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Original Article

Assessment of the Relationship Between Amino Acid Status and Parkinson's Disease: A Comprehensive Review and Meta-analysis

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ABSTRACT: ***Background:*** Parkinson's disease (PD) is characterized by the inability of dopamine production from amino acids. Therefore, changes in amino acid profile in PD patients are very critical for understanding disease development. Determination of amino acid levels in PD patients with a cumulative approach may enlighten the disease pathophysiology. ***Methods:*** A systematic search was performed until February 2023, resulting in 733 articles in PubMed, Web of Science and Scopus databases to evaluate the serum amino acid profile of PD patients. Relevant articles in English with mean/standard deviation values of serum amino acid levels of patients and their healthy controls were included in the meta-analysis. ***Results:*** Our results suggest that valine, proline, ornithine and homocysteine levels were increased, while aspartate, citrulline, lysine and serine levels were significantly decreased in PD patients compared to healthy controls. Homocysteine showed positive correlations with glutamate and ornithine levels. We also analyzed the disease stage parameters: Unified Parkinson's Disease Rating Scale III (UPDRS III) score, Hoehn–Yahr Stage Score, disease duration and levodopa equivalent daily dose (LEDD) of patients. It was observed that LEDD has a negative correlation with arginine levels in patients. UPDRS III score is negatively correlated with phenylalanine levels, and it also tends to show a negative correlation with tyrosine levels. Disease duration tends to be negatively correlated with citrulline levels in PD patients. ***Conclusion:*** This cumulative analysis shows evidence of the relation between the mechanisms underlying amino acid metabolism in PD, which may have a great impact on disease development and new therapeutic strategies.

RÉSUMÉ : Évaluation de la relation entre le profil des acides aminés et la maladie de Parkinson : une revue complète et une méta-analyse. ***Contexte :*** La maladie de Parkinson (MP) est caractérisée par l'incapacité de produire de la dopamine à partir d'acides aminés. Par conséquent, les changements dans le profil des acides aminés chez les patients atteints de cette maladie sont très importants pour en comprendre le développement. Il s'ensuit que la détermination des niveaux d'acides aminés par une approche cumulative chez les patients atteints de la MP peut éclairer la physiopathologie de cette maladie. ***Méthodes :*** Une recherche systématique a été effectuée jusqu'en février 2023, aboutissant à un total de 733 articles identifiés dans les bases de données PubMed, Web of Science et Scopus et permettant d'évaluer le profil des acides aminés sériques chez les patients atteints de la MP. En fin de compte, ce sont des articles pertinents en anglais, avec les valeurs moyennes/écart-type des niveaux d'acides aminés sériques de patients et de leurs témoins en santé, qui ont été inclus dans notre méta-analyse. ***Résultats :*** Nos résultats suggèrent que les niveaux de valine, de proline, d'ornithine et d'homocystéine ont augmenté, tandis que les niveaux d'aspartate, de citrulline, de lysine et de sérine ont diminué de manière significative chez les patients atteints de la MP par rapport à des témoins en santé. L'homocystéine a montré des corrélations positives avec les niveaux de glutamate et d'ornithine. Nous avons également analysé les paramètres relatifs au stade de la maladie, à savoir le score à la *Unified Parkinson Disease Rating Scale* III (UPDRS III), le score du stade de Hoehn Yahr, la durée de la maladie et la dose journalière équivalente de lévodopa (DJEL ou *levodopa equivalent daily dose*) procurée aux patients. À cet égard, il a été observé que la DJEL possède une corrélation négative avec les niveaux d'arginine chez les patients. Le score à la UPDRS III donne à voir une corrélation négative avec les niveaux de phénylalanine et tend également à montrer une corrélation négative avec les niveaux de tyrosine. Enfin, la durée de la maladie tend à être corrélée négativement avec les niveaux de citrulline des patients atteints de la MP. ***Conclusion :*** Cette analyse cumulative met en évidence la relation entre les mécanismes qui sous-tendent le métabolisme des acides aminés dans la MP, ce qui pourrait avoir un impact important sur le développement de la maladie et sur les nouvelles stratégies thérapeutiques.

Keywords: Metabolism; neurochemistry; neurodegenerative diseases; neurodegenerative disorders; Parkinson's disease

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Highlights

- Amino acid profiling in Parkinson's Disease (PD) shows unique changes for each amino acid.
- Elevated proline levels may indicate disturbed collagen/glutamate pathways.
- Changes in ornithine, citrulline, and aspartate levels may be indicators of mitochondrial dysfunction, and increased ornithine, a precursor to glutamate, urea, and polyamines, may influence α-synuclein-associated PD pathology.

Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders with a worldwide prevalence of over six million individuals. This number is expected to double to over 12 million by 2040. Over the past generation, its prevalence has increased by 2.5 times, making it a leading contributor to neurological disability.[1,2]

PD is characterized by the presence of involuntary or dysregulated motor symptoms, including tremors, rigidity and impaired coordination. The clinical presentation typically unfolds gradually, displaying a progressive nature. As the disease advances, patients often encounter challenges in ambulation and speech production. Additionally, various non-motor manifestations emerge, encompassing cognitive and affective alterations, sleep disturbances, depressive symptoms, cognitive impairments and persistent fatigue.[3]

The cardinal features of PD result from the degeneration of dopaminergic neurons in the basal ganglia, a critical hub for motor function regulation. These neurons are responsible for synthesizing and releasing dopamine, a neurotransmitter essential for smooth motor control. The loss of dopaminergic neurons leads to insufficient dopamine levels, causing the characteristic motor impairments in PD.[4]

PD is also characterized by the presence of Lewy bodies and Lewy neurites, which are neural inclusions, along with cell loss in the substantia nigra and other areas of the brain. The primary components of Lewy bodies are aggregated and misfolded α-synuclein species, indicating that PD falls under the category of synucleinopathies.[5]

Misfolded α-synuclein species include polyamines, leading to the accumulation and fibril formation of putrescine, spermine and spermidine. Its accumulation in neurons is playing a key role in PD development.[6,7] Polyamines are molecules including two to four amino groups and play a role in several mechanisms in living organisms including apoptosis, cell division and differentiation, cell proliferation, DNA and protein synthesis, gene expression, homeostasis and signal transduction. Dietary amino acid intake and serum amino acid profile contribute to polyamine biosynthesis, and the accumulation of polyamines has been reported to be related to several diseases including neurological diseases.[8,9]

Furthermore, amino acids are the precursors of the neurotransmitters regulating all the neurological activities of the brain. A deficiency or excess of a specific amino acid can significantly impact neurotransmitter synthesis.[10]

Therefore, it is important to indicate the serum amino acid profile of PD patients to understand the underlying mechanism and dietary factors for the development and treatment procedures of the disease.

Methods

Eligibility criteria

To investigate the serum amino acid profile and metabolism in PD, a comprehensive review of human studies was conducted, including those involving the serum amino acid level of PD patients. Data on mean and standard deviation were collected and used in the meta-analysis, without imposing any restrictions on age, gender, race or body mass index.

To be included in the meta-analysis review, studies had to meet the following inclusion criteria: (i) Measurement of serum amino acid levels with reported mean and standard deviation values; (ii) Provision of sample size information; (iii) Use of accepted diagnostic criteria for the disease; (iv) Adherence to appropriate sample collection conditions. Studies that did not meet these criteria were excluded (see Table 1). Detailed information about the included studies is provided in the "Characteristics of Studies" section and Table 2.

Systematic search

In this study, a systematic research was conducted in the PubMed, Scopus and Web of Science databases with keywords "serum amino acid" or "serum amino acid level" and "Parkinson" or "Parkinson's disease" without any date restriction. The systematic screening was conducted until February 15, 2023. The PRISMA procedures were followed for searching and evaluating the data[11] The articles that were identified as duplicates among the articles found commonly in the databases have been eliminated.

Table 1. PICO table for the inclusion and exclusion criteria

P	I	C	O
Patients	Intervention or exposure (treatment, diagnoses, observations)	Comparison	Outcome
Individuals were Parkinson's disease (PD) patients and their control groups. All articles including PD patients and control group serum amino acid data (mean, SD) were included in the meta-analysis. The diagnosis of PD should be mentioned and accepted diagnosis criteria such as the Unified Parkinson's Disease Rating Scale (UPDRS).	Any study including serum amino acid levels in PD patients without any specific intervention that can affect the amino acid level was accepted. Intervention studies giving the baseline level of serum amino acid status were also included.	The comparison data were taken from control groups of each study. These control groups should be healthy people regarding with PD or other neurological diseases. However, other chronic diseases (such as diabetes, hypertension, etc.) were accepted due to the natural profile of the aged individuals.	Serum amino acid levels were the main target of this meta-analysis. Furthermore, the UPDRS III score, Hoehn–Yahr Stage Score, disease duration (months) and levodopa equivalent daily dose were also evaluated as the outcomes of patients.

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Table 2. Characteristics of studies

Article	Author, year	Diagnosis	Assessment of amino acid level	Case (*n*)	Control (*n*)	Case age		Control age	
						Mean	SD	Mean	SD
Alterations of Sphingolipid and Phospholipid Pathways and Ornithine Level in the Plasma as Biomarkers of Parkinson's Disease	Chang 2022	• UK PD Society Brain Bank clinical diagnostic criteria • The Hoehn–Yahr stage • The levodopa equivalent daily dose • Psychiatric symptoms (e.g., hallucinations or delusions) and dementia (clinical dementia rating ≥ 1 or Mini-Mental State Examination ≤ 24) were assessed.	Ultra-performance liquid chromatography system (UPLC-MS)	92	60	67.63	10.65	67.35	8.08
Plasma branched-chain and aromatic amino acids correlate with the gut microbiota and severity of Parkinson's disease	Zhang 2022	The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale and using antiparkinsonian medications were assessed.	Liquid chromatography–tandem mass spectrometry (LC–MS)	106	114	67.9	6.5	68	6.4
The Metabolomic Approach Reveals the Alteration in Human Serum and Cerebrospinal Fluid Composition in Parkinson's Disease Patients	Plewa 2021	The UK Parkinson's Disease Society Brain Bank criteria were assessed.	High-performance liquid chromatography (HPLC)	11	10	60	52	52	13
The Metabolomic Approach Reveals the Alteration in Human Serum and Cerebrospinal Fluid Composition in Parkinson's Disease Patients	Plewa 2021 (atypical parkinsonian disorder)			8	10	63	12	52	13
A six-metabolite panel as a potential blood-based biomarkers for Parkinson's disease	Klatt 2021 (naive idiopathic Parkinson's disease)	Diagnosis criteria and age information were not defined – risk of bias.	LC–MS	7	93	–	–	–	–
A six-metabolite panel as a potential blood-based biomarkers for Parkinson's disease	Klatt 2021 (idiopathic Parkinson's disease)			103	93				
A novel multi-marker discovery approach identifies new serum biomarkers for Parkinson's disease in older people: an EXosomes in PArkiNson Disease (EXPAND) ancillary study	Calvani 2020	The Queen Square Brain Bank criteria and being under stable dopaminergic therapy were assessed.	UPLC-MS	20	30	73.1	10.2	74.6	4.3
Circulating amino acid signature in older people with Parkinson's disease: A metabolic complement to the EXosomes in PArkiNson Disease (EXPAND) study	Picca 2019	• The Queen Square Brain Bank criteria and being under stable dopaminergic therapy for at least one month prior to enrollment, • The Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr staging scale, • The levodopa equivalent daily dose were assessed.	UPLC-MS	20	30	73.1	10.2	74.6	4.3
The Importance of Increased Serum Ornithine Levels in the Pathogenesis of Alzheimer and Parkinson's Diseases	Celik 2018	Diagnosis criteria were not defined – risk of bias.	Assessment tool was not clear – risk of bias.	35	35	6 8	11	67	12
Serum metabolomics study in a group of Parkinson's disease patients from Northern India	Babu 2018	The National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy criteria were assessed.	NMR spectrometer	17	7	58	45–75	54	44-70

(*Continued*)

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Table 2. Characteristics of studies (*Continued*)

Article	Author, year	Diagnosis	Assessment of amino acid level	Case (*n*)	Control (*n*)	Case age		Control age	
						Mean	SD	Mean	SD
Alternations of Metabolic Profile and Kynurenine Metabolism in the Plasma of Parkinson's Disease	Chang 2018	• The UK PD Society Brain Bank clinical diagnostic criteria, • The Unified Parkinson's Disease Rating Scale and Hoehn and Yahr stage, • The Mini-Mental State Examination, • The Montreal Cognitive Assessment (MoCA), • The Clinical Dementia Rating, • The Beck Depression Inventory II, • The Hamilton Depression Rating Scale, • The Activities of Daily Living, • The Parkinson's Disease Questionnaire (PDQ-39) and Neuropsychiatric Inventory Questionnaire were assessed.	LC–MS	82	82	66.77	10.26	65.32	8.62
Evaluation of cardiovascular risk in patients with Parkinson's disease under levodopa treatment	Günaydın 2016	• The UK Parkinson's Disease Society Brain Bank Criteria, • The Unified Parkinson's Disease rating scale, • The Hoehn–Yahr scale were assessed.	Assessment tool was not clear – risk of bias.	65	32	70	9	69	8
Correlations between plasma levels of amino acids and non-motor symptoms in Parkinson's disease	Tong 2014	• The UK PD Brain Bank criteria, • The Unified Parkinson's Disease Rating Scale scores, • The levodopa equivalent daily dose were assessed. • The Mini-Mental State Examination score, • The Hamilton depression scale, • The McGill Pain Questionnaire (SF-MPQ, • The Pittsburgh Sleep Quality Index, • The Scale for Outcomes in Parkinson's disease for Autonomic Symptoms were assessed.	HPLC	92	60	61.6	10.7	64.1	13
Change in Plasma Levels of Amino Acid Neurotransmitters and Its Correlation with Clinical Heterogeneity in Early Parkinson's Disease Patients	Yuan 2013	• The UK Parkinson's brain bank criteria, • The Unified Parkinson's Disease Rating Scale were assessed.	HPLC	51	48	61.9	13.2	63.7	12
Comparison of Endothelial Progenitor Cells in Parkinson's Disease Patients Treated with Levodopa and Levodopa/COMT Inhibitor	Lee 2011 (levodopa)	• The UK Parkinson's brain bank criteria, • The Unified Parkinson's Disease Rating Scale,	HPLC	28	23	67.2	6.6	66.8	4.9
Comparison of Endothelial Progenitor Cells in Parkinson's Disease Patients Treated with Levodopa and Levodopa/COMT Inhibitor	Lee 2011 (levodopa+COMT inh)	• The levodopa equivalent daily dose were assessed.		25	23	68.5	5.4	67.2	6.6
Serum homocysteine and physical exercise in patients with Parkinson's disease	Nascimento 2011	• The UK Parkinson's Disease Society Brain Bank criteria and motor symptoms, such as rigidity, rest tremor and postural instability, were assessed.	Immunonephelometric kit	17	19	66.3	2	70.8	2.2
Elevated Levels of Methylmalonate and Homocysteine in Parkinson's Disease, Progressive Supranuclear Palsy and Amyotrophic Lateral Sclerosis	Levin 2010	• The UK Parkinson's Disease Society Brain Bank criteria,	Automated ligand binding assay	30	24	66.29	7.69	63.62	11.32

Changes in the concentration of amino acids in serum and cerebrospinal fluid of patients with Parkinson's disease	Mally 1997	• The Parkinson's Disease Rating Scale, • The Hoehn–Yahr stages were assessed.	High-pressure liquid chromatography	10	10	65.9	3	57	10
Decreased CSF levels of neutral and basic amino acids in patients with PD	Molina 1997	• The Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr staging scale were assessed.	Ionic exchange chromatography	31	45	62.6	12.5	57.8	15.4
Increased plasma concentrations of aspartate, glutamate and glycine in Parkinson's disease	Iwasaki 1992	• The Hoehn and Yahr scale was assessed.	Ionic exchange chromatography	20	20	68.7	9.2	64.7	10.1

Statistical analysis

Pooled data were analyzed to examine the relationship between serum amino acid levels and PD. Heterogeneity among the studies was assessed using the I^2 statistic, which quantifies the percentage of total variation across studies that is due to heterogeneity rather than random chance. An I^2 value of 0% indicates no observed heterogeneity, while higher values suggest increasing degrees of heterogeneity.

Based on the I^2 statistic, either fixed-effect or random-effect models were chosen for combining the study results. Fixed-effect models assume that the effect size is the same across all studies, while random-effect models account for variability in effect sizes between studies. Sensitivity and specificity analyses were performed following established guidelines[12–14] to assess the diagnostic accuracy and reliability of the findings.

Meta-analysis was carried out using RevMan 5.3, a specialized software for systematic reviews. GraphPad Prism 6 was used to generate figures and perform correlation analyses, including matrix visualizations of the data.

Risk of bias assessment

The risk of bias for each study was assessed either as low, unclear or high risk for each of the following criteria: selection bias, performance bias, detection bias, attrition bias and reporting bias and other as described in the Cochrane Handbook. The bias detections were given in Table 2 as relevant.

Results

A systematic search was conducted on three databases until February 15, 2023, yielding a total of 733 records. Using the exclusion criteria, 368 non-related studies; 145 reviews and meta-analyses; 136 animal studies; 25 non-English articles; 4 studies that did not include control groups; 3 articles unavailable in full text due to subscription barriers, institutional access restrictions or publication issues; and 2 studies that did not provide mean and SD values were excluded (Figure 1) regarding the criteria that are given in PICO table (Table 1). After combining common studies included in more than one database, 18 studies were available for meta-analysis. Included studies were published between 1992 and 2022 (as shown in Table 2).[6,15–31]

According to the meta-analysis results, it was observed that valine level was significantly increased in the PD group (p: 0.02, mean difference: 37.47, 95% CI: 6.86, 68.08) (as shown in Figure 2). The levels of isoleucine (p: 0.25) and leucine (p: 0.65) were not significantly different between groups.

Aliphatic non-essential amino acids were also analyzed, and it was seen that proline levels were significantly higher in the PD group than in the controls (p: 0.002, mean difference: 36.87 µmol/L, 95% CI: 13.54, 60.20). However, alanine and glycine levels weren't significantly different between groups (p: 0.09 and p: 0.43) (Figure 2).

There were no significant differences seen in the serum levels of the aromatic amino acids, namely, phenylalanine, tryptophan and tyrosine (previously p-values of 0.95, 0.78 and 0.60, respectively, shown in Figure 3).

The acidic amino acids, aspartate and glutamate were analyzed and presented in Figure 3. It was found that the level of aspartate was significantly lower in the Parkinson's group than in the controls (p: 0.01, mean difference: -10.45 µmol/L, 95% -18.63, -2.27). However, the level of glutamate did not show any difference

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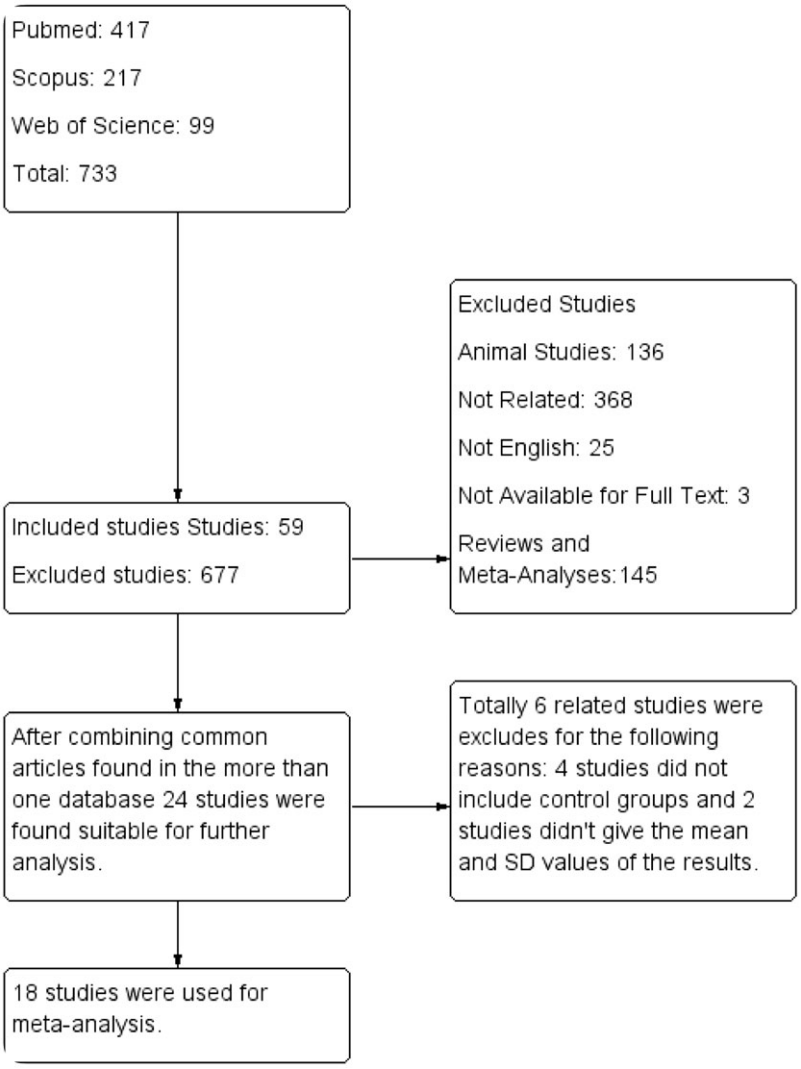

Figure 1. Study identification and selection PRISMA flow diagram.

between the groups (p: 0.73). The histidine level wasn't significantly different between groups (p: 0.08, mean difference: 10.58, 95% CI: -1.44, 22.60); however, further sensitivity analysis showed that the study of Mally et al. in 1997 is responsible for these results. When this study was excluded from the meta-analysis, histidine became a significantly increased amino acid in PD patients. Therefore, it might be mentioned that histidine levels tend to be increased in PD development.

It was found that the arginine level wasn't significantly different between groups (p: 0.17); however, the ornithine level was significantly higher in the disease group than in the control group (p: 0.002, mean difference: 11.78 µmol/L, 95% 4.21, 19.34). The citrulline level was significantly decreased in the PD group (p: 0.02, mean difference: -3.53 µmol/L, 95% CI: -6.50, -0.56). Similarly, the lysine level was also decreased in the patients with PD compared to controls (p: 0.01, mean difference: -8.58 µmol/L, 95% CI: -15.22, -1.94). Serine level was significantly decreased in the PD group compared to controls (p: 0.05, mean difference: -17.03 µmol/L, 95% CI: -33.81, -0.25). Threonine level wasn't different between groups (p: 0.26) (Figure 4).

The levels of sulfur-containing amino acids, cysteine and methionine, were not found significantly different between groups (p: 0.70 and p: 0.14). However, homocysteine level was found significantly increased ($p < 0.00001$), as shown in Figure 5. Glutamine, taurine and gamma-aminobutyric acid (GABA) levels were not changed with PD (p: 0.39, p: 0.51 and p: 0.99 (Figure 5).

Based on our analysis of cumulative correlations between amino acids, we observed homocysteine showed positive correlations with glutamate ($p < 0.001$; r: 0.99) and ornithine (p: 0.02; r: 0.87). In our analysis of disease stage parameters and their relationship with amino acid levels, we also observed several significant correlations. The Unified Parkinson's Disease Rating Scale III (UPDRS III) score, Hoehn and Yahr stage score, disease duration and levodopa equivalent daily dose (LEDD) were examined for their association with amino acids.

There was a significant negative correlation between LEDD and arginine levels (p: 0.02, r: -0.99), indicating that higher medication doses might be associated with lower levels of arginine. Additionally, the UPDRS III score, which reflects motor symptom severity, showed a significant negative correlation with phenylalanine levels (p: 0.01, r: -0.95). This suggests that lower phenylalanine levels may be associated with more severe motor symptoms. There was also a tendency for tyrosine levels to

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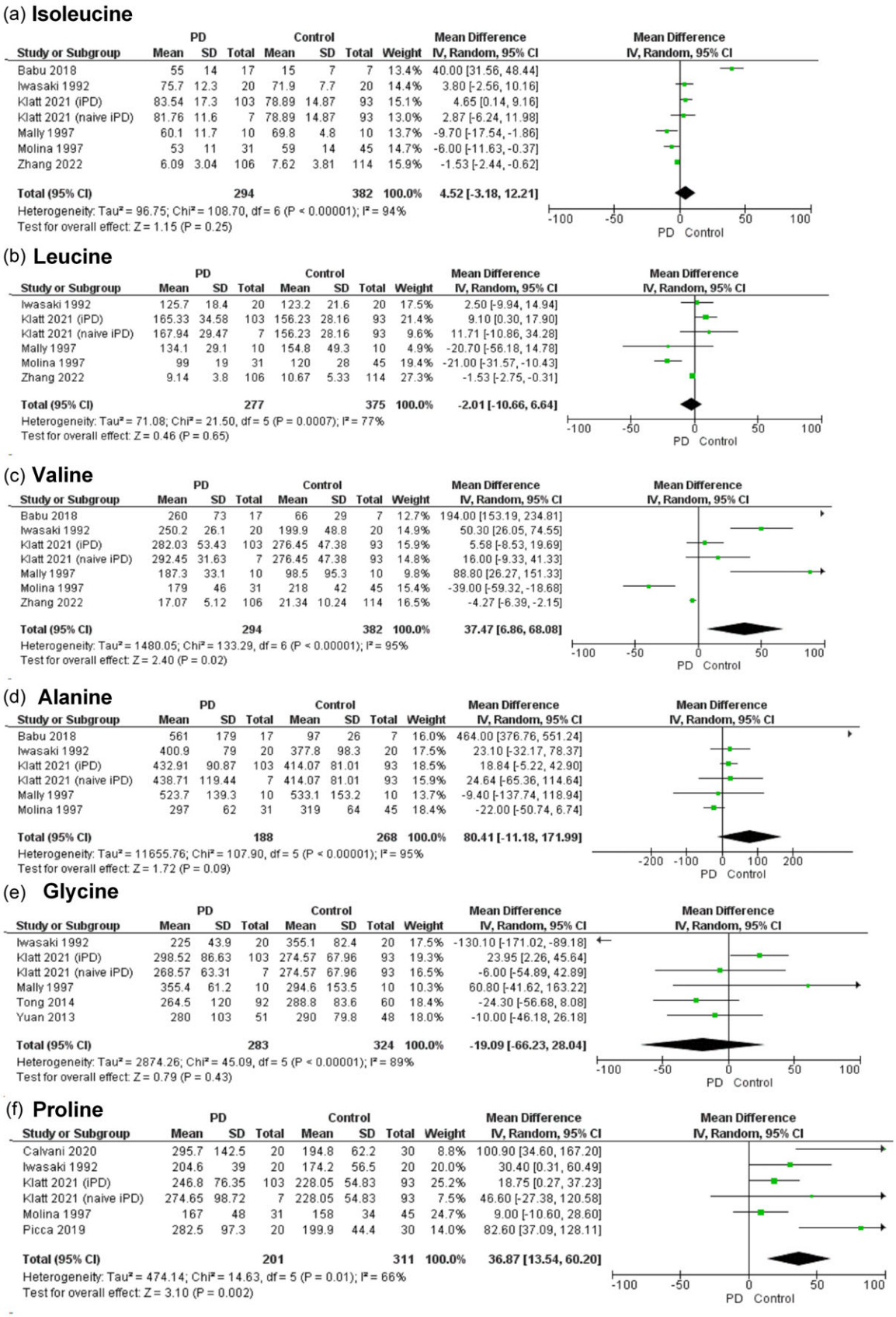

Figure 2. Aliphatic amino acids: (a) isoleucine, (b) leucine, (c) valine, (d) alanine, (e) glycine, (f) proline levels of Parkinson's disease patients and control group.

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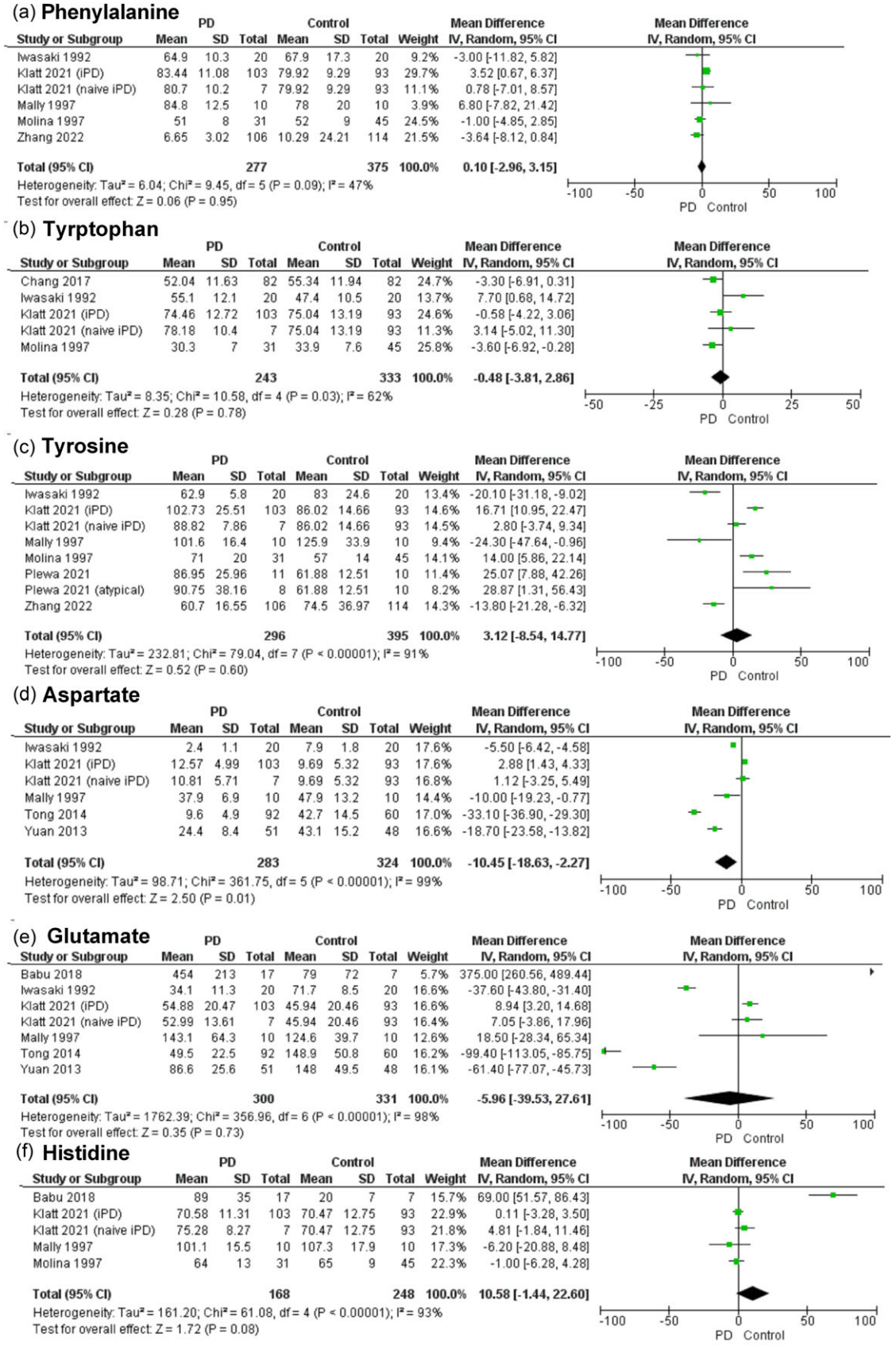

Figure 3. (a) Phenylalanine, (b) tryptophan, (c) tyrosine, (d) aspartate, (e) glutamate, (f) histidine levels of Parkinson's disease patients and control group.

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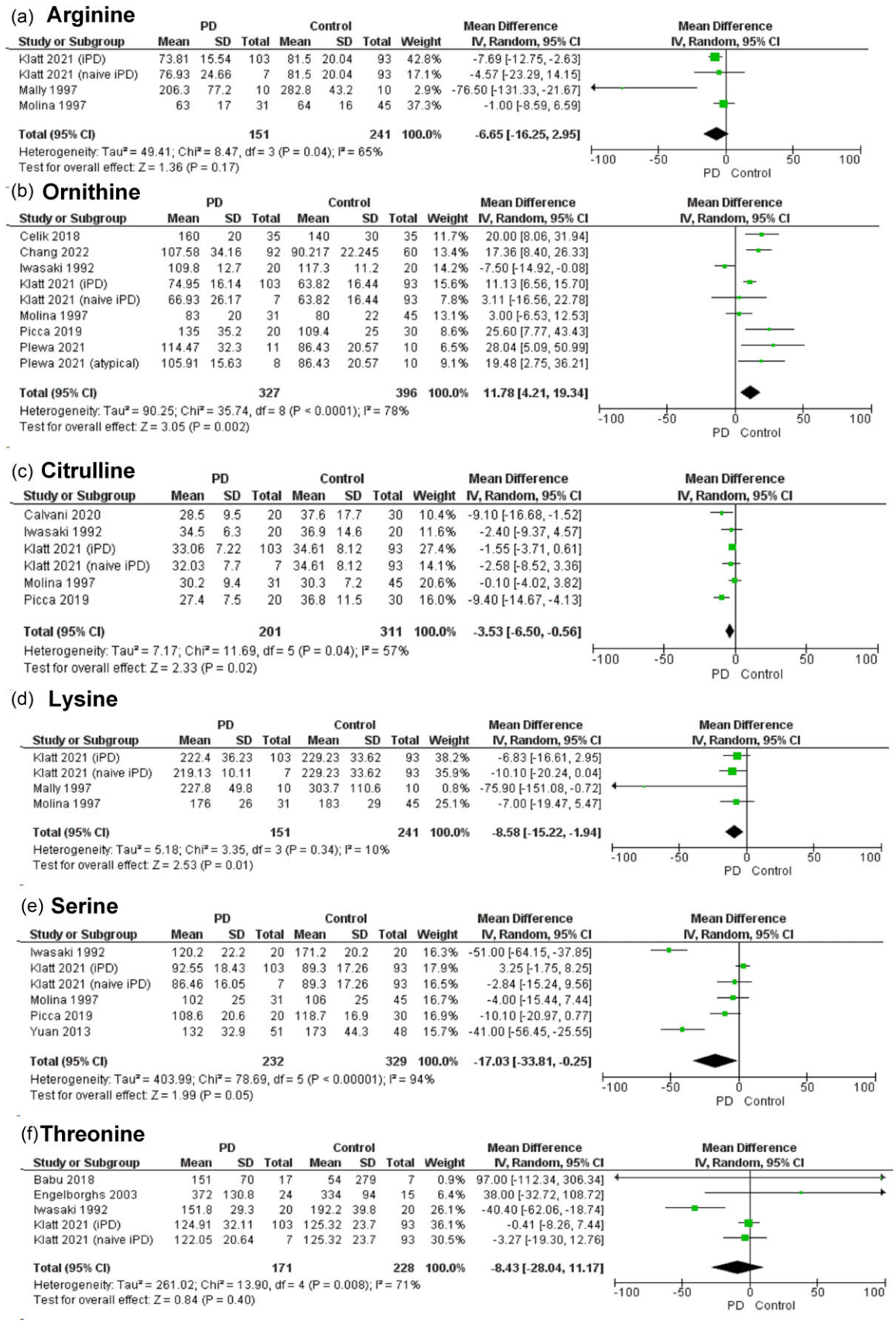

Figure 4. (a) Arginine, (b) ornithine, (c) citrulline, (d) lysine, (e) serine, (f) threonine levels of Parkinson's disease patients and control group.

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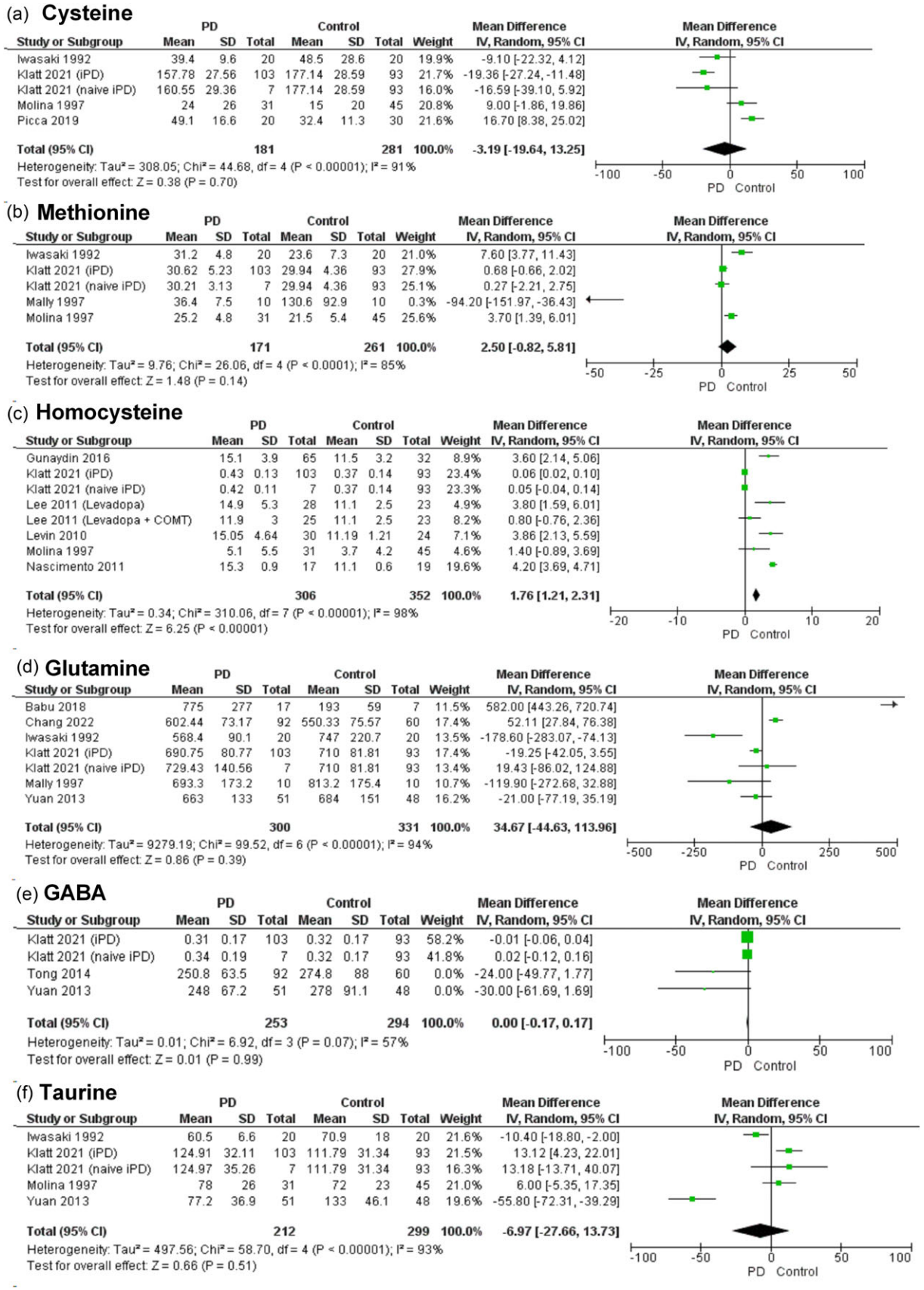

Figure 5. (a) Cysteine, (b) methionine, (c) homocysteine, (d) glutamine, (e) GABA, (f) taurine levels of Parkinson's disease patients and control group.

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negatively correlate with UPDRS III scores (p: 0.059, r: -0.99), hinting at a possible link between tyrosine metabolism and motor symptom severity, though this correlation did not reach statistical significance.

Furthermore, disease duration showed a tendency toward a negative correlation with citrulline levels (p: 0.05, r: -0.99), suggesting that prolonged disease duration might be associated with reduced citrulline levels.

Three studies were found with a high risk of bias. In the studies held by Klatt et al.[17] and Celik et al.,[20] there were no defined diagnosis criteria, and/or age information was not given, which is accepted as a risk of selection bias and reporting bias. The assessment of amino acid levels was not clear in the studies of Celik et al.[20] and Gunaydin et al.,[23] which is accepted as performance bias and reporting bias. Furthermore, subgroup analysis depending on patients' characteristics could not performed due to the limitation of the data for meta-analysis.

Discussion

This study provides strong evidence that neurodegenerative diseases, particularly PD, are closely related to the amino acid profiles of individuals. Our results suggest that valine, proline, ornithine and homocysteine levels were increased in PD patients, while aspartate, citrulline, lysine and serine levels were significantly decreased. Furthermore, alanine and histidine levels had a tendency to change with PD progression.

A meta-analysis study found decreased aspartate, serine, tryptophan and lysine and increased proline and homocysteine levels in PD patients.[32] However, according to our literature records and analysis, we observed that there are important differences between our results and this meta-analysis results.

Our systematic search resulted in more available and up-to-date data about PD patients' amino acid profiles. While there are some similarities between our results and this meta-analysis such as increased proline and homocysteine levels and decreased aspartate, serine and lysine levels, our study also found significantly increased levels of ornithine and valine and a significant decreased in citrulline levels.

We believe that our findings significantly contribute to this meta-analysis[32] through the inclusion of more recent and different studies evaluating blood amino acid levels.[15–18,20,23,26–28] In the discussion, we explored the pathways that may be associated with the different results we found and their potential relevance to PD development mechanisms. From these perspectives, we found that citrulline, valine, ornithine and proline metabolism may also be related to PD by using a meta-analytic approach for the first time in the literature.

Amino acid metabolism in Parkinson's disease

Amino acid metabolism is a highly intricate and dynamic process that plays a vital role in the synthesis and catabolism of biomolecules in living organisms. The interconversion of amino acids through various metabolic pathways allows for a highly regulated and interconnected network of biochemical reactions that maintain the delicate balance of amino acid levels in the body.

The interaction of amino acids with transport systems underscores the complex balance of amino acid levels in the brain. For example, specific groups of amino acids share the same transporters across the blood-brain barrier, influencing their dynamic interplay. Branched-chain amino acids (BCAAs), methionine, phenylalanine, tryptophan, tyrosine, histidine, threonine and glycine are transported bidirectionally between the blood and brain via the Large Neutral Amino Acid Transporter 1. Similarly, arginine, lysine and ornithine are transported bidirectionally through the Cationic Amino Acid Transporter 1. Glutamate is transported into the brain either via its own System N transporter or through the Anionic Amino Acid Transporter System X/EAA T 1–3, which it shares with aspartate.[33,34]

Changes in BCAA levels in Parkinson's disease

BCAAs are essential amino acids that are required for growth, development, nutrient signaling, providing nitrogen to neurotransmitter synthesis and glutamate/glutamine cycling. These are crucial roles of BCAAs to maintain body and brain health. However, in recent years, there is an important debate about BCAA's effects on neurodegenerative diseases that has arisen.

While some research groups suggest that BCAAs may benefit brain function and cognitive aging, there are differing hypotheses about their role in neurodegenerative diseases.[35–41] One hypothesis is that excessive dietary intake of BCAAs may interfere with the uptake of neutral amino acids such as tryptophan and tyrosine, which are essential for serotonin and dopamine production. BCAAs and these neutral amino acids share the same transporters across the blood-brain barrier. Therefore, high BCAA levels could compete with tryptophan and tyrosine for transport into the brain, potentially impairing the synthesis of 5-hydroxytryptophan (5-HT) and dopamine. Our cumulative results showed a significant increase in valine levels in the PD group, while levels of isoleucine and leucine did not change significantly. This suggests that the altered BCAA profile, particularly the increase in valine, may influence the balance of neurotransmitter synthesis, potentially contributing to the neurochemical disruptions observed in PD.

A study reported that high plasma BCAA levels resulted in low central 5-HT levels. Anxiety-like behavioral changes were observed in rats fed a high-fat, high-carbohydrate diet enriched with BCAAs.[35] With BCAA supplementation, a decrease was observed in tryptophan and its metabolite kynurenic acid.[35] Oral BCAA supplementation during exercise has been shown to reduce brain catecholamine levels.[36] In another study, it was determined that tyrosine and dopamine levels in the brain were decreased with BCAA supplementation.[37] In a study conducted on healthy people, when they evaluated the effect of BCAA supplementation on dopamine levels by plasma prolactin levels, it was shown that BCAA supplementation could cause an increase in prolactin secretion by suppressing dopamine levels.[38] In addition, the BCAA supplements used in the studies typically show short-term effects, and it remains unclear how neurotransmitter levels might be affected by long-term BCAA consumption over extended periods.[39]

The study by Zhang et al. (2022), which is also included in this meta-analysis, found that patients with PD have lower plasma BCAA and aromatic amino acid levels.[15] Another study investigating the effects of whey protein supplementation, which is a good source of BCAAs, on PD showed favorable results.[39] With the whey protein intake, the serum homocysteine level was decreased, while oxidized glutathione level was increased in PD patients. However, they also reported that there were no changes in the clinical outcomes.[40] Also, in a recent animal study, researchers revealed that rotenone-induced PD may lead to alteration in the gut microbiota, which may be the possible cause of peripheral BCAA deficiency. When they fed the animals with a high BCAAs diet, they found improvements in the inflammatory levels, motor

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and non-motor dysfunctions and dopaminergic neuron impairment in PD mice.[41]

A very recent study in 2023, which analyzed data from 21,982 Alzheimer's disease (AD) cases and 41,944 controls, found an association between decreased levels of BCAAs and the presence of AD in patients.[42]

A study with app/ps1 double transgenic mice published in the Cells journal in 2022 reports that higher plasma BCAA levels were displayed in this AD model, and reducing BCAA daily intake alleviates AD-related pathology and cognitive decline. The same study highlighted a potential link between BCAAs and AD progression.[43]

Furthermore, the consumption of BCAAs in a high-fat diet may be an important factor for neurological impairment as shown in an animal study of Alzheimer's disease model. Mice fed with a high BCAA-high-fat diet showed higher tau neuropathology, and only 4 out of 13 animals survived. Mice fed with a low-BCAA diet showed higher threonine and tryptophan cortical levels.[44]

In a recent study in 2023, leucine-rich α2 glycoprotein was investigated to be a biomarker of systemic inflammation in PD in 66 patients and 31 age-matched controls. It was significantly higher in the patient group than in the control group and also correlated with Charlson comorbidity index, C-reactive protein levels and dementia.[45]

There are conflicting results in the literature; however, our study may help to clarify the relationship between BCAA intake and PD and neurological functions. By examining the serum levels of BCAAs in PD patients, as well as the mechanistic relationships of transporters, the effects of BCAA supplements and their potential impact on disease progression in the literature, our findings provide a more comprehensive understanding of how BCAAs influence PD and may inform future research and therapeutic strategies. It might be better to separate BCAAs as each of these amino acids might be changed in patients or affect the disease progression in a different way. To understand the underlying mechanism, more studies on BCAA's effects on brain and neurodegenerative disease development are needed. Also, it is important to examine the BCAAs in the other dietary and lifestyle factors that can change the effects of amino acids and disease progression.

Altered proline metabolism

Besides BCAAs, there were several amino acids found to be significantly changed in the patients compared to control.

Our results showed that proline levels were significantly higher in the PD group than in the controls; however, alanine and glycine levels weren't changed.

Proline constitutes one-third of amino acids in the collagen proteins, comprising nearly 30% of body proteins. To understand the increase in proline levels it is beneficial to examine the stress response of the body. L-proline has the role of a chemical chaperone, preventing protein unfolding or misfolding for endoplasmic reticulum stress;[46] however, at high levels, it can be harmful to neural activity.

L-proline metabolism might be related to the development of neurodegenerative diseases associated with the formation of protein aggregates, such as Parkinson's, Alzheimer's, etc. These diseases have a number of common features in their processes. Energy metabolism dysfunction, glutamate excitotoxicity and oxidative stress seem to be underlying in the pathophysiology of these disorders.[47]

The process of proline catabolism involves the conversion of proline to pyrroline-5-carboxylate (P5C) by proline dehydrogenase (PRODH) in the mitochondrial matrix. This generates glutamate through NAD-dependent P5C dehydrogenase (P5CDH), which is an essential excitatory neurotransmitter in neurons and a precursor to glutamine, GABA and mitochondrial TCA cycle intermediates. On the other hand, glutamate can be converted into a P5C intermediate through P5C synthase (P5 CS) and further reduced to proline by P5C reductases (PYCRs). All the enzymes involved in the proline metabolism pathway have been reported to be associated with neurological or psychiatric disorders in human and animal models.[48–50] Also, hypovitaminosis B complex especially vitamin B_6 and B_{12} are important for proline metabolism and hyperhomocysteinemia through impaired remethylation.

As a part of neural metabolism, proline has the capability to function as a metabolic precursor of L-glutamate. PRODH knockout mice have shown that the cytosolic accumulation of L-proline disrupts GABAergic transmission through glutamate decarboxylase blockade.[51] Moreover, normally, proline induces L-glutamate synthesis and acts as a GABA-mimetic inhibitor of the GAD enzyme.[52] Therefore, proline can reduce the synthesis of the GABA neurotransmitter and accumulation of L-glutamate, thereby leading to synaptic dysfunction in some forms of disease.[53] On the other hand, if proline cannot contribute glutamate or collagen synthesis due to the lack of these metabolic paths, it may accumulate. Dysfunctional proline metabolism could be one of the underlying mechanisms of muscle weakness in PD. Further studies are needed to elucidate this hypothesis.

Related to this excitotoxicity, particularly in neural glutamate metabolism, patients with genetic defects in PRODH or in P5CDH, called hyperprolinemia I/hyperprolinemia II, have higher proline levels up to 10–15-fold than in normal people and may have developed schizophrenia-related phenotypes (learning, memory and sensorimotor gating) and schizophrenia.[47,54]

Studies have shown that stress and anxiety can influence the concentrations of hydroxyproline and proline in urine.[55] Long-term exposure to proline has also been linked to behavioral changes in zebrafish, which were reversed by antipsychotics, indicating a relationship between proline and psychiatric diseases.[56] Given these findings, it is important to explore how elevated proline levels observed in PD patients might be related to similar stress or behavioral mechanisms.

In vitro studies have revealed that differentiated neurons depleted of PYCR2 showed thinner neuronal fibers and significantly increased axonal beading, an early morphological hallmark of neuronal injury.[57] Furthermore, there is a hypothesis that PRODH deficiency could lead to hyperactivation of the dopaminergic system due to dysregulated astroglial control of dopamine homeostasis.[58] Other studies suggest that in the hypothalamus, proline is taken up by astrocytes and converted into lactate, which is then released from astrocytes and taken up by neurons. In neurons, lactate is oxidized for energy production.[59]

There is significant evidence that PRODH polymorphisms are associated with susceptibility to schizophrenia and defects in PRODH have been linked to glutamatergic and GABAergic neuron dysfunctions.[48,52]

In the literature, it was also stated that proline-rich protein 14, which is involved in the alteration and activation of the mTOR signaling pathway, was upregulated in PD patients.[60] Its expression was found higher in whole blood, substantia nigra and medial substantia in the PD group than in healthy controls. They

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mentioned that the detection of proline-rich protein 14 levels in serum/plasma can be a biomarker for PD.[60]

Another reason for proline accumulation might be also related to the arginine-ornithine cycle. Our results showed that while arginine levels in PD patients were decreased, there was a significant increase in ornithine levels. In the urea cycle, ornithine-arginine transferase converts L-ornithine to proline-5 carboxylase, which is a precursor of L-proline via proline-5 carboxylase reductase.[61]

Examining proline metabolism could provide valuable insights into the mechanisms underlying neurodegenerative diseases. By understanding how proline levels and their metabolic pathways interact with disease processes, we can gain a better understanding of the causes of PD and potentially identify new therapeutic targets.

Excessive ornithine levels in Parkinson's disease

Ornithine levels were found to be elevated in PD patients and were also associated with the severity of the disease. Advanced-stage PD patients had higher ornithine levels than early-stage PD patients. Ornithine levels were found correlated with α-synuclein protein, which includes polyamines leading to the accumulation and fibril formation of putrescine, spermine and spermidine. Its accumulation in neurons is playing a key role in PD development.[6,7]

Polyamines are molecules including two to four amino groups. They play a critical role in several mechanisms in living organisms including apoptosis, cell division and differentiation, cell proliferation, DNA and protein synthesis, gene expression, homeostasis and signal transduction. Polyamine biosynthesis initiates from arginine and ornithine. Arginine is first converted to ornithine, and ornithine decarboxylase leads to putrescine synthesis. Then putrescine can be converted to spermidine and spermine. The accumulation of polyamines has been reported to be related to several diseases.[8]

The major metabolic ways that can be activated when ornithine levels are increased include the synthasis of L-proline, L-glutamate, GABA and polyamines and the activation of urea cycle.[62] Also, the activation of the urea cycle may contribute to the excessive urea production, which can increase of osmolarity in the cerebellum, cerebral cortex and brain stem.[63] Ornithine-related osmotic pressure also affects plasticity in the hippocampal region with the tonic inhibition of the GABA receptors.[64] An in vitro study showed that osmotic stress is also a causative factor for α-synuclein accumulation.[65]

Homocysteine as a biomarker of pathogenesis

The non-proteinogenic α-amino acid homocysteine is directly linked to diseases such as dementia, heart disease and stroke, with elevated blood levels indicating underlying physiological issues.[66,67]

As it is expected and well-studied and approved with meta-analysis studies, homocysteine level was found significantly increased in PD, as high homocysteine leads to nerve cell apoptosis, oxidative stress and DNA damage of neuron cells.[16,68] Increased homocysteine levels in PD patients showed an association with frontal cortical thinning and microstructural damage in frontal and posterior-cortical regions.[69]

Therefore, our results suggest that its positive correlation with glutamate and ornithine may need to be considered in the potential relationships that could be established with PD.

Histidine tendency to increase in Parkinson's disease

We found histidine levels tend to be increased in PD patients, and further sensitivity analysis showed that this was due to one study that gave contrary results to the rest of the studies.[21] With the elimination of that study, histidine levels significantly increased in the PD group (p: 0.04). The dimerization of α-synuclein protein requires histidine, which is an important aggregation for PD development.[70] Histidine is converted into histamine by the enzyme histidine decarboxylase. Regarding the effects of histamine on PD, animal experiments showed that increased histamine levels may lead to the degeneration of dopaminergic neurons in the substantia nigra.[71] The enzyme responsible for the clearance of histamine, histamine N-methyltransferase, has been found to play an important role in the pathogenesis of PD.[72] A negative correlation was observed between the mRNA expression of histamine N-methyltransferase in the substantia nigra and disease progression inPD patients.[72] Evidence indicated that excessive histamine production may be related to PD and other neurodegenerative diseases, which are also related to increased histidine amino acid levels.[73]

Also, histidine is a precursor of carnosine (β-alanyl-L-histidine), which is a dipeptide synthesized from b-alanine and histidine. Blockage of the carnosine pathway or over-hydrolysis of carnosine may result in histidine accumulation. Carnosine is a neuroprotective agent and a potential additive for Parkinson's patients.[74]

Decrease in specific amino acids in Parkinson's disease

Aspartate

We found that aspartate levels were lower in PD patients. Aspartate is an acidic amino acid that plays a role in the citric acid cycle. Aspartate is also involved in the production of other amino acids and in the synthesis of nucleotides, which are the building blocks of DNA and RNA.

There is significant evidence suggesting that L-aspartate can be transported into nerve cells through excitatory amino acid transporters, stored in vesicles and released through a process called Ca2+-dependent vesicular exocytosis in various parts of the brain. Based on these properties, L-aspartate has the potential to be considered a classical neurotransmitter in the central nervous system (CNS) from a presynaptic standpoint.[75] In the literature, it was stated that N-acetyl-aspartate is an important metabolite for energy metabolism of the brain especially in stress-induced brain injury, cognitive impairment and PD.[76–79]

Citrulline

Furthermore, we found citrulline levels decreased in PD patients, and disease duration was negatively correlated with citrulline levels in PD patients. Citrulline is a non-proteinogenic amino acid that is synthesized in the urea cycle, which is responsible for removing toxic ammonia from the body. Citrulline is also involved in the production of nitric oxide, which is important for blood vessel dilation and cardiovascular health.[80] Citrulline has not been extensively studied in the context of PD, but it has been shown to have a neuroprotective effect in other neurological disorders, such as stroke and traumatic brain injury. This may be due to its ability to increase the production of nitric oxide, which can improve blood flow and reduce inflammation in the brain.

There is a research on the potential neuroprotective benefits of L-citrulline for CNS disorders, such as brain ischemia. Previous

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studies have indicated that L-citrulline could not only prevent neuronal cell death but also prevent capillary loss in the hippocampal region caused by cerebral ischemia. The protective effect of L-citrulline on cerebrovascular function is thought to be linked to the restoration of endothelial nitric oxide synthase expression in the hippocampus.[80] Furthermore, as an important relation, a study showed that citrullinated proteins in control substantia nigra only occur in astrocytes. However, in PD substantia nigra, citrullinated proteins are also found in the cytoplasm of neurons, including dopamine neurons. Abnormal protein citrullination might be related to PD, including Lewy bodies and prion diseases.[81] Together with our results, the decrease in blood citrulline levels in patients might depend on the accumulation of citrulline in neurons.

Lysine

Lysine is a basic amino acid that is involved in protein synthesis and is important for the growth and maintenance of tissues. Lysine is also involved in the production of carnitine, which is important for energy metabolism, and in the regulation of gene expression.

There are several studies that show the impaired acetylation/deacetylation of lysine in histones and alpha-synuclein-Lewy bodies in PD patients. Impairment in acetylation/deacetylation mechanisms is also closely related to aging. According to these studies, lysine acetylation is aberrant in PD patients, while deacetylation mechanisms were decreased.[82–84] Therefore, a lower level of serum lysine level might be a marker for this mechanism in PD patients.

Serine

We found that serine levels were decreased in PD patients. Serine is a neutral amino acid that is involved in the synthesis of proteins, nucleotides and phospholipids, which are important components of cell membranes. Serine is also involved in the regulation of enzyme activity and in the synthesis of neurotransmitters, which are chemical messengers in the brain.[85]

According to recent research, parkin, an E3 ubiquitin ligase involved in PD, regulates the synthesis of serine through its interaction with PHGDH, an enzyme involved in the serine biosynthesis pathway. Parkin ubiquitinates and degrades PHGDH, thereby suppressing serine synthesis.[86]

Studies have demonstrated that the L-serine pathway is related to both Parkinson's and Alzheimer's diseases. Beta-N-methyl-amino-L-alanine (L-BMAA) leads to protein misfolding in neurons and symptoms of Alzheimer's-like dementia and Parkinsonism. It was shown that L-serine suppresses the erroneous incorporation of L-BMAA into proteins in the nervous system and improves cognition and electrophysiological dysfunction.[87]

L-serine serves as a precursor for D-serine, which acts as a co-agonist of synaptic NMDA receptors that are necessary for synaptic plasticity. It was observed that L-serine-supplemented diet effectively prevents both synaptic and behavioral deficits in AD mice.[88,89] The effects of serine in AD are a topic of ongoing debate, and its role in PD remains poorly understood. Therefore, further studies need to clarify the relation between serine and neurodegenerative diseases.

Motor and non-motor symptoms

Our cumulative analysis revealed correlations between amino acid levels and disease severity indicators such as the UPDRS III score, Hoehn and Yahr stage and disease duration. Notably, arginine levels negatively correlated with the LEDD, suggesting that alterations in arginine metabolism might be associated with the progression of motor symptoms and medication requirements. Arginine serves as a precursor for nitric oxide (NO) synthesis, which is crucial for neurotransmission and neurovascular function.[80] Elevated levels of neuronal and inducible NO synthase (NOS) have been observed in the substantia nigra of PD patients and animal models.[90] The negative correlation between LEDD and decreasing arginine levels may indicate the depletion of arginine for NO synthesis. However, arginine levels were not significantly different between groups, highlighting the need for further studies to clarify its role in PD symptoms.

Similarly, phenylalanine levels negatively correlated with UPDRS III scores, suggesting a potential link between this amino acid and motor symptom severity, although phenylalanine levels were not significantly different between PD and healthy groups. As a precursor to tyrosine, which is then converted to dopamine, lower phenylalanine levels may reduce the availability of tyrosine and subsequently dopamine,[91] potentially leading to more severe motor symptoms as reflected by the UPDRS III score.

Additionally, citrulline levels tended to decrease with disease duration, highlighting its potential role in disease progression. Our findings also showed that citrulline levels were significantly decreased in the PD group compared to controls, indicating a strong mechanism underlying PD. Citrulline, like arginine, is crucial in the NO production pathway. Although NO has neuroprotective effects,[80] elevated levels of neuronal and inducible NOS observed in the substantia nigra of PD patients[90] suggest that disruptions in these pathways could negatively affect neuronal health and function, potentially influencing disease progression.

We acknowledge several limitations in our study that arise from the quality of the studies and the data available in the literature. A primary limitation is the insufficient reporting of amino acid levels by disease stage, gender and ethnicity, which restricted our ability to perform analyses across these variables. Consequently, we were unable to conduct subgroup analyses based on disease stage or demographic characteristics, limiting our exploration of potential variations in amino acid profiles. Additionally, the studies included in our meta-analysis did not provide information on amino acid levels at various stages of PD or before disease onset, precluding an assessment of when these changes first occurred.

Our meta-analysis also encountered challenges due to high statistical heterogeneity, as reflected by the I^2 values in each amino acid analysis. This heterogeneity is indicative of variations in study design, diagnostic criteria and measurement methods, which can affect the consistency of findings across studies. While clinical heterogeneity is expected in meta-analyses, it underscores the necessity for future research to address these issues by providing more detailed and consistent reporting. Future studies should aim to include data stratified by disease stage and patient characteristics.

Conclusion

In conclusion, amino acid metabolism appears to play a critical role in PD pathogenesis. Our study found that BCAAs, particularly valine, might have a negative impact on PD. The effect of BCAA intake on neurotransmitter levels needs to be further investigated in long-term studies. Proline levels were also found to be significantly higher in PD patients, which may contribute to the formation of protein aggregates associated with neurodegenerative diseases or may accumulate due to the metabolic disturbs in the production of collagen and glutamate. Ornithine levels may also

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contribute to the disease progression as a precursor for glutamate, urea and polyamines, which are closely related to the α-synuclein protein. Furthermore, there were close relationship between decreased citrulline and serine levels in PD patients. This cumulative analysis provides evidence that understanding the mechanisms underlying amino acid metabolism in PD could lead to new therapeutic strategies.

Author contributions. SA: design, data collection and processing, analyses, literature review, writing and editing; DY: data collection; NY: design, supervision, analyses, literature review, writing and critical review.

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