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Assess the Diagnostic Potential of Several Significant Biomarkers for Parkinson's Disease

Khalid M. Khudhur Al-Bofkane, Mohammed Bahry Hassin
Chemistry Department, College of Science, University of Mosul, Mosul, Iraq

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Annotation: Parkinson's disease (PD), a neurodegenerative disorder, is associated with altered blood biochemistry, this study investigates key biomarkers like dopamine, alpha-synuclein, Tau protein, TNF, beta-amyloid, IL-6, copper, and iron in both healthy individuals and PD patients, the study was conducted on (90) for both healthy and patients, both males and females were between the ages of 50 and 85 years old. The findings show that PD patients have significantly lower levels of dopamine (19.40 ± 0.82 pg/mL) than healthy people (31.58 ± 1.07 pg/mL, $p < 0.01$), which demonstrates its part in the disease's pathogenesis.; elevated levels of Tau protein (41.58 ± 2.97 ng/L vs. 9.85 ± 3.6 ng/L, $p < 0.01$) and alpha-synuclein (47.31 ± 1.91 pg/mL vs. 25.84 ± 2.07 pg/mL, $p < 0.01$) suggest neurodegenerative involvement; PD patients have higher levels of the markers of inflammation TNF and IL-6. further indicate neuroinflammation; and beta-amyloid levels are significantly higher in PD patients (168.78 ± 0.27 pg/mL) than in controls (80.65 ± 1.13 pg/mL, $p < 0.01$), highlighting the role of amyloid pathology in disease progression. A gender-based investigation showed only small variations, with females having slightly greater levels of alpha-synuclein and IL-6. The age-dependent character of PD-related biochemical alterations is further supported by age-stratified data in PD patients, which indicate gradual decreases in dopamine and iron along with rising

levels of Tau protein and alpha-synuclein across age groups.

Keywords: Parkinson disease, biomarkers, blood plasma, alpha-synuclein, Tau protein.

1. Introduction

Neurodegenerative diseases are the leading cause of morbidity and disability worldwide, particularly among the elderly. They are identified by the ongoing decline in neuronal function, which causes the brain to atrophy. Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis and Huntington's disease, are the neurological disorders that are the most widespread. [1]. It is anticipated that rising life expectancy in many countries will increase the rate and occurrence of illnesses, particularly those linked to aging [2].

2. Parkinson disease

(PD) is an idiopathic neurological disorder that affects both the motor and non-motor systems. It is a degenerative, long-term neurological disease that mainly affects the elderly, however it can also afflict people far younger. Aging, family history, and exposure to environmental pollutants like synthetic heroin or pesticides are all associated with idiopathic Parkinson's disease [3].

According to the World Health Organization (WHO), 80 percent of the world's 2.1 billion elderly residents will reside in low- and middle-income nations by 2050. Age-related diseases have increased as human life expectancy has increased due to improved quality of life. Without a doubt, this is a challenge for the entire world [4]. Debilitating motor symptoms brought on by age-related progressive neurodegeneration are the hallmark of Parkinson's disease, the second most prevalent neurodegenerative illness. However, the early pathophysiological processes remain poorly understood [5]. Parkinson's disease is characterized by cell loss in the substance nigra and other cerebral areas, as well as neural aggregates known as Lewy bodies and Lewy neurites. Parkinson's disease is categorized as a synucleinopathy since the main constituents of Lewy bodies are aggregated and misfolded α-synuclein species [6]. With the goal to improve diagnostic accuracy, clinical diagnostic standards for (PD) have been proved within the preceding five years. The inability of current tests or biomarkers to offer a conclusive diagnosis in the early stages and the overlapping clinical symptoms with other neurodegenerative disorders, however, continue to present difficulties. As a result, even when the disease is completely present, clinical diagnostic accuracy is still insufficient [7]. The majority of the time, Parkinson's disease (PD) has been diagnosed using motor symptoms. A number of rating scales used to assess the severity of Parkinson's disease have not been thoroughly investigated or validated, even though the condition's cardinal indications for clinical evaluations have been established. Non-motor symptoms, such as cognitive issues (such as trouble focusing and planning), sleep disturbances, and sensory impairments including olfactory impairment, sometimes precede the onset of Parkinson's disease (PD) [8]. These symptoms can vary considerably from patient to patient, are difficult to assess, and are not specific. Therefore, while some non-motor symptoms may be utilized as a diagnostic criterion, non-motor symptoms alone cannot be used to diagnose Parkinson's disease (PD) [9].

Age is the primary risk factor for Parkinson's disease, and the likelihood of having it is almost three times higher in males than in women. There is a substantial genetic component, with about 90 connected loci. Additionally, a range of environmental factors (like pesticides and water toxins) and changeable lifestyle factors (like smoking, drinking coffee, exercising, and brain trauma) contribute to the condition's development in varied groups [10].

3. The aim of this study

This study compares key biochemical markers in the blood plasma from healthy individuals and patients with Parkinson's disease to identify potential diagnostic and pathological indicators.

These markers may also help track disease progression and assess treatment effectiveness.

4. aterials and Methods

4.1. Study design

90 blood samples were taken from People with PD, ages 50 to 85 years, who had been diagnosed by specialists in Ibn Sina Teaching Hospital diagnosed with Parkinson disease. There were 66 males and 24 females in the study, and they were split into three age groups: 50–60 years old, 61–70 years old, and 71–85 years old.

Control group: Healthy individuals selected from the general population during hospital checkups or from patient attendants.

5. Experimental and diagnostic methods

Venous blood was collected from 90 (PD) patients using 9-ml K3-EDTA tubes. Plasma was extracted by centrifuging samples at 2500 g for 15 minutes at 15–25°C within one hour of collection. Plasma samples were then separated, stored at -80°C, and hemolysis was excluded [11].

Blood plasma levels of Dopamine, Alpha synuclein, Tau protein, TNF, Beta amyloid, IL-6 were measured using ready-made kits from SunLong Biotech, China, employing the ELISA method. Iron and copper were measured using ready-made kits provided by the Jordan company (bio research).

5.1. Statistical analysis

Data were analyzed using ANOVA ($p < 0.01$) with Duncan's post-hoc test ($p < 0.05$) in SPSS (version 18) to compare variables.

6. Results and discussion

Table (1) Blood plasma levels of biochemical variables in Parkinson's disease patients compared to controls.

Biochemical variables	Healthy (n =90)	Patient (n=90)	P value
	Mean ± SE	Mean ± SE	
Dopamine (pg/mL)	31.58 ± 1.07	19.40 ± 0.82	< 0.01
Alpha synuclein (pg/mL)	25.84 ± 2.07	47.31 ± 1.91	< 0.01
Tau protein (ng/L)	9.85 ± 3.6	41.58 ± 2.97	< 0.01
TNF (pg/mL)	21.17 ± 1.29	28.21 ± 0.84	< 0.01
Beta amyloid (pg/mL)	80.65 ± 1.13	168.78 ± 0.27	< 0.01
IL6 (ng/L)	6.79 ± 0.27	9.89 ± 0.72	< 0.01
Copper (mg/dL)	128.66 ± 1.98	173.87 ±1.87	< 0.01
Iron (mg/dL)	63.80 ± 2.03	143.39 ±1.71	< 0.01

According to the findings, plasma dopamine levels are significantly lower in (PD) patients (19.4 ± 0.82) compared to healthy individuals (31.58 ± 1.07, $p < 0.01$). This decline correlates with dopaminergic neuron degeneration in the substantia nigra, contributing to PD's characteristic motor symptoms. Tremor, postural instability, bradykinesia, and muscle rigidity are among the clinical signs of Parkinson's disease (PD) that begin as dopaminergic neurons gradually degenerate, lowering the amount of dopamine in the SN and striatum [12].

PD patients also exhibit significantly elevated alpha-synuclein levels (47.31 ± 1.91 vs. 25.84 ±

2.07, $p < 0.01$), consistent with previous research linking alpha-synuclein accumulation to PD pathology. These outcomes are consistent with research that indicates patients with Parkinson disease have a markedly elevated plasma alpha synuclein in compare with healthy group [13]. Actually, the gold standard for evaluating the neuropathology of Parkinson's disease at this time is α-synuclein immunohistochemistry. Major revelations came from repeated studies: α-synuclein pathology in Parkinson's disease (PD) is not limited to the cell soma; it is also significant in neuritic processes, and it is pervasive throughout the brain [14]

PD patients exhibit significantly elevated Tau protein levels (41.54 ± 2.95) compared to controls (9.85 ± 3.6, $p \leq 0.01$), consistent with previous findings and supporting Tau's role in neurodegeneration [15] PD objective biomarkers could help with better clinical trial design and interpretation, early and precise diagnosis, and efficient tracking of illness development. The need for a PD biomarker panel is underscored by the complex and heterogeneous nature of Parkinson's disease. The best biomarker candidates are those that represent the underlying degenerative process of Parkinson's disease and may be found in readily available samples, preferably blood [16] Age-related hyperphosphorylation reduces Tau's microtubule affinity, which promotes aggregation, and Tau protein is released into the bloodstream when neurons are injured or die due to increased neuronal stress and damage caused by aging [17]

Additionally, beta-amyloid levels in PD patients (168.78 ± 0.27) are significantly higher than in controls (80.65 ± 1.13, $p < 0.01$), supporting its involvement in cognitive decline. Elevated TNF levels in PD patients (28.21 ± 0.84) compared to healthy individuals (21.17 ± 1.29, $p < 0.01$) indicate chronic neuroinflammation, which may contribute to disease progression.

As seen in Table (1), there was a significant difference in the IL-6 concentrations between the two patient and healthy groups at less or equal to 0.01 probability level. Parkinson's disease caused IL-6 to rise to (9.89 ± 0.72), whereas the healthy group's IL-6 concentration reached (6.79 ± 0.27). These findings are in line with earlier research showing a high level of IL-6 in Parkinson's disease patients [18]. Compared to healthy persons, patient's group had considerably higher levels of iron (143.39 ± 1.71 vs. 63.8 ± 2.03, $p < 0.01$) and copper (173.87 ± 1.87 vs. 128.66 ± 0.98, $p < 0.01$). While iron dyshomeostasis leads to neurotoxicity and oxidative stress associated with aging, excessive copper buildup is linked to oxidative damage and cellular instability [19] [20].

Impact of the sex of an individual

Table (2) Levels of biochemical variables measured in the plasma of males compared with females with Parkinson disease.

Biochemical variables	Male (n =61)	Female (n=29)	
	Mean ± SE	Mean ± SE	P value
Dopamine (pg/mL)	19.55 ± 4.23	19.14 ± 3.93	NS
Alpha synuclein (pg/mL)	46.52 ± 2.54	48.62 ± 2.97	NS
Tau protein (ng/L)	8.33 ± 1.58	32.10 ± 1.95	*
TNF (pg/mL)	28.43 ± 1.24	27.83 ± 0.95	NS
Beta amyloid (pg/mL)	166.95 ± 0.35	171.84 ± 0.37	NS
IL6 (ng/L)	9.41 ± 0.028	10.69 ± 0.045	NS
Copper (mg/dL)	173.93 ± 0.10	173.77 ± 0.80	NS
Iron (mg/dL)	150.13 ± 0.031	139.48 ± 0.036	*

N.S It means there is no significant difference.

The table's results showed no significant differences in most biochemical variables between males and females Parkinson's disease groups. Beta-amyloid results corroborated [21] research, showing no significant sex difference in PD patients. Despite the fact that the male group of Parkinson's disease patients had significantly higher Tau protein levels (43.33 ± 1.58 vs 32.10 ±

1.95, P < 0.05) than the female group, these results are in line with those of [22] who also found that the male group of patients had significantly higher Tau protein levels than the female group.

While no overall difference in alpha-synuclein levels was observed between male and female Parkinson's disease patients, [23] reported significantly higher levels in females with Parkinson's disease compared to males. Between affected males and females, there was no discernible difference in copper levels, but iron levels were significantly higher in male, Males have higher ferritin levels than females, which could be the cause. According to recent studies, women seem to have higher striatal dopaminergic activity, a preponderance of tremor, and a later onset of motor symptoms than men [24]. Dementia and cognitive impairment are significantly more common in men with PD, according to research, and cognitive, emotional, and mental deficits are particularly important in the manifestation of PD [25].

Impact of the age of an individual

Table (3) Comparing several parameters between individuals suffering from Parkinson disease and the healthy in various age groups: (50-60 years), (61-70 years), and (71 – 85 years).

Biochemical Variables	Patients group 50 – 60 years old	Patients group 61 – 70 y ears old	Patients group 71 – 85 years old
	Mean ± SE	Mean ± SE	Mean ± SE
Dopamine (pg/mL)	25.29 ± 0.03 a	20.89 ± 3.1 ab	19.72 ± 0.07 c
Alpha synuclein (pg/mL)	35.79 ± 1.1 a	41.9299 ± 0.98 b	47.3646 ± 0.87 c
Tau protein (ng/L)	32.61 ± 0.25 a	38.61 ± 3.1 a	44.09 ± 1.28 b
TNF-α (pg/mL)	26.92 ± 1.25 a	26.45 ± 0.98 a	30.07 ± 1.5 ab
Beta amyloid (pg/mL)	161.71 ± 1.28 ab	177.36 ± 0.9 a	165.76 ± 0.85 ab
IL-6 (ng/L)	10.93 ± 0.024 a	9.98 ± 0.08 a	9.35 ± 1.1 a
Copper (mg/dL)	175.60 ± 1.28 a	173.25 ± 0.9 a	173.54 ± 0.04 a
Iron (mg/dL)	127.29 ± 2.35 a	141.75 ± 0.25 b	151.89 ± 0.4 c

Table (4) Comparing several parameters between individuals suffering from parkinson disease and the healthy in age groups (50 – 60) years old

Biochemical variables	Control group 50 – 60 years old	Patients group 50 – 60 years old
	Mean ± SE	Mean ± SE
Dopamine (pg/mL)	32.18 ± 0.02	25.29 ± 0.03 a
Alpha synuclein (pg/mL)	27.46 ± 0.25 a	35.79 b ± 1.1
Tau protein (ng/L)	5.907 ± 0.32	32.61 ± 0.25 c
TNF-α (pg/mL)	18.44 ± 0.27 a	26.92 ± 1.25 ab
Beta amyloid (pg/mL)	74.25 ± 1.35 a	161.71 ± 1.28 b
IL-6 (ng/L)	6.31 ± 0.13 a	10.93 ± 0.024 c
Copper (mg/dL)	141.37 ± 0.85 a	175.60 ± 1.28 b
Iron (mg/dL)	67.24 ± 1.98 a	127.29 ± 2.35 b

Table (5) Comparing several parameters between individuals suffering from parkinson disease and the healthy in age groups (61 – 70) years old.

Biochemical variables	Control group 61 – 70 years old	Patients group 61 – 70 years old
	Mean ± SE	Mean ± SE
Dopamine (pg/mL)	33.28 ± 2.6 b	20.89 ± 3.1 a
Alpha synuclein (pg/mL)	26.8694 ± 0.08 a	41.9299 ± 0.98 b

Tau protein (ng/L)	10.91 ± 2.8 a	38.61 ± 3.1 c
TNF-α (pg/mL)	21.96 ± 0.78 a	26.45 ± 0.98 bc
Beta amyloid (pg/mL)	85.30 ± 1.9 a	177.36 ± 0.9 b
IL-6 (ng/L)	7.22 ± 0.05 ab	9.98 ± 0.08 bc
Copper (mg/dL)	117.42 ± 1.2 a	173.25 ± 0.9 b
Iron (mg/dL)	59.90 ± 0.32 a	141.75 ± 0.25 b

Table (6) Comparing several parameters between individuals suffering from parkinson disease and the healthy in age groups (71 – 85) years old

Biochemical variable	Control group 71 – 85 years old	Patients group 71 – 85 years old
	Mean ± SE	Mean ± SE
Dopamine (pg/mL)	31.50 ± 0.08 b	19.72 ± 0.07 a
Alpha synuclein (pg/mL)	27.15± 0.67a	47.3646 ± 0.87
Tau protein (ng/L)	11.8 ± 8.5 a	44.09 ± 1.28 c
TNF-α (pg/mL)	22.98 ± 1.9 a	30.07 ± 1.5 c
Beta amyloid (pg/mL)	82.72 ± 0.9 a	165.76 ± 0.85 b
IL-6 (ng/L)	6.88 ± 1.5 ab	9.35 ± 1.1 abc
Copper (mg/dL)	126.11 ± 0.08 a	173.54 ± 0.04 b
Iron (mg/dL)	63.78 ± 1.3 a	151.89 ± 0.4 b

Aging is considered a stochastic process involving both predictable and random factors, reducing cellular repair and compensation mechanisms and causing an accumulation of unrepaired cellular damage [26], In addition to analyzing stratifying patients into three age groups to assess age's impact (50 - 60), (61 - 70), and (71 – 85) years, the effect of age on all biochemical variables in the plasma of the patient and control groups was also investigated. The levels of biochemical variables across various ages and categories within the patient group were compared, as indicated in Tables (3), Many parameters remain stable between the youngest and middle groups, then shift more markedly in the oldest. Dopamine steadily decrease in all groups at a probability ($p \leq 0.05$), potentially indicating declining dopaminergic activity, Aging involves a progressive loss of dopaminergic neurons and receptors, particularly in the substantia nigra. This neuronal decline reduces dopamine synthesis, resulting in lower levels of dopamine [26] [27]. Neurodegenerative risk rises with the gradual accumulation of beta-amyloid, Tau, and alpha-synuclein, compounded by age-related increases in inflammatory markers TNF and IL-6 which in oxidative stress results from aging's disruption of the equilibrium between the generation of reactive oxygen species and antioxidant defenses. This increases the production of cytokines by activating inflammatory pathways [17] [28] . There were no discernible differences in copper level between Parkinson's disease age groups. Iron levels progressively increase significantly at a probability ($p \leq 0.05$) across all age groups; age-related cellular damage or turnover may result in the release of stored iron from tissues into the bloodstream. This process could contribute to an overall increase in plasma iron, despite a complex interplay with iron storage markers as ferritin [29].

Impact of illness duration

Table (4) Table showing comparing variable levels in Parkinson's disease patients, categorized by disease duration.

Duration of illness	1 – 3 years	4 – 7 years	8 – 12 years
Biochemical variables	Mean ± SE	Mean ± SE	Mean ± SE
Dopamine (pg/mL)	21.34 ± 0.36 a	18.40 ± 0.65 b	17.49 ± 1.02 bc
Alpha synuclein (pg/mL)	41.64 ± 2.6 ab	49.50 ± 2.1 b	48.95 ± 1.98 bc

Tau protein (ng/L)	23.25 ± 0.05 a	39.99 ± 0.3 b	58.65 ± 0.35 c
TNF- α(pg/mL)	29.31 ± 2.68 a	26.67± 0.28 a	28.77 ± 1.28 b
Beta amyloid (pg/mL)	158.08 ± 0.36 a	166.99 ± 0.65 ab	176.64 ± 0.98 b
IL-6 (ng/L)	10.53 ± 1.36 a	8.87 ± 1.68 a	10.32 ± 1.47 a
Copper (mg/dL)	176.33 ± 0.05 a	173.37 ± 0.98 a	172.80 ± 0.07 a
Iron (mg/dL)	133.62 ± 1.2 a	142.92 ± 0.95 ab	160.29 ± 0.35 c

The table (4) shows that in Parkinson's disease patients, categorized by illness duration (1–3 years, 4–7 years, and 8–12 years), alpha-synuclein and tau protein levels increased, suggesting pathological aggregation, the results corroborate researchers' findings that CSF α-Synuclein and Tau protein levels increase with age and are higher in males. While these levels remained stable in early symptomatic PD they increased as the disease progressed [30] [31] [32]. Age-induced accumulation and interaction of tau and α-synuclein promotes their co-aggregation, which may be identified by CSF biomarkers and leads to motor and cognitive impairment in Parkinson's disease, according to post-mortem investigations, tyrosine hydroxylase immunoreactivity in the substantia nigra and putamen sharply declines throughout the first four to five years of Parkinson's disease before stabilizing, indicating a decreased capacity for dopamine synthesis as the illness worsens [33]. Subsequently, inflammatory markers (TNF-α and beta-amyloid) significantly increased, correlating with heightened neuroinflammation and amyloid accumulation. Oxidative stress indicators, such as glutathione, declined sharply over time, while malondialdehyde levels, a marker of lipid peroxidation, increased, Meta-analyses and reviews indicate elevated TNF-α levels in the cerebrospinal fluid and serum of Parkinson's disease patients, suggesting chronic neuroinflammation [34]. Elevated mineral levels, such as iron, suggest metal dyshomeostasis may contribute to disease progression. Significant differences ($P \leq 0.05$) between groups indicate dynamic biochemical changes in Parkinson's disease, revealing potential biomarkers for monitoring and treatment, SN iron decreases early in drug-naïve patients but rises with treatment and disease progression, plateauing after ~6 years [35].

Impact of the smoking of an individual

Table (5) Comparative levels of several parameters in the blood of individuals suffering from Parkinson disease, smokers, and non-smokers.

Biochemical variables	Non-Smoker	Smoker	
	Mean ± SE	Mean ±SE	P value
Dopamine (pg/mL)	26.90 ± 2.15	24.48 ± 1.9	NS
Alpha synuclein (pg/mL)	36.84 ± 0.23	28.38 ± 0.34	NS
Tau protein (ng/L)	28.78 ± 2.36	30.53 ± 2.68	NS
TNF (pg/mL)	25.45 ± 1.85	24.14 ± 1.68	NS
Beta amyloid (pg/mL)	120.68 ± 0.36	127.60 ± 0.78	NS
IL6 (ng/L)	7.81± 0.68	8.72 ± 0.85	*
Copper (mg/dL)	144.40 ± 0.12	156.17 ± 0.32	*
Iron (mg/dL)	96.17 ± 1.6	108.90 ± 1.9	NS

N.S It means there is no significant difference.

The risk of (PD) is inversely correlated with cigarette smoking, according to a meta-analysis of observational data [36]. Biochemical marker analysis in Parkinson's disease patients showed no significant differences between smokers and non-smokers in dopamine, alpha-synuclein, Tau protein, TNF, beta-amyloid, and iron levels. However, smokers had significantly higher IL-6 (8.72 ± 0.85 vs. 7.81 ± 0.68, $p < 0.05$), indicating increased systemic inflammation, and elevated copper levels (156.17 ± 0.32 vs. 144.40 ± 0.12, $p < 0.05$), suggesting increased oxidative stress [37]. These results suggest that while smoking may not directly alter PD-related protein markers, it may worsen neuroinflammation and oxidative stress. Smoking-induced epigenetic changes

affecting genes related to inflammation, synaptic plasticity, and neuronal survival warrant investigation to understand smoking's role in neurodegeneration. Research should also explore how smoking-related gut symbiosis, potentially leading to altered neurotransmitter synthesis, systemic inflammation, and increased gut permeability, contributes to cognitive decline and neurodegenerative processes [38] [39] [40]

Conclusion

however, there is still a lack of information on Parkinson's disease (PD). Blood-based biomarkers offer a potential game-changer for Parkinson's disease management. Like routine check-ups, these biomarkers could track disease progression, allowing doctors to assess treatment effectiveness and adjust therapies as needed. This could lead to more focused and effective treatments, ultimately improving patients' lives. Blood testing is becoming increasingly vital and may revolutionize Parkinson's treatment. While current progress is promising, further research is crucial.

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