of triglycerides to high-density lipoprotein cholesterol (HDL-C).[9] This index is thought to be strongly correlated with a hyperglycemic profile, including insulin resistance, central obesity, and thyroid hormone disturbances, all key aspects of MetS, and may increase the risk of carotid vascular disease.[10,11] It is important to note the strong association between MetS and CAD risk, including coronary artery disease, peripheral artery disease, and other cardiovascular and cerebrovascular conditions. These have been attributed to various atherogenic processes, such as elevated levels of low-density lipoprotein cholesterol (LDL-C) and TG, along with reduced high-density lipoprotein cholesterol.

Although the relationship between neurodegenerative diseases and atherosclerotic processes has been reported in various studies,[12,13] current evidence remains insufficient to establish reliable risk stratification for cerebrovascular and cardiovascular diseases based on the assessment of objective ferroptopathologic, metabolic, and lipidemic proportional indices in PD. Additionally, the evaluation of carotid plaque types and their potential association with steno-occlusive pathologies is unexplored. In this study, ferropathologic indices were analyzed alongside quantified alterations in peripheral iron parameters, glycemic and lipidemic profiles, and peripheral inflammatory biomarkers. A correlative evaluation was then performed to assess the relevance of these processes to steno-occlusive pathologies.

Materials and Methods

Study Design and Participants

This cross-sectional case-control study was conducted between May 2023 and May 2024, involving 125 patients who were newly diagnosed and treated for PD at the Movement Disorder Clinic, along with 50 age- and sex-matched healthy controls who presented at the Neurology Outpatient Clinic of the same center. Before the study began, written informed consent was obtained from each participant. This research complies with the ethical standards of the relevant national and institutional committees on human experimentation, as well as with the Declaration of Helsinki (1975), revised in 2008. Ethics approval was provided by Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (Approval Number: AEŞH-BADEK-2024-332, Date: 08.05.2024). The diagnosis of idiopathic PD was made in accordance with the International Parkinson and Movement Disorder Society (MDS) Clinical Diagnostic Criteria.[14] Inclusion criteria for the PD group were as follows: age between 18 and 80 years; newly diagnosed with idiopathic PD at the research center; no comorbidities that could suggest an alternative diagnosis (e.g., stroke, intracerebral hemorrhage, tumor, demyelinating disease, intracerebral parenchymal or meningeal infection, cerebrovascular diseases, or other Parkinson-plus disease syndromes such as multiple system atrophy [MSA], progressive supranuclear palsy [PSP], or corticobasal degeneration [CBD]); and completion of all required neuroradiological and serum biochemical tests within the specified study timeframe. To optimize case selection in PD patients, inclusion required at least two or more outpatient clinic visits and the use of at least two anti-Parkinson medications, one of which had to be a levodopa-containing drug. Patients with atypical parkinsonism or other causes of secondary parkinsonism were excluded. The control group consisted of volunteers who visited the outpatient clinic during the study period and had no comorbidities and/or medication use that could affect the relevant parameters. These exclusion criteria included stroke (with or without clinical comorbidities), intracranial hemorrhage and/or malignancy, demyelinating diseases, neurodegenerative conditions, and other infectious diseases. All laboratory and clinical parameters were evaluated at the same center. All PD patients included in the study underwent a comprehensive clinical examination during their outpatient visits and were assessed using the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the modified Hoehn and Yahr (H&Y) scale. Only patients classified as having early-stage Parkinson's disease were included—defined as UPDRS-III scores between 10–15 (lower scores) and H&Y stages 1 or 2. Body mass index (BMI) was calculated for each participant.

Scanning Protocol and Carotid Duplex Studies

The radiological protocol for each participant was meticulously developed using standard processing procedures.[15] All imaging procedures were performed by certified expert technicians under the close supervision of experienced radiologists at the study center. Evaluation of intima thickness, plaque formation, and/or stenosis in the bilateral internal carotid arteries (ICA), including both bulbous and distal segments, as well as in the common carotid arteries (CCA) (proximal and distal segments) was conducted using a high-resolution instrument (DIASONICS VST Gateway) equipped with a 5-MHz linear-array transducer using B-mode ultrasound. Each section was visualized in multiple planes: longitudinal, coronal, and transversal. As part of the center's routine Doppler ultrasonographic radiological procedure, scan data were recorded from the distal straight portion (1 cm in length) of both common carotid arteries. Mean far-wall intima-media thickness (IMT) measurements were digitized along the axis of the distal straight portion (1 cm in length) of both common carotid arteries, starting from the bulb on each side. The presence of atherosclerotic plaque was defined as a focal expansion in the adjacent segment and/or a focal thickness increase in the intima-media layer within the segment. Plaque frequency was recorded as the presence of one or more plaques. The walls of the CCA (near and far), internal carotid arteries, and bilateral carotid bifurcations were meticulously evaluated for atherosclerotic plaques, intima thickness, and/or stenosis by expert radiologists (double-blind readers and observers) at the study center. All findings were documented in the hospital's patient record system. Carotid system evaluations were subsequently performed

offline by the responsible investigator, who was blinded to participant data, using information retrieved from the hospital database. Plaque assessments were conducted according to the classification system developed by the American Heart Association and the American College of Cardiology (AHA-ACC).[16] The main purpose of this classification is to evaluate arterial disease in clinical practice based on the type and characteristics of atherosclerotic plaques. It includes the following categories:

- Type 1-2 Plaques: Plaques with normal wall thickness,
- Type 3 Plaques: Plaques with diffuse intima-media thickness and no calcification,
- Type 4-5 Plaques: Calcified plaques with a lipid or necrotic core surrounded by fibrous tissue,
- Type 6 Plaques: Plaques with a complex structure containing surface defects, hemorrhage, or thrombus,
- Type 7 Plaques: Calcific plaques, and
- Type 8 Plaques: Fibrous plaques without a lipid core.

This classification provides a grading system based on the structural features of plaques and can aid in clinical management and treatment decision-making.

Biochemical Investigations

In accordance with the local hospital's routine biochemical laboratory procedures, 5 mL of blood samples were collected from the antecubital vein of the forearm into vacuum-sealed propylene tubes using a holder. Samples were taken between 08:00 and 12:00, following a fasting period of at least 8-12 hours and without the intake of any medications prior to collection. After sample collection, the blood was immediately centrifuged using a Hettich® Universal 30 RF at 1300 x g for 10 minutes, and the plasma was separated. Plasma samples were stored in a -80°C deep freezer until the time of analysis. All samples were analyzed simultaneously in the same laboratory and under identical conditions at the research center. Among the participants who met the study criteria, only those with at least two different biochemical parameters evaluated on at least two separate visits (per parameter) were included, to minimize the influence of acute metabolic and infectious fluctuations. The parameters measured during both visits were subjected to periodic quality control, and the inter- and intra-assay coefficients of variation (CV) were maintained below 5%. Serum biochemical values were standardized according to the protocols of the research center.

Serum iron status was assessed using the following parameters: serum ferritin (13-232 mcg/L), transferrin saturation (TSAT) (30-35%), total iron-binding capacity (TIBC) (240-450 µg/dL), and iron levels (120-370 mcg/dL). Hematological evaluation also included measurements of serum hemoglobin (11.8-15.8 g/dL), hematocrit (35-45%), red blood cell count (4.2-5.4 g/dL), and platelet count (10^3/mL). TSAT was calculated by dividing the proportion of transferrin bound to iron by the total serum transferrin, with a cut-off value of < 20%.[17] Ferritin levels were measured using the electrochemiluminescence method (Elecsys 2010, Germany), while serum iron levels were determined by the colorimetric method (Roche Automatic Analyzer, Germany). TIBC and TSAT values were calculated following standard analytical procedures as outlined in the literature.[18]

The serum glycemic and lipidemic profile was evaluated using the following parameters: serum fasting blood glucose (70-115 mg/dL), hemoglobin A1C (HbA1c) (4.7-5.6%), total cholesterol (TC) (0-200 mg/dL), triglycerides (0-150 mg/dL), HDL-C (40-60 mg/dL), non-HDL cholesterol (non-HDL-C) (< 120 mg/dL), calculated by subtracting HDL-C from TC, LDL-C (100-159 mg/dL), and very low-density lipoprotein cholesterol (VLDL-C) (< 150 mg/dL). In addition, TC/HDL-C, LDL-C/HDL-C, and triglyceride/HDL ratios were calculated to assess risk stratification for MetS and cardiovascular disease (CVD). Serum TC, triglycerides, and HDL-C levels were measured using a spectrophotometric method on an Abbott Aeroset automatic analyzer (Abbott Laboratories, Diagnostics Division, Abbott Park, IL 60064, USA). Serum LDL-C levels were calculated using the Friedewald formula.[19] Proportional parameters analyzed in the study were calculated by dividing the absolute values obtained from routine complete blood counts of peripheral blood samples.

Serum peripheral inflammatory status was assessed using the following markers: C-reactive protein (CRP) (< 1.0 mg/L), white blood cell count (WBC) ($4-10\times10^9$/L), and inflammatory hematological ratios, including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR). CRP levels were measured using the nephelometric method on a RADIM Delta nephelometer (Radim Diagnostics, Pomezia, Italy; Ref. 010138).

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA: IBM Corp.). The normality of variable distributions was evaluated using the Shapiro-Wilk test. Descriptive statistics for the variables were presented as mean ± standard deviation (SD), median with interquartile range (IQR), and minimum-maximum values. Numbers (n) and percentages (%) were used to summarize all demographic variables and blood values. The Mann-Whitney U test and t-tests were used to compare continuous blood measurement parameters between the patient and control groups. The relationship between demographic variables and radiological findings was evaluated using the Chi-Square test. Correlations between continuous variables obtained from serum laboratory tests in both the patient and control groups were assessed using the Spearman correlation coefficient. For the patient group, multinomial logistic regression analysis was performed, with ultrasound findings as the dependent variables and blood measurement parameters as the independent variables. A significance level of $P < 0.05$ was accepted as statistically significant, underscoring the relevance of the study's findings. Based on a power analysis conducted for the study, the required sample size was determined to be 29 participants per group, with a 95% confidence level ($1-\alpha$), 95% test power ($1-\beta$), and an effect size of d = 0.0.9795918.[20]

Table 1. Distribution Analysis of Participants' Descriptive Characteristics

	PD Group n (%)	Control Group n (%)	χ^2	P
Hypertension			19.870	**< 0.001***
No	20 (44.4)	25 (55.6)		
Yes	105 (80.8)	25 (19.2)		
Hyperlipidemia			–	**0.043****
No	109 (69.4)	48 (30.6)		
Yes	16 (94.1)	1 (5.9)		
Congestive Heart Failure			7.521	**0.006***
No	105 (67.7)	50 (32.3)		
Yes	20 (100.0)	0 (0.0)		
Ischemic Heart Dsease			10.794	**0.001***
No	83 (64.3)	46 (35.7)		
Yes	42 (91.3)	4 (8.7)		
Peripheral Vascular Disease			8.441	**0.004***
No	84 (65.1)	45 (34.9)		
Yes	41 (89.1)	5 (10.9)		
Carotid Plaque Type			21.717	**< 0.001**
Soft	42 (53.8)	36 (46.2)		
Calcified	62 (87.3)	9 (12.7)		
Heterogenous	21 (80.8)	5 (19.2)		
Plaque Classification			60.609	**< 0.001**
Type 1	16 (32.0)	34 (68.0)		
Type 2	49 (76.6)	15 (23.4)		
Type 4	51 (98.1)	1 (1.9)		
Type 7	9 (100.0)	0 (0.0)		

PD, Parkinson's Disease. *Yates Continuity Correction; **Fisher's Exact Test.

Results

Demographic Data

The distribution of participants by age and gender was found to be homogeneous between the groups (P > 0.05). However, a significant difference was observed between groups in the presence of hypertension (HT) and CHF, with these conditions being significantly more prevalent in the PD group (χ^2 = 0.046, χ^2 = 7.521, respectively; P < 0.005). Similarly, the prevalence of hyperlipidemia, ischemic heart disease (IHD), and peripheral vascular disease (PVD) was significantly higher in the PD group (P = 0.043, P = 0.001, and P = 0.004, respectively). A statistically significant difference was also found between the groups in terms of both plaque formation type and stenosis pattern (χ^2 = 21.717, χ^2 = 60.609, respectively; P < 0.001). Calcified plaque formation, which poses a higher atherogenic risk, was more frequently observed in the PD group (62, IQR = 87.3). Likewise, Type 4 stenosis, representing a higher-risk stenosis pattern, was significantly more common in the PD group compared to the control group (51, IQR = 98.1) (Table 1). No significant differences were found between the groups regarding BMI, smoking and/or alcohol use, oral contraceptive use, diabetes mellitus (DM), previous stroke, and/or transient ischemic attack incidence.

Comparison Analyses of Serum Iron Status in the PD and Control Groups

In the PD group, the median ferritin level was 86.50 (IQR = 105.0), which was significantly higher than that of the control group (P < 0.001). In contrast, the median values of hematocrit, red blood cell (RBC) count, and TSAT were higher in the control group (P < 0.005) (Table 2).

Comparison Analyses of Metabolic Parameters in the PD and Control Groups

Table 2 presents the distribution of metabolic parameters between the groups. Significant differences were observed in glycemic and lipidemic profiles. The PD group exhibited higher levels of glucose, HbA1c, TC, triglycerides, LDL-C, VLDL-C, and non-HDL-C compared to the control group (P < 0.001 (z = 5.303), P < 0.001 (z = 4.054), P = 0.003 (z = 2.961), P = 0.007 (z = 2.700), P = 0.044 (z = 2.015), P = 0.022 (z = 2.299), P < 0.001 (z = 3.656), respectively). Additionally, the PD group cholesterol/HDL-C and triglyceride/HDL-C ratios, indicating an increased risk for MetS and CVD (P = 0.015 (z = 2.434), P = 0.013 (z = 2.471), respectively).

Comparison Analyses of Peripheral Inflammatory Parameters in the PD and Control Groups

Table 2 presents the distribution of peripheral inflammatory parameters between the PD and control groups. Significant

Table 2. Comparison of Peripheral Biochemical Parameters Between Groups

	PD Group Median (IQR) Mean ± SD	Control Group Median (IQR) Mean ± SD	Z, t	P
Ferritin	86.50 (105.0)	39.30 (36.5)	5.017	**< 0.001**
TSAT	0.00 (1.0)	24.85 (17.0)	10.873	**< 0.001**
Hematocrit	41.67 ± 4.99	43.37 ± 3.67	2.465	**0.015**
RBC	4.71 ± 0.64	4.92 ± 0.59	2.044	**0.042**
Glucose (mg/dL)	108.00 (25.1)	93.85 (17.5)	5.303	**< 0.001**
HbA1c	5.60 (1.70)	4.95 (0.90)	4.054	**< 0.001**
TC (mg/dL)	192.00 (60.2)	180.50 (41.6)	2.961	**0.003**
Triglycerides (mg/dL)	140.00 (80.8)	112.50 (61.6)	2.700	**0.007**
LDL-C (mg/dL)	121.40 (46.1)	110.30 (34.6)	2.015	**0.044**
VLDL-C (mg/dL)	26.50 (18.30)	21.90 (10.25)	2.299	**0.022**
Non-HDL-C (mg/dL)	141.50 (44.56)	120.90 (45.4)	3.656	**< 0.001**
Cholesterol/HDL-C Ratio	4.05 (1.39)	3.54 (1.22)	2.434	**0.015**
Triglyceride/HDL-C Ratio	2.97 (2.63)	2.39 (1.76)	2.471	**0.013**
CRP (mg/L)	4.80 (8.50)	3.50 (1.83)	4.540	**< 0.001**
WBC (10^3/uL)	7.50 (3.00)	6.80 (2.83)	2.567	**0.010**
NLR	2.47 (1.63)	1.65 (0.83)	4.981	**< 0.001**
LMR	3.70 (1.92)	5.25 (1.95)	4.834	**< 0.001**
PLR	140.30 (94.63)	112.70 (45.58)	3.166	**0.002**

CRP, C-Reactive Protein; HbA1c, Hemoglobin A1C; HDL-C, High-Density Lipoprotein Cholesterol; IQR, Interquartile Range; LDL-C, Low-Density Lipoprotein Cholesterol; LMR, Lymphocyte-to-Monocyte Ratio; NLR, Neutrophil-to-Lymphocyte Ratio; PD, Parkinson's Disease; PLR, Platelet-to-Lymphocyte Ratio; RBC, Red Blood Cell Count; TC, Total Cholesterol; TSAT, Transferrin Saturation; VLDL-C, Very Low-Density Lipoprotein Cholesterol; WBC, White Blood Cell Count.

Table 3. Intercorrelation Analyses of Serum Iron Status in the PD Group

	Hemoglobin	Hematocrit	RBC	Platelet Count	Ferritin	Transferrin	TIBC	Serum Iron	TSAT
Hemoglobin	1								
Hematocrit	**0.701****	1							
RBC	0.519**	**0.668****	1						
Platelet Count	-0.048	-0.054	-0.022	1					
Ferritin	0.156	0.116	0.021	**-0.191***	1				
Transferrin	**0.214***	**0.217***	0.02	**-0.195***	**0.368****	1			
TIBC	-0.128	-0.058	0.095	0.172	**-0.374****	**-0.482****	1		
Serum Iron	**0.219***	**0.248****	0.092	-0.165	0.251**	**0.873****	-0.078	1	
TSAT	**-0.214***	**-0.223***	0.037	0.034	0.003	**-0.196***	0.025	**-0.207***	1

RBC, Red Blood Cell Count; TIBC, Total Iron Binding Capacity; TSAT, Transferrin Saturation. *P < 0.05; **P < 0.01.

differences were observed in CRP and WBC levels between the groups [P < 0.001 (z = 4.540), P = 0.010 (z = 2.567], respectively). Importantly, these values were significantly higher in the PD group compared to the control group. In addition, inflammatory hematological ratios were compared between groups, and higher NLR, LMR, and PLR values were observed [P < 0.001 (z = 4.981), P < 0.001 (z = 4.834), P = 0.002 (z = 3.166), respectively].

Intercorrelation Analyses of Serum Iron Status and Pattern Evaluation

Intercorrelation analyses of serum iron status parameters were conducted for both the PD and control groups. Only correlations with a relationship percentage between two variables between 0.50 and 1.0 were included in the statistical analysis and interpretation. In the PD group, strong positive correlations were observed between serum iron and transferrin, hematocrit and hemoglobin, and RBC and hematocrit (r = 0.873, r = 0.701, and r = 0.668, respectively) (Table 3). In the control group (Table 4), transferrin showed a strong negative correlation with TIBC (r = -0.620), a strong positive correlation with serum iron (r = 0.730), and a strong positive correlation with TSAT (r = 0.997). In addition, a moderate negative correlation (r = -0.614) was found between TSAT and TIBC, a strong positive correlation (r = 0.733) between TSAT and serum iron, and a moderate positive correlation (r = 0.615) between hematocrit and hemoglobin.

Table 4. Intercorrelation Analyses of Serum Iron Status in the Control Group

	Hemoglobin	Hematocrit	RBC	Platelet Count	Ferritin	Transferrin	TIBC	Serum Iron	TSAT
Hemoglobin	1								
Hematocrit	**0.615****	1							
RBC	**0.356***	**0.469****	1						
Platelet Count	-0.054	0.019	0.044	1					
Ferritin	0.223	0.053	-0.202	**-0.324***	1				
Transferrin	0.222	0.286*	-0.146	**-0.381****	0.179	1			
TIBC	-0.214	-0.252	-0.013	**0.419****	-0.173	**-0.620****	1		
Serum Iron	0.177	0.303*	-0.052	-0.104	0.111	**0.730****	-0.047	1	
TSAT	0.205	0.279*	-0.134	**-0.392****	0.16	**0.997****	**-0.614****	**0.733****	1

RBC, Red Blood Cell Count; TIBC, Total Iron Binding Capacity; TSAT, Transferrin Saturation. *P < 0.05; **P < 0.01.

Table 5. Correlation Analyses Between Steno-Occlusive Pattern and Demographic Data in PD

	Type 1 n (%)	Type 2 n (%)	Type 3 n (%)	Type 4 n (%)	χ^2	P
Diabetes Mellitus					14.776	**0.002***
No	11 (17.5)	27 (42.9)	17 (27.0)	8 (12.7)		
Yes	4 (6.6)	22 (36.1)	34 (55.7)	1 (1.6)		
Congestive Heart Failure					8.67	**0.024***
No	16 (15.2)	43 (41.0)	41 (39.0)	5 (4.8)		
Yes	0 (0.0)	6 (30.0)	10 (50.0)	4 (20.0)		
Ischemic Heart Disease					8.682	**0.029***
No	13 (15.7)	37 (44.6)	30 (36.1)	3 (3.6)		
Yes	1 (20.0)	0 (0.0)	4 (80.0)	0 (0.0)		
Carotid Plaque Type					70.168	**< 0.001***
Soft	12 (28.6)	30 (71.4)	0 (0.0)	0 (0.0)		
Calcified	4 (6.5)	15 (24.2)	37 (59.7)	6 (9.7)		
Heterogeneous	0 (0.0)	4 (19.0)	14 (66.7)	3 (14.3)		

*Fisher-Freeman-Halton test was used.

Correlation Analyses Between Steno-Occlusive Pattern and Demographic Data

The relationship between demographic variables and ultrasound findings in PD patients was analyzed. The presence of DM was found to affect the distribution of steno-occlusive patterns (χ^2 = 14.776, P = 0.002). Additionally, significant associations were identified between the presence of congestive heart failure and IHD with carotid plaque type (χ^2 = 8.670 and χ^2 = 8.682, respectively; P < 0.05). A significant correlation was also observed between carotid plaque type and occlusion pattern (χ^2 = 70.168, P < 0.001) (Table 5).

Regression Analysis Between Serum Parameters and Steno-Occlusive Pattern

In the PD group, carotid ultrasonography data and peripheral markers were evaluated using multinomial logistic regression analysis. Ultrasound results were selected as the dependent variables, with the Type 1 plaque pattern used as the reference category for practical interpretation. The model including HbA1c, HDL-C, LDL-C, and VLDL-C as independent variables was found to be statistically significant (P < 0.001). According to the analysis, a 1-unit increase in HbA1c was associated with a 1.967-fold increase in the risk of developing more advanced plaque classifications (Odds Ratio = 1.967). Likewise, a 1-unit increase in LDL-C was associated with a slightly decreased risk (Odds Ratio = 0.981). The Pseudo-R2 values, which represent the explanatory power of the independent variables on the ultrasound findings, were Cox-Snell = 0.266 and Nagelkerke = 0.294 (Table 6). Our regression analysis revealed significant associations between HbA1c, HDL-C, LDL-C, and VLDL-C levels and plaque formation in PD patients.

Discussion

In PD research, the primary focus has traditionally been on genetic, metabolic, and inflammatory degeneration processes within the central nervous system. However, the impact of peripheral metabo-inflammatory and ferro-pathological processes on the central nervous system, particularly in relation to the carotid system, remains largely unexplored. This study represents a pioneering effort to investigate this connection by evaluating the relationship between steno-occlusive pathologies and peripheral disruptions in iron status, metabolic parameters,

Table 6. Multinomial Logistic Regression Analysis Between Serum Biochemical Parameters and Steno-Occlusive Patterns in Parkinson's Disease (PD)

	B	SEM	Odds Ratio	95% CI
HbA1c	0.377	0.316	1.458	0.785-2.708
HDL-C	-0.054	0.029	0.947	0.895-1.003
LDL-C	-0.001	0.008	0.999	0.983-1.015
VLDL-C	-0.025	0.021	0.975	0.936-1.015
Type 4 Plaque				
HbA1c	0.676*	0.315	1.967	1.061-3.647
HDL-C	-0.024	0.029	0.976	0.923-1.033
LDL-C	-0.020*	0.009	0.981	0.963-0.998
VLDL-C	0.003	0.02	1.003	0.965-1.042
Type 7 Plaque				
HbA1c	-0.042	0.509	0.959	0.353-2.604
HDL-C	0.068	0.041	1.07	0.987-1.160
LDL-C	-0.027	0.014	0.973	0.946-1.001
VLDL-C	0.037	0.027	1.038	0.984-1.095

Cox-Snell = 0.266, Nagelkerke = 0.294, Model x^2 = 38.419, P < 0.001. CI, Confidence Interval; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; SEM, Standard Error of the Mean; VLDL-C, Very Low-Density Lipoprotein Cholesterol. *P < 0.05, **P < 0.01.

and hyperinflammatory markers in PD. This was achieved through objective correlative and regression analyses, providing an intercorrelated perspective.

PD and CVD are both mutagenetic, metabo-inflammatory conditions in which atherogenesis-related risk factors, both non-modifiable (such as age and gender) and modifiable (such as diabetes), are known to play a crucial role in their etiopathogenesis. These comorbidities were observed more frequently in the PD group.[21] Currently, carotid artery stenosis caused by atherosclerosis affects approximately 4.8% of men and 2.2% of women under the age of 70. After age 70, this risk increases at least threefold in both sexes.[22] In clinical practice, atherosclerotic processes are observed in individuals with PD at roughly twice the rate seen in the general population, and it is suggested that the underlying pathogenetic mechanisms of PD and CVD may mutually reinforce one another.[23,24] Atherosclerotic processes can accelerate cognitive decline in PD by causing microstructural and macrostructural changes in cerebrovascular regions, as well as in cardiovascular structures.[25] These pathological changes, particularly those affecting the basal ganglia, are associated with high mortality and may further provoke degenerative processes, leading to rapid clinical and cognitive deterioration in PD patients.[26] In this study, the PD and control groups were compared in terms of demographic characteristics and CVD comorbidities. HT, hyperlipidemia, ischemic heart disease, CHF, and PVD were all found to be significantly more prevalent in the PD group (P < 0.005) (Table 1).

Although several epidemiological studies have explored the relationship between cardiovascular and cerebrovascular risks and PD, research on the specific patterns of extracranial carotid plaque formation and stenosis in PD is still limited. The AZSAND study (Arizona Study of Aging and Neurodegenerative Disorder) investigated the correlation between cerebral neurodegenerative processes and extracranial carotid artery disease (ECAD) by analyzing neurofibrillary tangles (NFT), beta-amyloid plaques, and cerebral amyloid angiopathy (CAA) through histopathological density scores in postmortem examinations of individuals with clinically diagnosed ECAD. The presence of ECAD was associated with a 21% greater NFT burden at death compared to individuals without ECAD (P < 0.02). Additionally, an increased NFT burden (P < 0.02) was observed in all cerebral regions, particularly in the temporal lobe.[27] In a study conducted by Nakaso et al.[28] involving PD patients, mild hypertrophy of the carotid artery intima-media thickness was found to be more common in the PD group compared to controls, and a positive correlation was reported between steno-occlusive patterns and L-dopa use. Peripheral iron disturbance also plays a notable role in ECAD. In one study examining the relationship between elevated peripheral iron indices and carotid intima-media thickness, a positive correlation was identified between high ferritin levels and carotid plaque formation, especially in males (odds ratio per 1-SD increase in serum ferritin levels: 1.33; 95% confidence interval: 1.08-1.44). Higher serum ferritin levels were also associated with increased odds for carotid plaque prevalence in both sexes.[29] In our study, extracranial carotid duplex assessments of plaque formation type and stenosis pattern were compared between groups. Calcified plaque formation, associated with a higher atherogenic risk, was observed more frequently in the PD group. Additionally, the Type 4 stenosis pattern, considered one of the highest risk categories for critical stenosis and atherosclerotic stroke, was significantly more prevalent (Table 1). Distribution analyses also revealed a statistically significant relationship between the presence of congestive heart failure, IHD, and carotid plaque type (P < 0.05) (Table 5). Multinomial logistic regression analysis further demonstrated a significant association between metabolic disturbances and plaque formation risk (HbA1c Odds Ratio = 1.967 and LDL-C Odds Ratio = 0.981) (Table 6). In contrast, peripheral iron status did not show a correlation with plaque type or stenosis pattern. These findings underscore the reliability and robustness of our results and provide valuable insights into the factors contributing to plaque formation in PD.

Active ferrous iron (Fe^{2+}) is an atherogenic oxidant molecule that can penetrate subintimal spaces, where it catalyzes lipid peroxidation in the endothelium. This process is primarily facilitated by sources such as ubiquitous ferritin, hemin deposits, iron compounds complexed with proteoglycans, receding macrophages (via lysosomal iron exocytosis), and damaged vascular cells. The most critical factor triggering the release of free iron is the disruption of oxygen transport, which occurs as a result of various atherosclerotic processes affecting the endothelial surface.[30] *In vitro* studies have shown that disturbed iron status, particularly elevated ferritin levels, induces pro-oxidation of LDL alkyl groups, leading to oxidative modification of LDL. One of the earliest descriptions of this mechanism was reported in a 1993 study examining atherosclerotic processes in the carotid artery. It demonstrated that serum ferritin acts as

an effective inducer, especially in the early stages, of carotid atherogenesis over a 5-year period by increasing the atherogenic potential of LDL.[31] Quantitative alterations of peripheral iron status were evaluated between groups, and a significant increase in ferritin levels was found in the PD group ($P < 0.001$) (Table 2). In a study examining peripheral serum status after the onset of PD, hemoglobin levels in PD patients were lower than in controls (125.1 ± 15.68 g/L vs. 139.9 ± 11.83 g/L; $P < 0.001$), while no significant differences were observed in other serum iron parameters or TIBC.[32] In our intercorrelation analyses, strong positive correlations were observed in the PD group between serum iron and transferrin, hematocrit and hemoglobin, and RBC and hematocrit. These patterns differed from those typically expected in the healthy population (Tables 3 and 4).[33,34]

Several studies have also reported a relationship between plasma lipoproteins and PD. It has been found that lower levels of plasma HDL-C and apolipoprotein A1 (ApoA1) are associated with an increased risk of earlier PD onset,[35] and a positive correlation has also been observed with disease duration. Studies examining the relationship between LDL-C and PD have also reported that LDL-C levels tend to be higher in individuals with PD.[36] Additionally, recent research has suggested that the TG/HDL-C ratio may serve as a useful marker for identifying insulin resistance, one of the core criteria of metabolic syndrome, and may even be used for the early detection of cardiometabolic risk and prevention of complications, offering a potential alternative to conventional insulin testing.[37] In a cohort study investigating the likelihood of developing both MetS and PD, a positive correlation was found between MetS risk and PD incidence (log-rank $P < 0.001$). The study also reported that the risk of developing PD increased progressively with the number of MetS components present ($P < 0.001$).[38] In our study, TC, triglycerides, LDL-C, VLDL-C, and non-HDL-C levels were significantly higher in the PD group compared to the control group ($P < 0.05$) (Table 2). Furthermore, correlation analyses (Tables 1 and 2) showed that hypertension and hyperlipidemia were significantly more prevalent in the PD group, along with elevated glucose and HbA1C levels ($P < 0.001$), indicating a higher MetS index in individuals with PD.

Peripheral immune cell-mediated hyperinflammatory conditions can enhance microglial activation and T-lymphocyte infiltration, contributing to neurodegeneration in the substantia nigra pars compacta (SNpc) via microglial activation and T-lymphocyte infiltration. In one study, PD and control groups were compared in terms of NLR, LMR, and PLR. The NLR was found to be higher in the PD group and was positively correlated with both the UPDRS and H&Y scores.[39] In a population-based study, peripheral immune cell markers, including differential leukocyte and platelet counts, granulocyte-to-lymphocyte ratio (GLR), PLR, the adapted systemic immune-inflammation index (adapted SII), and CRP, were analyzed. The study found that individuals with higher GLR, PLR, and adapted SII values had an increased risk of developing PD.[40] In our study, the distribution of peripheral inflammatory parameters between groups was examined, and significant differences were observed in CRP and WBC counts. Among the hyperinflammation indices, NLR, LMR, and PLR values were significantly higher in the PD group ($P < 0.005$) (Table 2).

PD is a multifactorial disorder that reflects a range of molecular deteriorations, including carotid-cerebral and cardiovascular atherosclerotic processes, as part of its etiology. Iron dysregulation and the resulting induction of reactive oxidative processes in the central nervous system play a crucial role in its fundamental etiopathogenesi.[41] In recent years, increasing attention has been given to the potential role of peripheral ferro-pathologic processes in the development and progression of these disturbances. The contribution of steno-occlusive pathologies to clinical morbidity and mortality in PD is becoming increasingly well understood. The findings of this comprehensive study are significant, as they demonstrate the progression of ferro-pathologic and metabo-inflammatory disturbances in PD, along with their contribution to steno-occlusive pathologies. Moreover, the type and pattern of occlusion in the extracranial carotid system appear to differ in PD patients compared to healthy individuals. This study sheds light on carotid system-related atherogenic processes in PD, which have not been adequately explained to date, and explores their relationship with atherogenic risk factors. The study primarily reflects the interactions observed in the population of the country where it was conducted, and different results may emerge from analyses involving larger and more ethnically diverse populations.

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