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RESEARCH

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Apolipoprotein D concentration in Parkinson's disease patients

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Abstract

Background Parkinson's disease (PD) is distinguished recently by an increase in inflammation and oxidative stress. Apolipoprotein D (Apo D) is a neuroprotective protein that was discovered to be increased in PD-affected brains. The aim of our study was to measure the ApoD serum level in individuals with PD and to correlate it with the clinical data of those individuals. Thirty individuals suffering from idiopathic PD were subjected to neurological examination, disease intensity by applying the Unified Parkinson's Disease Rating Scale (UPDRS) and measurement of Apo D blood levels. Thirty age and sex matched controls were included for comparison of Apo D concentration.

Results Apolipoprotein D levels were substantially greater in PD individuals than in controls. The correlation between Apo D serum level and PD severity determined by the UPDRS and its subscales was positive.

Conclusion PD patients had increased blood level concentration of Apo D, which was associated positively with disease intensity. We suggest that Apo D serum level can be used as a predictor factor for PD severity. More studies are warranted to study how to target the Apo D in PD patients and thus helping to reduce the oxidative stress and inflammatory cascade involved in the pathogenesis of the disease.

Keywords Parkinson's disease, Apolipoprotein D, Unified Parkinson's Disease Rating Scale

Background

Parkinson's disease (PD) is considered the second most prevalent age-related neurodegenerative disease after Alzheimer's disease (AD). PD impacts 1% of those over 65 years old [1].

PD is clinically described by a triad of rigidity, tremor, and bradykinesia. This occurs due to gradual neuron degeneration in the substantia nigra (SN) and the accumulation of Lewy bodies in the same region. Both idiopathic and hereditary PD are characterized by a pathological rise in inflammation and oxidative stress-related processes. [2].

In the existence of iron ions and the creation of hydroxyl radicals, the dopamine (DA) levels in synaptic terminals decrease. Also, it was shown an increased in quantities of proteins, oxidized lipids, and deoxyribonucleic acid (DNA) in the SN of PD patients, together with lower levels of the antioxidant glutathione. All the previously mentioned pathophysiological processes create the characteristic movement disorders of PD [3, 4].

The reduction in glutathione concentration is correlated with an elevation in arachidonic acid (AA) release through phospholipase A2. This is accompanied by a build-up of inflammatory mediators as well as reactive nitrogen and oxygen species (RNS/ROS) [5].

Apolipoprotein D is a glycoprotein of 29 kDa that belongs to the lipocalin family. It is made up of an eight-stranded anti-parallel barrel bordered by an α-helix [6]. This framework provides a skeleton with a hydrophobic

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ligand pocket that interacts with progesterone and AA [6].

It is primarily synthesized in the plasma and in the brain. In the later, it is abundantly represented in the fronto-temporal cortex, the cerebellum, and the SN [7]. It significantly impacts the neuronal function and survival in healthy SN [8]. Apo D affects the metabolism of AA in an anti-inflammatory and antioxidant way, as well as its involvement in extracellular lipid transport [7].

Apolipoprotein D inhibits membrane-associated AA release from phospholipids, leading to it stabilization [9]. It binds free AA and prevents its transformation into pro-inflammatory eicosanoids or oxidants. Furthermore, it converts AA hydroperoxides to lipid hydroxides, regulating the inflammatory pathways and controlling the lipid peroxidation chain events [10].

It was found to be elevated in spongiform encephalopathy, AD, Niemann–Pick type C disease, PD, and ischemic stroke. These diseases are distinguished by the abnormal metabolism of AA in the brain and enhanced excitotoxicity [5]. Thus, we intended to measure Apolipoprotein D serum levels in PD patients and correlate it with the clinical data of those patients.

Methods

This case–control cross-sectional research was established in the department of Neurology of Fayoum University Hospitals, in the period from March 2019 and January 2021. Thirty PD patients of both sexes (diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank) were recruited. The sample size was calculated using Epicalc 2000 for comparing two mean levels of Apo D in patients and controls based on a previous study assuming that the power is 90% and the significance level is 5% [4].

A comparison group of 30 healthy volunteers, matching in age and sex, was selected. The exclusion criteria: any individuals from both patient and control groups complaining of any other pathological/physiological conditions that can affect the plasma levels of Apo D, such as stroke, antipsychotic drugs treatment, obesity (body mass index > 27), traumatic brain injury, Paget's disease, breast cancer, idiopathic normal pressure hydrocephalus, glucose-6-phosphate deficiency, prostate adenocarcinoma, and insulin resistance-associated disorders.

Cases were classified according to the predominant motor sign into two groups: group 1; bradykinesia-rigidity dominant phenotype (BRD) having a mean tremor score: mean bradykinesia-rigidity score (of UPDRS) ratio of ≤ 1, and group 2; tremor dominant (TD) phenotype with a mean tremor score: mean bradykinesia-rigidity score ratio of ≥ 1.5 [11].

All of the patients underwent thorough history taking, general and neurological examinations. We applied the Unified Parkinson's Disease Rating Scale to determine the severity of the disease (UPDRS) with its four parts. Part I: evaluation of mentation, behavior, and mood, Part II: self-evaluation of the activities of daily life (ADLs), Part III: clinician-scored monitored motor evaluation, Part IV: complication of therapy which measures complications of levodopa therapy: dyskinesia and fluctuations in medication effectiveness depending on the patients' symptoms.

Each part has multiple points that are individually scored, using zero for normal or no problems up to 4 for severe problems. These scores are indicator of the severity of the disease, with 199 points being the worst disability and 0 meaning no disability.

Serum Apo D levels were assessed in both patients and controls. Human plasma was collected and Apo D levels were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits. The samples were collected according to the protocol adopted by Waldner and colleagues [4].

The Research Ethical Committee of the Faculty of Medicine, Fayoum University, accepted the research. All participants were told about the study's aims, assessment, and investigations. All of them provided written informed permission. The personal information's confidentiality and their freedom to refuse the participation were considered.

Data were analyzed utilizing the Statistical Package for Social Science (SPSS) software version 22. (SPSS Inc., Chicago, Illinois, USA) [12]. Qualitative data were processed using simple parametric descriptive analysis in the form of percentages and numbers; for measuring quantitative parametric data, we used mean and standard deviation. For quantitative data, in the case of independent samples, to contrast quantitative variables between two independent groups, the t-test was employed. To assess the relationship between variables, use the bivariate Person correlation test. A P-value < 0.05 was considered statistically significant.

Results

The age range of the patient group was 51–77 years, with a mean of 53.6 ± 12.9 years. The age of the controls group ranged from 51–78 years, with a mean of 55.4 ± 13 years. Male patients with PD were 13 (43.3%), while the females were 17 (56.7%). Regarding the controls, males were 12 (40%), and females were 18(60%). The disease duration varied from 6 months to 9 years with a mean (3.5 ± 2.8) years. The clinical phenotypes were TD (tremor dominant) in 11 patients (36.7%) and BRD (bradykinesia-rigidity dominant phenotype) in 19 patients (63.3%). The

Table 1 Description of disease severity among PD patients using the Unified Parkinson's Disease Rating Scale (subdivisions and total)

	Mean	Range
Mentation, behavior and mood	3.5 ± 2.1	1–9
Daily living activities	14.3 ± 6.8	5–30
Motor	34.1 ± 20.5	9–78
Complications of therapy	4.2 ± 2.5	0–11
UPDRS	56.7 ± 29.5	18–117

UPDRS Unified Parkinson's Disease Rating Scale

Table 2 Comparisons of disease characters in different clinical phenotypes

Variables	TD phenotype		BRD phenotype		*P*-value
	Mean	SD	Mean	SD	
Age (years)	52.7	12.4	57.2	13.2	0.4
Disease duration (years)	3.1	2.5	3.7	2.9	0.5
Severity scales					
Mentation, behavior and mood	2.1	1.2	4.3	2	**0.003***
Daily living activities	10.4	5.6	16.6	6.5	**0.01***
Motor	27.4	24.6	37.9	17.4	**0.02***
Complications of therapy	3.2	1.5	4.8	2.8	0.08
UPDRS	44.7	32.7	63.6	25.8	**0.007***
Apo D	106.9	6.7	110.1	6.1	**0.006***

Bold mean that the results have significant value (P values < 0.05)

TD tremor dominant, *BRD* bradykinesia and rigidity dominant, *UPDRS* Unified Parkinson's Disease Rating Scale, *Apo D* apolipoprotein D

* Significant

mean total score of UPDRS varied from 18 to 117, with a mean of 56.7 ± 29.5. The data of UPDRS and its subscales are shown in Table 1.

The serum level of Apo D among the patients ranged from (102.31 to 122.31) ng/ml with a mean of 108.9 ± 6.4, and for controls, it ranged between 55.1 and 90.98 ng/ml with a mean of 75.4 ± 13.7. Comparisons of Apo D serum levels between patients and controls displayed a statistically significant variance (*P*-value > 0.001) as the patients had higher serum levels compared to controls. Comparisons of demographic characters in both studied groups revealed that there was no statistically significant variation regarding the sex nor the age.

The comparison of the clinical characteristics of the disease severity using the UPDRS and its subscales and also the serum level of Apo D among the two phenotypes of the patients are shown in Table 2.

The correlation between Apo D serum level and the age of the patients was not statistically significant. However, there was a statistically significant positive correlation between Apo D serum level and the disease duration (Fig. 1).

There was a statistically significant positive relationship between the blood concentration of Apo D and the illness severity as measured by the total UPDRS and its subscales (Table 3 and Fig. 2).

Discussion

Since ApoD is a small protein implicated in many pathologies, and its mechanistic mode of action is largely unknown, its therapeutic potential has yet to be fully understood. For now, since it positively affects oxidative stress, downregulates inflammation, and also has relatively positive effects on the metabolic syndrome in some tissues, its potential as a therapeutic protein can be considered high, and its effects are worth exploring [13].

Parkinson's disease is connected to a pathological events related to inflammation as well as oxidative stress, which are thought to contribute to dopaminergic neurodegeneration through a neurotoxic process mediated by free radicals [14].

Apolipoprotein D changes AA hydroperoxides into lipid hydroxides, which inhibits lipid peroxidation chain reactions and modifies the inflammatory pathways in PD [10].

This study showed that individuals with PD had considerably greater blood levels of Apo D than the controls. This finding is consistent with that obtained by Waldner and his group [4].

No difference in serum level of Apo D was observed in our study in PD patients among the genders which is in agreement with Waldner and his colleagues in their study [4]. Previous studies explained that Apo D level is increased in response to neurodegeneration and oxidative stress [15], and this has no relation to the patients' gender [16].

We showed in our study that there was no statistically significant difference between TD, and BRD phenotypes in terms of age and duration of disease, which is consistent with previous study [16].

According to other researches, PD patients with TD who still experience it after several years progress more slowly than those who suffer from other motor symptoms [11, 17, 18]. Also patients with BRD experience significantly greater subjective motor and occupational impairment than people with TD [19].

When comparing the serum level of Apo D and clinical types of the patient, there was a statistically significant difference with higher mean of Apo D serum level among BRD phenotype. This finding agrees with Selikhova and his group, who noted that PD cases with bradykinesia and rigidity predominant have a more pathological burden [20]. Autopsy results from neuroimaging studies

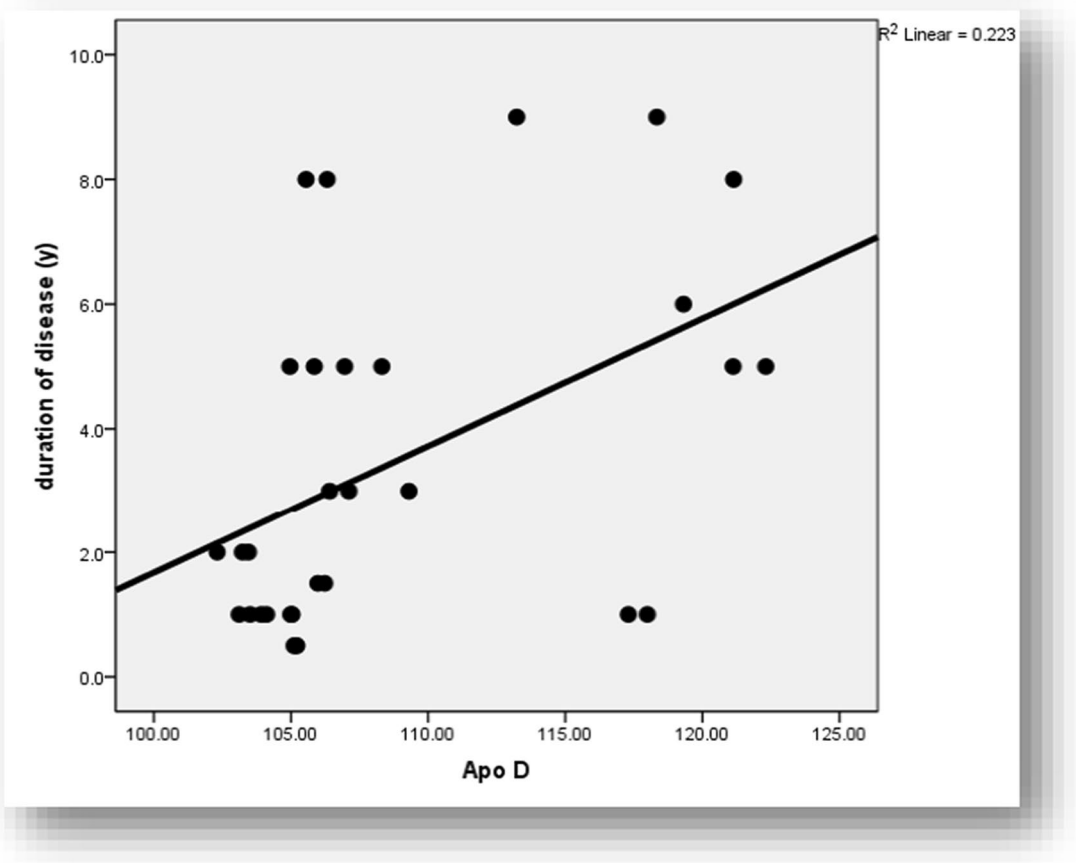

Fig. 1 Correlation between apolipoprotein D level and the disease duration

Table 3 Correlation between ApoD serum level and severity of the disease

	ApoD serum level	
	r	*P*-value
UPRDS		
Mentation, behavior and mood	**0.65**	**< 0.001****
Daily living activities	**0.86**	**< 0.001****
Motor	**0.95**	**< 0.001****
Complications of therapy	**0.76**	**< 0.001****
Total UPDRS	**0.98**	**< 0.001****

Bold mean that the results have significant value (P values < 0.05)

UPDRS: Unified Parkinson's Disease Rating Scale

** Highly significant

have revealed higher levels of dopaminergic denervation and grey matter atrophy [21, 22], with resultant increased Apo D in response to neurodegeneration [15].

By applying the immunohistochemistry technique in a previous research, it has been shown a significant rise in the Apo D positive cells' number, predominantly glial cells, in the cortex of the aging human. Apo D protects against age-related oxidative stress caused by rising ROS levels via its antioxidant and anti-inflammatory action [5]. However, in this study, there was no statistically significant correlation between the serum level of Apo D and the patients' age in contrast to Waldner and his colleagues, who demonstrated a significant association in cases older than 65 years old [4]. This contradiction could be attributed to the difference in age group, as the mean age of their patients was 72.84 ± 7.07 while the mean age of our studied group was 53. 6 ± 12.9.

Finally, our results showed a significant positive association between Apo D serum levels and disease intensity as evaluated by the UPDRS, which is consistent with the findings of Waldner and his group [4].

These results are explained by Apo D growing involvement in shielding cells against astrogliosis, leading to worsening PD motor symptoms. When out of control, reactive astrocytes can be an obstacle because they are necessary to replace the lost dopaminergic neurons and

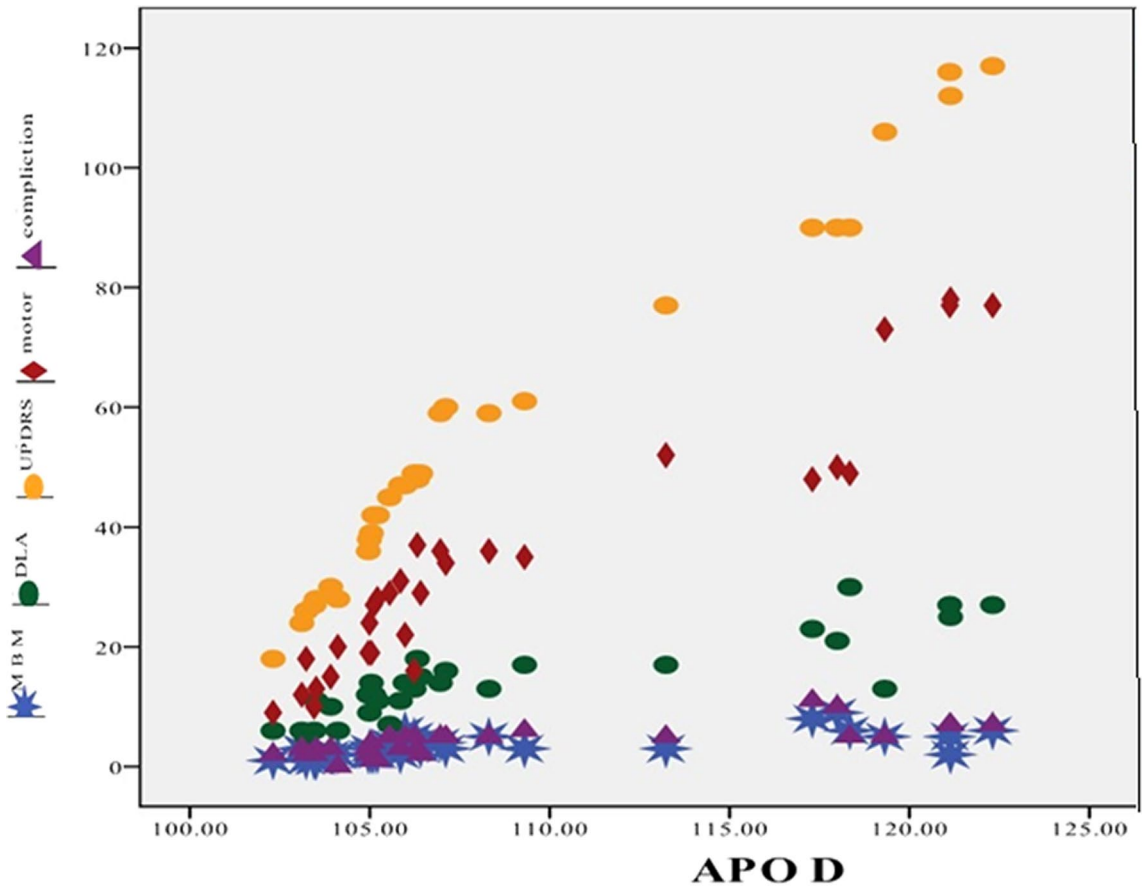

Fig. 2 Relationship between ApoD serum level and UPDRS and its subscales

prevent further damage from spreading. As a result, astrogliosis is a "two-edged sword". Apo D has been hypothesized to play a function in keeping the glial response to many ROS/RNS and inflammatory mediators within set limits [5].

Conclusions

Serum level of Apo D was significantly higher in patients with PD than the control group and it was positively correlated with the disease severity, thus, it can be used as a predictor for PD severity. More studies on larger group of PD patients with different characteristics are warranted to solidify our results, and to proceed more forwards in the future towards targeting the Apo D as a potential therapy for PD aiming to reduce the oxidative stress and inflammatory cascade involved in pathogenesis of this disease.

Abbreviations

AA	Arachidonic acid
AD	Alzheimer's disease
ADLs	Activities of daily living
Apo D	Apolipoprotein D
BRD	Bradykinesia-rigidity dominant phenotype
DA	Dopamine
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
LBs	Lewy bodies
MBM	Mentation, behavior, and mood scale
Mrna	Messenger ribonucleic acid
PD	Parkinson's disease
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SN	Substantia nigra
SPSS	Statistical Package of Social Science
TD	Tremor-dominant
UPDRS	Unified Parkinson Disease Rating Scale
USA	United States of America

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Author contributions

AA recruited the cases and collected all the needed data. HS, SS, SM, MG, and MH revised the clinical data obtained, and the results were also shared in the study design. MM was responsible for the laboratory part of the study. Finally, AA wrote the manuscript which was revised by the other authors to be ready for publication. MG is the corresponding author who is responsible for the publication. All authors read and approved the final manuscript. The authors declare that they have no competing interests.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Research Ethical Committee approved the study and waived informed consent of the Faculty of Medicine, Fayoum University, Egypt, on 17/2/2019. Session number (D192).

Consent for publication
Not applicable.

Competing interests
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