

Current advances in metabolomic studies on non-motor psychiatric manifestations of Parkinson's disease (Review)

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Abstract. Life expectancy has increased worldwide and, along with it, a greater prevalence of age-dependent disorders, chronic illnesses and comorbidities can be observed. In 2019, in both Europe and the Americas, dementias ranked 3rd among the top 10 causes of death. Parkinson's disease (PD) is the second most frequent type of neurodegenerative disease. In the last decades, globally, the number of people suffering from PD has more than doubled to over 6 million. Of all the neurological disorders, PD increased with the fastest rate. This troubling trend highlights the stringent need for accurate diagnostic biomarkers, especially in the early stages of the disease and to evaluate treatment response. To gain a broad and complex understanding of the recent advances in the '-omics' research fields, electronic databases such as PubMed, Google Academic, and Science Direct were searched for publications regarding metabolomic studies on PD to identify specific biomarkers for PD, and especially PD with associated psychiatric symptomatology. Discoveries in the fields of metagenomics, transcriptomics and proteomics, may lead to an improved comprehension of the metabolic pathways involved in disease etiology and progression and contribute to the discovery of novel therapeutic targets for effective treatment options.

Contents

1. Introduction
2. Methods
3. Cerebrospinal fluid biomarkers in PD
4. Blood biomarkers in PD
5. Urine biomarkers in PD
6. Fecal biomarkers in PD
7. Biomarker signatures in psychiatric symptomatology of PD
8. Conclusions

1. Introduction

Rather than being a single pathogenic entity, Parkinson's disease (PD) is now considered a complex syndrome that affects both the central and peripheral nervous systems, with various clinical presentations that have different disorder courses (1,2). PD is considered a prototypical basal ganglia disorder (3), where the loss of neurons in the substantia nigra pars compacta leads to a gradual dysfunction of the sensorimotor loops of the cortico-basal ganglia-thalamo-cortical pathway, causing the classical clinical motor signs: Resting tremor, hypokinesia, postural instability and rigidity, and may also be responsible for the cognitive deficits observed in some patients (4). However, it is essential to note that these motor manifestations, although most frequently associated with PD, appear in the late stages of the disease, when patients have lost 30-50% of dopaminergic neurons, as assessed post-mortem or 80% of striatal nerve terminals, as evaluated *in vivo* (5). More importantly, patients may experience a wide range of non-motor symptoms, such as gastrointestinal disturbances (e.g., sialorrhea, dysphagia, nausea and constipation), autonomic dysfunctions (e.g., orthostatic hypotension, sweating, bladder disturbances and erectile dysfunctions), sleep problems (e.g., daytime sleepiness, REM sleep behaviour disorder, restless leg syndrome and obstructive sleep apnea), sensory manifestations (e.g., pain and loss of

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smell) and neuropsychiatric symptoms (e.g., attention deficits, cognitive decline, depression, anxiety, apathy, dementia and psychosis). These symptoms appear early in the course of the disease, preceding the motor manifestations, and can dominate the clinical tableau in the late stages, reducing the life expectancy of the patients, negatively affecting the quality of life, and contributing to severe disability (6). Previous research on PD pathophysiology has focused on the degenerative processes that lead to dopaminergic neuronal cell loss in the substantia nigra pars compacta, but non-motor symptoms are not associated with a specific neurotransmitter dysfunction (7) and, as a result, they are not recognized and receive insufficient treatment (6). Conversely, recent research on PD addresses the complex changes that take place at the genetic, molecular, and metabolic levels, such as oxidative stress, neuroinflammation, protein misfolding, and excitotoxicity that play a crucial role in the pathogenesis of the disease (8,9).

The importance of biomarker research in PD resides in the need for early detection and accurate diagnosis with implications for future treatment strategies. The implications of this body of research are manifold: On the one hand, PD detection is fraught with high rates of misdiagnosis in the clinical practice; 25% of the patients diagnosed with idiopathic PD during their lifetime, are discovered post-mortem to have various parkinsonian syndrome (e.g., vascular modifications, atypical parkinsonism, corticobasal degeneration, progressive supranuclear palsy or multiple system atrophy), especially when only the initial diagnosis is taken into consideration (10-12). Furthermore, the numerous pathological processes involved in PD require specific therapeutic strategies for each subtype, beyond dopamine replacement therapy, that address only the clinical motor symptoms without affecting disease progression (13). In addition to this, given the rise of degenerative illnesses in the elderly population, effective screening tools that identify individuals at risk, monitor their progression, and ultimately influence the type of treatment requested for optimal outcomes are required (14).

There is an urgent need to discover improved clinical biomarkers with high sensitivity, specificity, and reliability. In recent years, numerous contributions in the field of PD biomarker discovery have been witnessed.

2. Methods

Databases such as PubMed, Google Academic and Science Direct were searched for publications in English on metabolomic studies on PD. In order to obtain a broad view on the subject, scientific publications from 2000 to 2021 containing the terms 'Parkinson's disease', 'biomarker', 'metabolomic' and 'psychiatric symptoms' were included. Cumulatively, a total of 791 articles on all three platforms were found. Articles that were not related to the research subject, repeated articles, and articles that access to could not be gained, were excluded. Articles that conceptualized or defined metabolomic terminology and analyzed theoretical causes as well as its effects, were included in the present review. Moreover, articles focusing on psychometric measurements and methodology, exploring metabolic biomarkers in PD having different non-motor symptoms and within specific population groups (e.g., with or without cognitive decline; with or without treatment) and assessing the

effect of various metabolic by-products on clinical manifestations and treatment efficacy, presenting biomarker measuring tests and methodology were also included. In order to gain a broad and comprehensive understanding of the scientific literature, notable studies from the reference section on the topics of interest were also included. After the inclusion and exclusion criteria were applied, 97 articles remained.

3. Cerebrospinal fluid biomarkers in PD

Because cerebrospinal fluid (CSF) is closely connected to the central nervous system (CNS), it is the preferred sample in neuropathological research on PD, as aberrancies in its composition reflect the pathological processes in the brain (15).

Catecholamines are significantly reduced in PD samples compared with control groups, with PD patients having lower CSF levels of dihydroxyphenylacetic acid (DOPAC), dihydroxyphenylglycol, and L-DOPA (16). It is worth mentioning that DOPAC levels are not PD-specific, and low values can be observed in other synucleinopathies. The levels of homovanillic acid (HVA; the main dopamine catabolite) in CSF were revealed to be significantly decreased in PD patients 5 days after L-DOPA therapy withdrawal vs. controls. A markedly high 5-S-cysteinyldopamine/homovanillic acid concentration ratio was observed in PD patients compared with controls, making it a useful marker for the early diagnosis of PD (17).

α -Synuclein is the main protein involved in the pathogenesis of Lewi bodies through misfolding as a result of genetic mutations that lead to post-translational modifications (e.g., ubiquitination, phosphorylation, oxidation, nitration and truncation); α -synuclein aggregates to form amyloid fibrils (18,19). A number of meta-analyses revealed CSF total α -synuclein levels to be lower in PD patients vs. controls or other neurological patients (20,21); however, it has exhibited low specificity (40-57%) and sensitivity (78-88%) as a diagnostic biomarker (22) and longitudinal studies (23,24) revealed no significant difference in PD compared with controls in CSF total α -synuclein. A recent review presented the aptamer- and antibody-based electrochemical biosensors for α -synuclein detection and quantification. The biosensors were also applied to investigation of α -synuclein aggregation kinetics and its interaction with small molecules (e.g., baicalein), in order to elucidate the structure-activity relationships (25).

Other forms of α -synuclein have been investigated. Oligomeric α -synuclein and phosphorylated α -synuclein were revealed to be consistently higher in PD patients compared with controls (19-21); however, they lack diagnostic accuracy (sensitivity 82 and 79%, respectively) and specificity (64 and 67%, respectively). Aggregates of the protein have been measured in the biological fluids of PD patients, of Lewi body dementia patients, and controls and could distinguish with 100% specificity and 92% sensitivity between groups.

A previous study analyzed the lysosomal enzymes involved in the intracellular degradation of α -synuclein. PD patients exhibited lower β -glucocerebrosidase (specificity, 77%; sensitivity, 67%), cathepsin D (specificity, 77%; sensitivity, 61%), and β -hexosaminidase activity compared with controls. The diagnostic accuracy was greatly improved when the lysosomal activity of all enzymes was combined (specificity, 85%; sensitivity, 71%) (22).

Neurofilaments (NfL) are products of axonal degeneration. Following injury, various neurofilamental subunits are released in the CNS interstitial space. As white matter degeneration is not typical in PD, but frequent in atypical parkinsonian disorders, measuring NfL concentrations is an excellent differential diagnostic tool (26,27).

There is an entire body of evidence that links purine metabolism to PD (28,29). A previous study revealed that xanthine and HVA ratio in CSF distinguished PD patients from controls, providing a trait marker for the disease, and correlated to UPDRS scores, exhibiting state marker characteristics (30). An explanation for these findings could be attributed to higher levels of CSF xanthine as a result of CNS inflammatory processes, physiological stress, such as ischemia or hypoxia, and glutamate-mediated excitotoxicity (31,32).

Urate, the anionic form of uric acid (2,6,8-trioxy-purine), has been extensively studied in relation to PD (33,34). It can be detected in serum and in the CNS, where it acts as a powerful antioxidant. High levels of urate indicate a lower risk for developing the disease, while low levels have been revealed in the serum of PD patients, compared with controls (35,36).

Parkinsonism-associated deglycase encoded by the PARK7 gene, also known as DJ-1, is a promising candidate for the early detection of PD (37). It is a protein that has a protective role during neurodegenerative processes, characterized by high levels of oxidative stress. As DJ-1 proteins are abundant in erythrocytes, an accurate association between high levels of this protein and neurodegenerative processes require samples from non-contaminated CSF. DJ-1 protein can be selectively detected, at femtogram levels, in CSF and saliva, with a disposable neuronal biosensor based on an indium tin oxide electrode modified with gold nanoparticles and multi-walled carbon nanotubes (38). Flexible platinum electrodes obtained by photolithography on bio-based polyethylene terephthalate (Bio-PET) were used for dopamine voltammetric quantification, whereas the immunosensors resulted after the functionalization of these electrodes with specific anti-PARK7/DJ-1 antibodies, were able to detect PARK7 at ng/ml levels (39).

4. Blood biomarkers in PD

Blood species of α -synuclein are mostly detected in red blood cells (>99%) and, consequently, are influenced by hemolysis (40). Oligomeric forms of the protein have been revealed to be consistently higher in PD patients compared with controls in a small group study. Although the results are promising 100% specificity; 75% sensitivity, the study needs to be replicated on a larger population (41). Daniele *et al* published in 2017 a study in which they combined three parameters: Total α -synuclein, α -synuclein-A β 1-42, and phosphorylated-tau, with an area under the curve (AUC) diagnostic accuracy of 0.98 compared with controls (42).

Kynurenine acts as a protective factor in the kynurenine pathway. A number of studies have demonstrated the dysregulation of this pathway in PD patients (43,44). Kynurenine is not only a promising biomarker in PD, but it also offers new therapeutic possibilities, as enzyme inhibitors could decrease pathogenic quinolinic acid and increase protective kynurenic acid (44).

Glutamate activity has been revealed to be increased in the basal ganglia following dopaminergic neuron injury. Excessive levels of the neurotransmitter have been revealed to exhibit an excitotoxic effect, leading to neuronal cell death (8). Statistically significant levels of glutamate have been detected in the blood of PD patients (45). One exciting perspective for future research considers the therapeutic inhibitors of glutamatergic hyperactivity as a potential treatment for PD symptomatology for patients with suboptimal response to L-dopa treatment (46).

Branch chain amino acids were revealed to be consistently higher in patients suffering from neurodegenerative diseases, including PD, compared with controls (47-49).

5. Urine biomarkers in PD

Urinary 8-hydroxydeoxyguanosine (8-OHdG) and 8-hydroxyguanosine (8-OHG) are both products of DNA damage caused by reactive oxidative species. They have been studied in PD as oxidative stress biomarkers (50-52) and are eliminated in urine, where they can be evaluated as an indicator of DNA injury (51). Biopyrrin, the result of bilirubin oxidative processes, represents a new biomarker for the oxidative stress in sporadic PD, with high accuracy in differentiating PD patients, that exhibit significantly increased levels of urinary biopyrrin, compared with controls (53).

6. Fecal biomarkers in PD

Previously, several studies have been conducted on the involvement of the gut microbiome in neurodegenerative diseases, including PD, as fecal metabolome biomarkers could offer valuable insight into the complex interactions between host, gut flora and diet (54,55). Specifically, a previous study revealed a reduction in fecal short-chain fatty acids (SCFAs) in PD patients, compared with controls, which may contribute to the gastrointestinal problems observed in the course of the illness (56).

7. Biomarker signatures in psychiatric symptomatology of PD

Depression biomarkers in PD. Clinical biomarkers such as depression, REM sleep behaviour disorders and olfactory impairment can often appear years before the onset of the motor symptoms (57,58). Depression has been identified as the main predictive factor of life quality in PD, with between 10-45% of patients suffering from major depressive disorder (59-61). However, as a previous study (62) revealed, it remains underdiagnosed and insufficiently treated, with only 20% of the people diagnosed actually receiving treatment. It is, in part, the result of dopaminergic, serotonergic and noradrenergic neurotransmission damage observed in the evolution of the disease, with depressed PD patients having lower plasma levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) ($P < 0.001$ and $P < 0.001$, respectively) compared with controls as evaluated using the Hamilton Depression Scale (63,64). Glucose (65,66) and lipid (65,67,68) metabolism were altered in depressed PD patients, with lower serum levels for both apolipoprotein B

and low-density lipoprotein cholesterol, alterations in the linoleic and lysophosphatidic acid metabolism, modifications in incretin and insulin signalling, and serum high-density lipoprotein cholesterol and triglyceride levels being associated with a clinical tableau of depression and suicide (69). Proteins synthesized by the NOTCH2 gene are being investigated as potential blood biomarkers in this regard (65).

Anxiety biomarkers in PD. Anxiety disorders are frequent in PD and can be present before the onset of motor symptoms as generalized anxiety disorder, panic attacks, or phobias, or can be related to high doses of dopamine or dopamine agonist treatment (70,71). The pathological mechanism involves disturbances in the noradrenergic system, and lower levels of noradrenaline have been detected in depressive PD patients (63), compared with PD patients without depression and anxiety. Clinical observations relate to a worsening of depressive and anxious symptomatology following inhibition of adrenergic neurotransmission and an improvement in symptomatology as well as executive functions and attention (7).

Psychosis biomarkers in PD. In PD, psychotic symptoms can either appear as a result of disease progression or as a side effect of treatment (72), and they exhibit a strong correlation with mortality and the need for nursing home placement (73). The most common types (40%) are visual hallucinations (74), frequently as a result of treatment, with sleep disturbances being identified as a possible risk factor (75). Auditory hallucinations (AH) take the form of verbal hallucinations originating from outside the body and are the most frequent, followed by non-verbal AH, musical AH being the rarest (76). Drug withdrawal upon sudden cessation of treatment can precipitate the appearance of a neuroleptic malignant syndrome, manifested with delirium and hyperpyrexia (72). Delirium, paranoid ideations, and delusions appear later in the disease course and are especially problematic for caregivers due to their accusatory and paranoid content (75).

A previous study conducted on urine samples from patients with PD revealed a positive correlation between 8-OHdG, one of the main biomarkers of DNA damage due to oxidative stress, and the presence of hallucinations (50), making it a promising prospect for future research. Low levels of α -synuclein-A β 42 in CSF have been correlated with the appearance of illusions and hallucinations in the early course of the disease (16).

Cognitive impairment biomarkers in PD. PD dementia can appear in 40% of patients (77), due to neurodegenerative processes (78-82) and neurotransmitter deficiencies (83-85). Cognitive disorders in PD are characterized by attention and memory dysfunctions, impairment of visuospatial abilities, and dysexecutive syndrome, with progressive evolution. Interestingly, a recent study established the deterioration of theory of mind in relationship with the impairment of visuospatial abilities in PD patients, but not attention or executive functions (86). Several studies have investigated the relationship between CSF or blood biomarkers and cognitive impairment. CSF A β 42 levels have been correlated with cognitive dysfunction and memory decline (87), with PD patients with dementia exhibiting lower concentrations compared with PD patients without cognitive impairment and compared with

healthy controls. A previous study reported that tau protein levels are higher in CSF due to other neurodegenerative illnesses and lower in PD, making it an effective biomarker for differential diagnosis (88), whereas other studies (22,89) revealed that CSF tau levels were higher in PD with dementia, visuospatial dysfunction, and memory impairment, compared with PD without cognitive dysfunctions. CSF neurofilament levels are high in other neurodegenerative diseases but do not increase in PD, making it a useful biomarker distinguishing between diagnoses (27). A recent study revealed that an electrochemical affinity immunosensor, having as recognition element anti-NfL light chain antibody covalently linked to a poly glycidyl methacrylate film, had the ability to detect NfL at ng/l levels (90). Brain-derived neurotrophic factor regulates synaptic plasticity and cognitive processes and inhibits apoptosis-mediated cell death. Decreased levels in blood and CSF have been detected in the early stages of the disease, making it an early diagnostic biomarker for cognitive decline (91). Insulin-like growth factor 1 (IGF-1) is secreted by microglial cells in the damaged brains of PD patients, and high levels can be detected in CSF, compared with healthy controls, but only in the advanced stages of the disease (>3.5 years) (92). Microglial cells, following dopaminergic neuron cell death, secrete inflammatory cytokines. Shen *et al* (93) reported an immunosensing platform for *in vivo* electrochemical monitoring of the proinflammatory cytokines tumor necrosis factor (TNF)- α , interleukin (IL)-6 and IL- β with the aim of future diagnosis of PD in its early stages. High levels of inflammatory biomarkers such as interferon (IFN)- γ , TNF- α , IL-2, 6, 10, IL-1 β can be detected in the blood and CSF of PD patients in the onset of the disease and are correlated with cognitive impairment (94,95).

8. Conclusions

Studying a complex disease such as Parkinson's requires a nuanced approach. The 2001 Biomarkers Definition Working Group defined biomarkers as characteristics that can be objectively measured and evaluated as indicators of both normal and pathogenic processes and as responses to therapeutic interventions (96). As it has been demonstrated in the present review, biomarkers can be obtained from various biological samples, such as human brain tissue, CSF, blood or plasma, urine or fecal samples (12). The scientific literature delivers a wide array of significant leads regarding early diagnosis (5-S-cysteinyl dopamine/homovanillic acid concentrations ratio in CSF), accurate diagnosis (α -synuclein levels in CSF and plasma, and lysosomal enzymes in CSF, biopyrrin in urine and SCFA in fecal samples), differential diagnosis (NfL in CSF), risk factors (low urate levels) and therapeutic targets (the kynurenine pathway, the glutamatergic pathway). Furthermore, a growing body of research aims to explore the complex connections between metabolic changes in the disease and psychiatric symptoms such as depression (reduced receptor binding capacity in the serotonergic pathway, decreased 5-hydroxyindolacetic acid concentrations in CSF, glucose and lipid metabolism alterations), anxiety (low noradrenaline levels), psychosis (low α -synuclein-A β 42 in CSF and urinary 8-OHdG) and cognitive impairment (lower A β 42 and tau protein levels in CSF,

decreased BDNF in blood and CSF). Novel and efficient ways to test and differentiate between patient subgroups will help to increase the specificity and sensibility of existing and new biomarkers. For example, one direction for future research with implications in rapid differentiation between dopamine treatment subgroups is the use of voltammetric techniques with different types of electrodes for the fast determination of the active components in multiple pharmaceutical formulations (L-DOPA and benserazide) (97) or biological fluids (98) and others, such as bradykinesia, correlate with dopaminergic neuron loss in the basal ganglia (2). In conclusion, the biomarkers presented in this review are all promising tools that will provide an improved understanding and contribute to treatment of PD. Urate, for example, is included in treatment studies as a neuroprotective agent in PD. As most of these markers have been studied in small groups or alone, clinical significance can be increased by combining biomarkers into classifying algorithms, offering new research perspectives. In an exciting development aiming to increase the reproducibility of the studies, various international programs have been put in place in order to address the need for standard research protocols, and the use of novel analysis methods can increase accuracy and speed, and help us develop improved experimental designs with sub-classes of patients, accurately mapping treatment response and side effects.

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AMC contributed in all the stages of the article and provided the final approval of the version to be published. II was involved in the writing, reviewing and editing of the manuscript. MB, IGD and DEP were involved in the conception of the study, analysis and interpretation of the literature data. AAC and MB were involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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